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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 10

MAY 18, 1973

Pyrazoles. XII. The Preparation of 3(5)-Nitropyrazoles by Thermal Rearrangement of *N*-Nitropyrazoles[1,2]

J. W. A. M. JANSSEN, H. J. KOENERS,[3] C. G. KRUSE,[3] AND CLARISSE L. HABRAKEN*

Gorlaeus Laboratories, University of Leiden, Leiden, The Netherlands

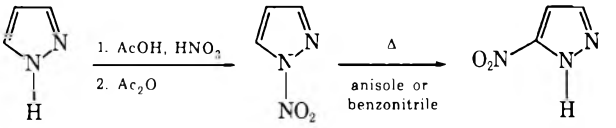
Received October 13, 1972

3(5)-Nitropyrazoles, such as 3,5-dinitropyrazole (**2f**), can be readily synthesized by thermal rearrangement of *N*-nitropyrazoles. In turn, 3(5),4-dinitropyrazoles are obtained by further nitration of some 3(5)-nitropyrazoles.

The direct nitration of pyrazole, using nitric acid or mixtures of nitric acid and sulfuric acid,[4,5] leads to substitution in the 4 position, in line with the behavior of other electrophilic reagents. Moreover, no further nitration of 4-nitropyrazoles has been reported in the literature. Reports on formation of 3-nitropyrazoles either concern compounds synthesized by other methods such as ring closure reactions[4,6] or by nitration of 1,4-disubstituted pyrazoles,[7,8a,b] neither of which appear to be general methods for the synthesis of 3-nitropyrazoles. It is worth notice that in the latter case further nitration to 3,5-dinitropyrazoles can occur.[7]

Recently three different groups of workers independently reported on the synthesis of the unsubstituted 3(5)-nitropyrazole (**2a**). Bagal, *et al.*,[9] obtained **2a** *via* diazotation of 3(5)-aminopyrazole, and Birkofer[10] substituted the trimethylsilyl group in 3(5)-trimethylsilylpyrazole by a nitroso group, which in turn was oxidized to give **2a**. We reported on a novel reaction, the thermal isomerization of *N*-nitropyrazoles into their corresponding 3(5)-nitro derivatives,[11] an example of an apparently characteristic property of *N*-nitroazoles to rearrange thermally into *C*-nitro compounds.[12,13] Using this rearrangement reaction, **2a** was obtained from pyrazole in a simple two-step synthesis in very high yield (see Scheme I).

SCHEME I



1a **2a**

The intramolecular migration of the nitro group can be visualized as a [1,5] sigmatropic shift giving a 3*H*-pyrazole followed by a fast tautomerization (see Scheme II).[13,14]

(1) Part XI: P. B. M W. M. Timmermans, A. P. Uijttewaal, and C. L. Habraken, *J. Heterocycl. Chem.*, **9**, 1347 (1972).

(2) This research was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

(3) Participant in the Undergraduate Research Project Program, supported by Pieter Langerhuizen Lzn. Fonds, administered by De Hollandsche Maatschappij der Wetenschappen.

(4) R. Fusco in "The Chemistry of Heterocyclic Compounds," Vol. 22, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1967, p 3.

(5) A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry," Methuen, London, 1967, p 148.

(6) W. E. Parham and J. L. Bleasdale, *J. Amer. Chem. Soc.*, **73**, 4664 (1951).

(7) M. D. Coburn, *J. Heterocycl. Chem.*, **7**, 707 (1970); **8**, 153, 293 (1971).

(8) (a) C. L. Habraken and P. Cohen Fernandes, *Recl. Trav. Chim. Pays-Bas*, **91**, 1185 (1972); (b) C. L. Habraken, P. Cohen Fernandes, S. Balian, and K. C. van Erk, *Tetrahedron Lett.*, 479 (1970).

(9) L. I. Bagal, M. S. Pevzner, A. N. Forlov, and N. I. Sheludyakova, *Khim. Geterosikl. Soedin.*, 259 (1970); *Chem. Abstr.*, **72**, 111383h (1970).

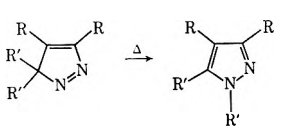
(10) L. Birkofer and M. Franz, *Chem. Ber.*, **104**, 3062 (1971).

(11) J. W. A. M. Janssen and C. L. Habraken, *J. Org. Chem.*, **36**, 3081 (1971).

(12) P. Cohen Fernandes and C. L. Habraken, *J. Org. Chem.*, **36**, 3084 (1971).

(13) C. L. Habraken and P. Cohen Fernandes, *Chem. Commun.*, 37 (1970).

(14) The presumed first step in this isomerization of *N*-nitropyrazoles resembles the reversed process of a van Alphen rearrangement[15] where 3,3,4,5-tetrasubstituted 3*H*-pyrazoles (pyrazolenines) rearrange into N-substituted pyrazoles, a reaction which was reported to be an uncatalyzed



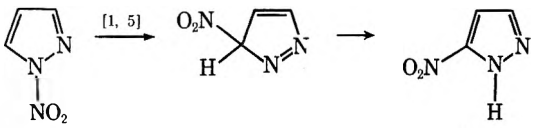
thermal rearrangement.[16] Recently, other examples of the pyrazolenine rearrangement were reported by Dürr and Sergio,[17a] and by Franck-Neumann and Buchecker,[17b] who observed migrations of ester, acyl, and cyano groups which they also explained in terms of [1,5] sigmatropic migrations.

(15) J. van Alphen, *Recl. Trav. Chim. Pays-Bas*, **62**, 485 (1943); **62**, 491 (1943).

(16) R. Hüttel, K. Francke, H. Martin, and J. Riedl, *Chem. Ber.*, **93**, 1433 (1960).

(17) (a) H. Dürr and R. Sergio, *Tetrahedron Lett.*, 3479 (1972); (b) M. Franck-Neumann and C. Buchecker, *ibid.*, 937 (1972).

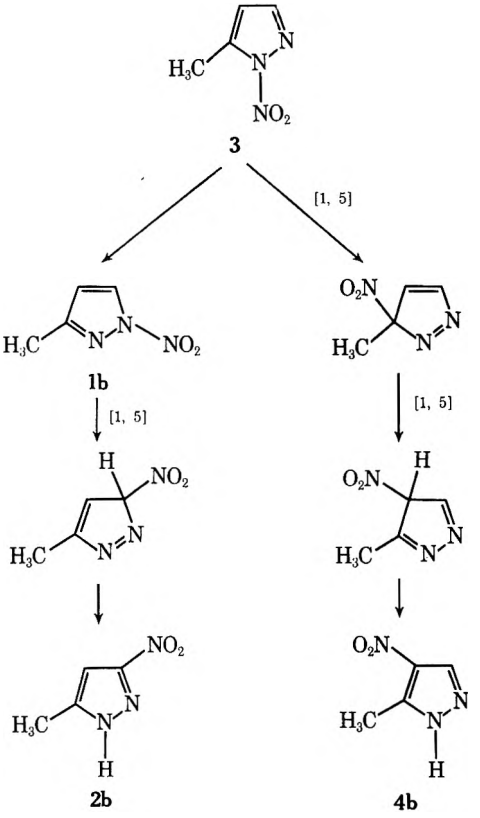
SCHEME II



1a 2a

The thermolysis of 5-methyl-1-nitropyrazole (**3**) affording 3(5)-methyl-4-nitropyrazole (**4b**) in addition to a small amount of 3(5)-methyl-5(3)-nitropyrazole (**2b**),[11] offers the only example so far encountered giving a 4-nitropyrazole. This result can be explained by assuming a subsequent sigmatropic rearrangement from a 3*H*- into a 4*H*-pyrazole followed by tautomerization. The concurrent formation of the 3(5)-methyl-5(3)-nitro isomer **2b** was demonstrated to originate from 3-methyl-1-nitropyrazole (**1b**), which in turn was demonstrated to arise from **3**, presumably by a competing [1,5] migration of the nitro group to the adjacent nitrogen atom (see Scheme III).

SCHEME III

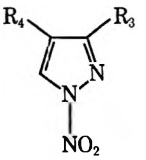


2b **4b**

In this paper we report on the general synthetic implications of this novel isomerization reaction for the preparation of 3(5)-nitropyrazoles.

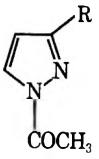
Results and Discussion

The required *N*-nitropyrazoles (**1a–k**) were obtained either by the original N-nitration procedure of Hüttel and Büchele[18] or by nitration of the pyrazole with a preformed mixture of nitric acid and acetic anhydride ("acetyl nitrate"). As described earlier,[11] N-nitration of 3(5)-methylpyrazole gave a mixture of the two isomers 3-methyl- and 5-methyl-1-nitropyrazole. Subsequently



1a, R_3 = H; R_4 = H
b, R_3 = CH_3; R_4 = H
c, R_3 = $C(CH_3)_3$; R_4 = H
d, R_3 = C_6H_5; R_4 = H
e, R_3 = *p*-$NO_2C_6H_4$; R_4 = H
f, R_3 = NO_2; R_4 = H
1g, R_3 = H; R_4 = CH_3
h, R_3 = H; R_4 = C_2H_5
i, R_3 = H; R_4 = C_6H_5
j, R_3 = H; R_4 = NO_2
k, R_3 = C_6H_5; R_4 = NO_2

we found that nitration of 3(5)-methylpyrazole with a large excess of acetyl nitrate *gives the 1,3 isomer* **1b** *as the only product* (see Experimental Section), whereas nitration with an equimolar amount of acetyl nitrate afforded primarily the 1,5 isomer **3** in addition to small amounts of **1b** and 1-acetyl-3-methylpyrazole (**5**).



5, R = CH_3
6, R = C_6H_5

The formation of small quantities of *N*-acetyl compounds as by-products on N-nitration was also observed in some other cases.[8a,11,19] Usually the *N*-nitropyrazoles could be purified by direct crystallization or by very mild acid hydrolysis of the *N*-acetyl derivatives prior to crystallization.[8a] N-Nitration of 3(5)-*tert*-butylpyrazole, 3(5)-phenylpyrazole, and 3(5)-(*p*-nitrophenyl)pyrazole afforded 1-nitro-3-*tert*-butylpyrazole (**1c**), 1-nitro-3-phenylpyrazole (**1d**),[19] and 1-nitro-3-(*p*-nitrophenyl)pyrazole (**1e**) in excellent yields. In these instances the formation of 5-substituted 1-nitropyrazoles is presumably prevented by the bulkiness of the sustituents. An attempt to prepare 1-nitro-5-phenylpyrazole according to the procedure developed for the synthesis of the 5-methyl analog **3** was unsuccessful; the only product obtained was 1-acetyl-3-phenylpyrazole (**6**)[19]. The N-nitration of 4-nitro-3(5)-phenylpyrazole (**4d**) also resulted in the formation of only one isomer, 1,4-dinitro-3-phenylpyrazole (**1k**). Contrary to what was reported by Hüttel and Büchele,[18] N-nitration of 4-nitropyrazole (**4a**) resulted in high yields of 1,4-dinitropyrazole (**1j**). Likewise, N-nitration of 3(5)-nitropyrazole easily afforded 1,3-dinitropyrazole (**1f**).

N-Nitropyrazoles, as in general *N*-nitroazoles, are readily characterized through tlc (see Experimental Section) and ir spectroscopy.[11,12] In addition to the absence of a N–H absorption band, the NO_2 stretching frequencies for a *N*-nitro group (as compared to those of a *C*-nitro group) are found at a lower wavenumber (1270–1295 cm^{-1}) for the symmetric vibration and a higher wavenumber (1600–1650 cm^{-1}) for the asymmetric vibration. In those instances where a decision between two possible isomeric structures was needed, namely compounds **1c–f**, structural assign-

(18) R. Hüttel and F. Büchele, *Chem. Ber.*, **88**, 1586 (1955).

(19) Dal Monte-Casoni[20] N-nitrated 3(5)-phenylpyrazole in two ways: on nitration by Hüttel's procedure she obtained an *N*-nitrophenylpyrazole with unassigned structure, presumably **1d**; on nitration with an excess of acetyl nitrate 1-acetyl-3-(*p*-nitrophenyl)pyrazole was obtained in addition to the same *N*-nitro compound.

(20) D. Dal Monte-Casoni, *Ann. Chim. (Rome)*, **48**, 783 (1958).

TABLE I

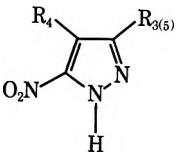
REARRANGEMENT OF *N*-NITROPYRAZOLES 1 INTO 3(5)-NITROPYRAZOLES 2

N-Nitropyrazole	Substituents		3(5)-Nitropyrazole	Rearrangement conditions[a]	Yield[b]
	R_3	R_4			
1a	H	H	**2a**	B, 3 hr, 180°	+++
1b	CH_3	H	**2b**	A, 2 hr, 145° [c]	+++
1c	$C(CH_3)_3$	H	**2c**	A, 2.5 hr, 130°	+++
1d	C_6H_5	H	**2d**	A, 1.5 hr, 130°	+++
1e	p-$NO_2C_6H_4$	H	**2e**	B, 1.5 hr, 140°	+++
1f	NO_2	H	**2f**	B, 110 hr, 140°	+++
1g	H	CH_3	**2g**	B, 20 hr, 160°	++
1h	H	C_2H_5	**2h**	A, 50 hr, 140° [c]	++
1i	H	C_6H_5	**2i**	B, 2.5 hr, 120°	+
1j	H	NO_2	**2j**	B, 6 hr, 191°	+
1k	C_6H_5	NO_2	**2k**	B, 1.5 hr, 140°	+++

[a] A = anisole solution, B = benzonitrile solution; the work-up of the reaction mixture is described in the Experimental Section. [b] See Experimental Section for more detailed information; +++ = 80% and above; ++ = 50–80%; + = low yield (see text). [c] This experiment is described in ref 11.

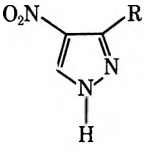
ments were based on their nmr spectral data. The chemical shifts of the 5 protons of these compounds were found at much lower external field as compared to those of the corresponding protons in the N-unsubstituted pyrazoles, owing to the nitro group on the adjacent nitrogen atom.[11,12] Moreover, as is known from investigations of Jacquier and others,[21] the coupling constant between a 4 and a 3 proton differs from that between a 4 and 5 proton ($J_{45} > J_{34}$). The distinct multiplet character of the signal of the phenyl protons in the nmr spectrum of **1d** indicating a phenylpyrazole unsubstituted in the ortho positions[22] furnishes additional support for these assignments.

The best results for the rearrangement reactions were obtained on heating 5–10% solutions of the *N*-nitropyrazole in anisole or benzonitrile. Thin layer chromatographic analysis was used to determine the end of the reaction. In some cases dilution with hexane of the chilled reaction mixture resulted in a nearly quantitative precipitation of the *C*-nitropyrazole. For example, 97% of 3(5)-nitropyrazole was obtained in this way from the rearrangement of 1-nitropyrazole in benzonitrile (see Experimental Section). In most of the remaining cases, *e.g.*, the conversion of 1,3-dinitropyrazole into 3,5-dinitropyrazole (**2f**), high yields were obtained *via* additional extraction with a sodium hydroxide solution (see Experimental Section and Table I). It appeared that isomerization of 4-substituted 1-nitropyrazoles was accompanied by considerable decomposition, resulting in fair to low yields. Thus, 4-methyl- and 4-ethyl-1-nitropyrazole (**1g** and **1h**) led to 4-methyl-3(5)-nitropyrazole (**2g**) and 4-ethyl-3(5)-nitropyrazole (**2h**), respectively, in isolated yields of *ca.* 60%. Likewise, thermolysis of 1-nitro-4-phenylpyrazole (**1i**) afforded (among many decomposition products) only small amounts of the known compound 3(5)-nitro-4-phenylpyrazole (**2i**),[6] as was observed on tlc. Thermolysis of the 1,4-dinitro compound, **1j**, gave but a small yield of 3(5),4-dinitropyrazole (**2j**). [Because it was found (*vide infra*) that the latter compound can be obtained in good yield on nitration of 3(5)-nitropyrazole in sulfuric acid, no further efforts were undertaken to obtain **2j** by preparative themolysis of 1,4-dinitropyrazole]. One of the decomposition reactions observed was a denitration of the *N*-nitropyrazole giving back the N-unsubstituted starting material. Such denitration also occurred in the case of the thermolysis of 1,3-dinitropyrazole, as observed from the presence of 10–15% of 3(5)-nitropyrazole on work-up of the reaction mixture.



2a, $R_{3(5)}$ = H; R_4 = H
b, $R_{3(5)}$ = CH_3; R_4 = H
c, $R_{3(5)}$ = $C(CH_3)_3$; R_4 = H
d, $R_{3(5)}$ = C_6H_5; R_4 = H
e, $R_{3(5)}$ = p-$NO_2C_6H_4$; R_4 = H
f, $R_{3(5)}$ = NO_2; R_4 = H
2g, $R_{3(5)}$ = H; R_4 = CH_3
h, $R_{3(5)}$ = H; R_4 = C_2H_5
i, $R_{3(5)}$ = H; R_4 = C_6H_5
j, $R_{3(5)}$ = H; R_4 = NO_2
k, $R_{3(5)}$ = C_6H_5; R_4 = NO_2

As expected, the thermal rearrangement of the 1-nitropyrazoles unsubstituted in the 5 position, **1a–k**, in all cases afforded the corresponding 3(5)-nitropyrazoles **2a–k**. Structural assignments of the 3(5)-*tert*-butyl-, 3(5)-phenyl-, and 3(5)-*p*-nitrophenyl-5(3)-nitropyrazoles (**2c**, **2d**, and **2e**) were based on comparison (tlc, melting points, uv[23] and ir spectra) with the isomeric 4-nitropyrazoles **4c**, **4d**, and **4e**, which were synthesized by unambiguous routes, **4d** being obtained from **4e** after selective reduction to 4-nitro-3(5)-



4a, R = H
b, R = CH_3
c, R = $C(CH_3)_3$
d, R = C_6H_5
e, R = p-$NO_2C_6H_4$

(*p*-aminophenyl)pyrazole followed by deamination. For those compounds originally possessing a substituent in the 4 position, the identifications were based on the presence of a *C*-nitro group in 4-methyl-3(5)-nitropyrazole (**2g**) and of a second *C*-nitro group in 3(5),4-dinitro- and 3(5),4-dinitro-5(3)-phenylpyrazole (**2j** and **2k**) (ir spectra and tlc and mass spectral

(21) J. Elguero, R. Jacquier, and H. C. N. Tien Duc, *Bull. Soc. Chim. Fr.*, 2327 (1966).

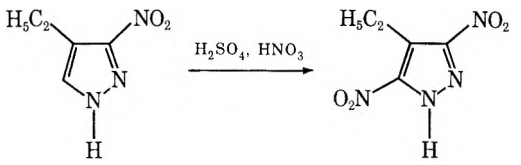
(22) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

(23) Uv spectra of a number of nitropyrazoles will be presented and discussed in a separate paper.

or elemental analysis). Compound **2f**, the isomerization product of 1,3-dinitropyrazole, was found to be a *C*-dinitropyrazole differing from the 3(5),4-dinitro isomer **2j** and was consequently assigned the structure of 3,5-dinitropyrazole. All assignments were corroborated by the nmr spectra.

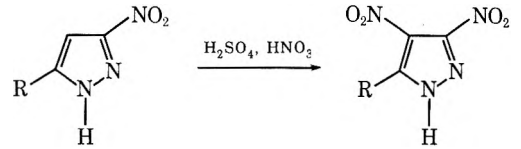
As mentioned before, 4-nitropyrazoles do not undergo further C-nitration, whereas 1,4-disubstituted pyrazoles can undergo dinitration to give 3,5-dinitro derivatives. These findings of Coburn[7] were confirmed by the synthesis of 4-ethyl-3,5-dinitropyrazole (**7**) on further nitration in mixed acid of the mononitropyrazole **2h** (Scheme IV) (see Experimental Section). Moreover, it appeared that the 3(5)-nitropyrazoles **2a** and **2b** on nitration with mixed acid afforded quite readily and in good yields 3(5),4-dinitropyrazole (**2j**) and 3(5),4-dinitro-5(3)-methylpyrazole (**8**) (Scheme V). No trace of 3(5),4-dinitropyrazole (**2j**) could be detected when 4-nitropyrazole was subjected to the same dinitration conditions of the 3(5)-nitropyrazoles. To our knowledge only one other example of further nitration of a 3(5)-nitropyrazole has been described, namely that of 3(5)-nitro-5(3)-(*m*-pyridyl)pyrazole giving the corresponding 3(5),4-dinitro derivative.[24] Apparently, and contrary to what is observed with 4-nitropyrazoles, 3(5)-nitropyrazoles can be C-nitrated further, and again in the 4 position, as readily as other 3(5)-substituted pyrazoles.

SCHEME IV



2h **7**

SCHEME V



2a, R = H **2j**, R = H
2b, R = CH_3 **8**, R = CH_3

In conclusion, thermal rearrangement of *N*-nitropyrazoles offers a convenient method to synthesize 3(5)-nitropyrazoles, which in turn may undergo electrophilic substitution preferably in the 4 position, as we observed for the nitration reaction.

Experimental Section[25]

General.—Nmr spectra (δ expressed in parts per million) were recorded on a JEOL 60-MHz Minimar or on a JEOL PS-100 instrument; ir spectra (KBr technique) were recorded on a Perkin-Elmer IR-137 spectrophotometer. Glc analyses were performed on a Varian Aerograph 1400 instrument. Spraying with Rhodamine B solution (0.05% in ethanol) was used for the detection of nitropyrazoles on tlc; in the case of *N*-nitropyrazoles the purple-colored spots characteristic for all nitroazoles turned into yellow or brownish yellow colored spots on standing. Elemental analyses were performed by Mr. W. J. Buis, TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands; mass spectra were recorded on a AE MS-902 spectrometer. All melting points are uncorrected.

Materials.—3(5)-Methylpyrazole, 3(5)-phenylpyrazole, and 4-nitropyrazole (**4a**) were synthesized by standard procedures. The syntheses of 1-nitropyrazole (**1a**), 5-methyl-1-nitropyrazole (**3**), 4-ethyl-1-nitropyrazole (**1h**), 3(5)-methyl-5(3)-nitropyrazole (**2b**), and 4-ethyl-3(5)-nitropyrazole (**2h**) were described in ref 11; the synthesis of 1-nitro-4-phenylpyrazole (**1i**) was described in ref 8a. 4-Methylpyrazole was prepared by reaction of 1,1,3,3-tetraethoxy-2-methylpropane with hydrazine hydrochloride;[26] 3(5)-*tert*-butylpyrazole was prepared by condensing pivaloyl acetaldehyde[27] with hydrazine hydrate, yield 71%, bp 110–112° (10 mm) [lit.[28] bp 106° (9 mm)]. 3(5)-(*p*-Nitrophenyl)pyrazole was made by nitrating 3(5)-phenylpyrazole with nitric acid (*d* 1.52) in sulfuric acid solution in the cold.[20] 1-Acetyl-3-methylpyrazole (**5**) was obtained by reaction of 3(5)-methylpyrazole with an excess of acetyl chloride.[29]

Acetyl nitrate was prepared freshly before use by adding nitric acid (*d* 1.52) to acetic anhydride.[8a] All chemicals, being high-grade commercial products, were used as such.

4-Nitro-3(5)-(*p*-nitrophenyl)pyrazole (4e).—While cooling, 7 g of 3(5)-phenylpyrazole was added to 100 ml of nitric acid (*d* 1.52); after stirring at 50° for 2 hr the solution was poured onto ice and the precipitated compound was collected by filtration. Ether extraction of the filtrate provided an additional amount of **4e**. Total yield after crystallization from ethanol was 7.5 g (66%): mp 210–212° (lit.[30] mp 212°); nmr (60 MHz, DMSO) δ 8.86 [s, 1, 5(3)-H], 8.37 and 7.97 (doublets, 4, J = 8 Hz, aromatic).

4-Nitro-3(5)-(*p*-aminophenyl)pyrazole.—Hydrogen sulfide was passed through a solution of 7.5 g of **4e** containing 4.2 g of NaOH, at a temperature of 80°; after a few minutes the temperature increased to *ca.* 90° and an orange-colored solid precipitated. H_2S was passed through for an additional 1 hr. The solid, collected by filtration, was washed with water: 4.9 g (75%); after crystallization from water, mp 187–187.5°; ir 3350 (NH_2), 3200 (NH), 1495 and 1320 cm^{-1} (NO_2); nmr (60 MHz, acetone) δ 8.25 [s, 1, 5(3)-H], 7.51 and 6.81 (doublets, 4, J = 8 Hz, aromatic).

Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.07; H, 3.76; N, 27.36.

4-Nitro-3(5)-phenylpyrazole (4d).—Sodium nitrite (1.4 g) was very slowly added to a cold solution (−5 to 0°) of 4-nitro-3(5)-(*p*-aminophenyl)pyrazole (4.0 g) in 20% hydrochloric acid; after stirring for 0.5 hr at 0°, 31.2 ml of cooled hypophosphoric acid (50%) was added. The mixture was allowed to stand for 24 hr at room temperature; the reaction mixture was diluted with *ca.* 50 ml of water and the solid was collected by filtration. Crystallization from a large amount of water yielded 3.1 g (84%) of **4d**. The compound was recrystallized from water to give an analytically pure sample: mp 185–185.5°; ir 3200 (NH), 1495 and 1320 cm^{-1} (NO_2); nmr (60 MHz, acetone) δ 8.44 [s, 1, 5(3)-H], 7.75–7.40 (m, 5, aromatic).

Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.16; H, 3.63; N, 22.32.

4-Nitro-3(5)-*tert*-butylpyrazole (4c).—A 1.5-g portion of 3(5)-*tert*-butylpyrazole was nitrated with "mixed acid" according to the method of Morgan and Ackerman;[31] the reaction mixture was poured onto ice and extracted with ether; evaporation of the solvent afforded 1.7 g (83%) of **4c**. A pure sample was obtained by crystallization from petroleum ether (bp 60–80°): mp 118.5–119°; ir 3235 (NH), 1510 and 1385 (1311?) cm^{-1} (NO_2); nmr (60 MHz, $CDCl_3$) δ 8.37 [s, 1, 5(3)-H] and 1.44 [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.80; H, 6.62; N, 24.93.

3(5)-Nitropyrazole (2a). Rearrangement of 1-Nitropyrazole

(24) H. Lund, *J. Chem. Soc.*, 418 (1935).

(25) The following experiments were performed by J. Duyfjes and R. Bosman: syntheses of compounds **1e**, **1f**, **2e**, and **2f**; additional synthetic help was obtained from R. Fransen, P. Cornelissen, and B. Poldermans.

(26) V. T. Klimko, T. V. Protopopova, and A. P. Skoldinov, *J. Gen. Chem. USSR*, **31**, 159 (1961).

(27) (a) J. T. Adams and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1220 (1944); (b) R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *ibid.*, **67**, 1510 (1945).

(28) I. I. Grandberg and A. N. Kost, *J. Gen. Chem. USSR*, **28**, 3102 (1958).

(29) K. v. Auwers and W. Daniel, *J. Prakt. Chem.*, **110**, 235 (1925).

(30) E. Buchner and C. Hachumian, *Chem. Ber.*, **35**, 37 (1902).

(31) J. T. Morgan and I. Ackerman, *J. Chem. Soc.*, **123**, 1308 (1923).

(1a).—A solution of 3.0 g of 1a in 30 ml of benzonitrile was heated for 3 hr at 180°; after cooling and the addition of a threefold quantity of hexane, compound 2a was collected by filtration. The crude yield, after washing with hexane and drying, was 2.9 g (97%), mp 173–174°; recrystallization from water gave mp 174–175° (lit.[9] mp 175°). Additional experiments (up to 10-g scale) afforded 95–99% yields.

Nitration of 3(5)-Methylpyrazole with an Excess of Acetyl Nitrate.—Acetyl nitrate (72 mmol, 3 ml of nitric acid in 7.5 ml of acetic anhydride) was added to a solution of 3(5)-methylpyrazole (2.5 g, 32 mmol) in 3 ml of acetic acid at 0°. After 2 hr the reaction mixture was poured onto ice; the resulting precipitate (0.7 g) appeared to be pure 3-methyl-1-nitropyrazole (1b) (glc, ir, nmr, and melting point); an additional 1.2-g portion of 1b was obtained after neutralization of the filtrate with sodium carbonate and extraction with ether; total yield was 49%.

Nitration of 3(5)-Methylpyrazole with an Equimolar Amount of Acetyl Nitrate.—A 5.9-g (72 mmol) portion of 3(5)-methylpyrazole was treated with 72 mmol of acetyl nitrate as described above; after neutralization and extraction with ether the product mixture was analyzed by glc and nmr; on comparison with authentic samples, it was found to consist of 3, 1b, and 5 (7:1:2).

1-Nitro-3-*tert*-butylpyrazole (1c).—A 3.0-g portion of 3(5)-*tert*-butylpyrazole was dissolved in 9.5 ml of acetic acid and N-nitrated[11,18] with 2.2 ml of nitric acid (*d* 1.52) and 16 ml of acetic anhydride. The crude product was crystallized from petroleum ether to yield 2.6 g (64%) of compound 1c. The analytical sample was obtained by recrystallization from petroleum ether: mp 66°; ir 1600 and 1285 cm^{-1} (NNO_2); nmr (60 MHz, $CDCl_3$) δ 8.23 (d, 1, J = 2.8 Hz, 5-H), 6.37 (d, 1, J = 2.8 Hz, 4-H), and 1.38 [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.66; H, 6.45; N, 24.81.

1-Nitro-3-phenylpyrazole (1d) was obtained when 6.0 g of 3(5)-phenylpyrazole, dissolved in 18 ml of acetic acid, was N-nitrated with 3.6 ml of nitric acid and 18 ml of acetic anhydride. The crude yield was 7.3 g (93%). Recrystallization from methanol gave an analytically pure sample: mp 119° (lit.[20] mp 122°); ir 1620 and 1290 cm^{-1} (NNO_2); nmr (60 MHz, $CDCl_3$) δ 8.20 (d, 1, J = 3.0 Hz, 5-H), 6.67 (d, 1, J = 3.0 Hz, 4-H), 7.90–7.65 (m, 2), and 7.45–7.20 (m, 3, aromatic).

Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.21; H, 3.75; N, 22.26.

Reaction of 3(5)-Phenylpyrazole with an Equimolar amount of Acetyl Nitrate.—Acetyl nitrate (14 mmol) was carefully added to a solution of 2 g (14 mmol) of 3(5)-phenylpyrazole in 15 ml of acetic acid at 0°. After 1.5 hr the reaction mixture was poured onto ice; the formed precipitate (2.1 g) appeared to be 1-acetyl-3-phenylpyrazole (6). After crystallization from petroleum ether 6 had mp 63° (lit.[32] mp 64–65°); ir 1725 cm^{-1} (C=O); nmr (100 MHz, $CDCl_3$) δ 8.16 (d, 1, J = 2.8 Hz, 5-H), 6.64 (d, 1, J = 2.8 Hz, 4-H), 7.9–7.7 (m, 2) and 7.4–7.3 (m, 3, aromatic), 2.70 (s, 3, CH_3).

1-Nitro-3-(*p*-nitrophenyl)pyrazole (1e).[25]—When 2.0 g of 3(5)-(*p*-nitrophenyl)pyrazole was dissolved in 35 ml of acetic acid and N-nitrated with 0.6 ml of nitric acid and 6 ml of acetic anhydride, 2.3 g (93%) of crude 1e was obtained. The compound was recrystallized from methanol to give a pure sample. A melting point was only observed when the temperature of the sample was raised rapidly, mp 184–186°. When the temperature was increased slowly, compound 1e rearranged into 2e without liquefying: ir 1625 and 1290 cm^{-1} (NNO_2), 1515 and 1340 cm^{-1} (CNO_2); nmr (60 MHz, DMSO) δ 8.86 (d, 1, J = 2.8 Hz, 5-H), 7.42 (d, 1, J = 2.8 Hz, 4-H), and 8.27 (symmetrical AA'BB' spectrum, 4, aromatic).

Anal. Calcd for $C_9H_6N_4O_4$: C, 46.16; H, 2.58; N, 23.93. Found: C, 46.15; H, 2.46; N, 23.86.

1,3-Dinitropyrazole (1f).[25]—A 2.9-g portion of 2a was suspended in 18 ml of acetic acid and N-nitrated with 2.4 ml of nitric acid and 6 ml of acetic anhydride. After 2.5 hr the reaction mixture was poured onto ice and the *N*-nitro compound was collected by filtration: 2.3 g (57%) of 1f; white crystals from hexane; mp 67°; ir 1645 and 1285 cm^{-1} (NNO_2), 1550 and 1350 cm^{-1} (CNO_2); nmr (60 MHz, $CDCl_3$) δ 8.45 (d, 1, J = 2.8 Hz, 5-H) and 7.17 (d, 1, J = 2.8 Hz, 4-H); mol wt, 158.0079 (calcd for $C_3H_2N_4O_4$, 158.0075).

4-Methyl-1-nitropyrazole (1g).—A 4.0-g portion of 4-methylpyrazole was dissolved in 15 ml of acetic acid and N-nitrated with 3 ml of nitric acid and 9 ml of acetic anhydride. After 2 hr the reaction mixture was poured on ice; 3.75 g (61%) of 1g precipitated from the solution after saturation with NaCl. Recrystallization from petroleum ether (bp 40–60°) gave an analytically pure sample: mp 42.5°; ir 1600 and 1290 cm^{-1} (NNO_2); nmr (60 MHz, $CDCl_3$) δ 8.11 (s, 1, 5-H), 7.48 (s, 1, 3-H), and 2.17 (s, 3, CH_3).

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 39.02; H, 3.85; N, 33.24.

1,4-Dinitropyrazole (1j).—4-Nitropyrazole (4a, 3.0 g) was suspended in 15 ml of acetic acid and N-nitrated with 3.5 ml of nitric acid and 5.5 ml of acetic anhydride; after 0.5 hr the reaction mixture was poured onto ice, neutralized with sodium carbonate, and repeatedly extracted with ether. The combined extracts were dried on $MgSO_4$ and evaporated to dryness: yield 3.4 g (81%) of crude 1j. The product was purified by column chromatography[11] (silica gel H according to Stahl, chloroform–ethyl acetate, 3:1) and crystallization from hexane: mp 54°; ir 1650 and 1280 cm^{-1} (NNO_2), 1515 and 1320 cm^{-1} (CNO_2); nmr (60 MHz, $CDCl_3$) δ 9.00 (s, 1, 5-H) and 8.17 (s, 1, 3-H); mol wt, 158.0079 (calcd for $C_3H_2N_4O_4$, 158.0075).

1,4-Dinitro-3-phenylpyrazole (1k).—Compound 4d (1.0 g) was dissolved in 10 ml of acetic acid and N-nitrated with 0.7 ml of nitric acid and 5 ml of acetic anhydride. After 1.5 hr the reaction mixture was poured onto ice; the resulting solution was saturated with NaCl; and the *N*-nitro compound was collected by filtration and washed with water. A crude yield of 1.2 g (97%) of 1k was obtained. The analytical sample was obtained after crystallization from methanol: mp 163° dec; ir 1650 and 1270 (NNO_2), 1545 (?), 1510 and 1350 cm^{-1} (CNO_2); nmr (100 MHz, $CDCl_3$) δ 9.10 (s, 1, 5-H), 7.8–7.7 (m, 2), and 7.6–7.4 (m, 3, aromatic).

Anal. Calcd for $C_9H_6N_4O_4$: C, 46.16; H, 2.58; N, 23.93. Found: C, 46.53; H, 2.74; N, 23.54.

3(5)-Nitro-5-(3)-*tert*-butylpyrazole (2c). Rearrangement of 1c.—The reaction mixture obtained after rearrangement of 1c (2.0 g in 25 ml of anisole) was diluted with hexane and extracted with 1 *N* NaOH solution; the NaOH layers were acidified with HCl and extracted with ether. The crude product obtained after evaporation of the solvent was crystallized from petroleum ether (bp 80–100°): yield 1.6 g (80%) of 2c; mp 190–190.5°; ir 3150 (NH), 1530 and 1335 cm^{-1} (CNO_2); nmr (60 MHz, $CDCl_3$) δ 6.59 (s, 1, 4-H) and 1.21 [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.74; H, 6.54; N, 25.00.

3(5)-Nitro-5(3)-phenylpyrazole (2d). Rearrangement of 1d.—A 4.0-g portion of 1d, dissolved in 40 ml of anisole, was thermolyzed at 130°; compound 2d precipitated from the chilled reaction mixture and was collected by filtration (3.3 g, 83%). An additional portion was obtained by extraction of the filtrate with NaOH solution. Crystallization from methanol gave an analytically pure sample: mp 198°; ir 3225 (NH), 1540 and 1335 cm^{-1} (CNO_2); nmr (60 MHz, acetone) δ 7.9–7.7 (m, 2) and 7.6–7.3 (m, 3, aromatic), 7.26 (s, 1, 4-H).

Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.33; H, 3.65; N, 22.35.

3(5)-Nitro-5(3)-(*p*-nitrophenyl)pyrazole (2e).[25] **Rearrangement of 1e.**—The solution obtained after rearrangement of 1e (0.50 g dissolved in 5 ml of benzonitrile) was diluted with hexane; compound 2e precipitated and was collected by filtration. The crude yield was 0.41 g (82%). Recrystallization from methanol gave an analytically pure sample: mp 260°; ir 3230 (NH), 1545, 1520, and 1335 cm^{-1} (CNO_2); nmr (60 MHz, DMSO) δ 8.23 (symmetrical AA'BB' spectrum, 4, aromatic) and 7.75 (s, 1, 4-H).

Anal. Calcd for $C_9H_6N_4O_4$: C, 46.16; H, 2.58; N, 23.93. Found: C, 46.13; H, 2.61; N, 24.10.

3,5-Dinitropyrazole (2f). Rearrangement of 1f.[25]—The reaction mixture that was obtained after thermolysis of 1.0 g of 1f in 20 ml of benzonitrile was worked up by dilution with hexane and extraction with NaOH solution. The product (1 g) was contaminated with 10–15% of 2a (nmr analysis). Crystallization from benzene afforded pure 2f: mp 173–174°; ir 3200 (NH), 1570(?), 1530, 1365, and 1340 cm^{-1} (CNO_2); nmr (60 MHz, acetone) δ 7.64 (s, 4-H).

Anal. Calcd for $C_3H_2N_4O_4$: C, 22.79; H, 1.28; N, 35.45. Found: C, 22.91; H, 1.42; N, 35.51.

4-Methyl-3(5)-nitropyrazole (2g). Rearrangement of 1g.—A 3.0-g portion of 1g, dissolved in 60 ml of benzonitrile, was

(32) K. v. Auwers and W. Schmidt, *Chem. Ber.*, **58**, 528 (1925).

thermolyzed at 160°. 2g was precipitated from the reaction mixture by the addition of hexane; the compound (1.25 g) was collected by filtration. An additional 0.60 g was obtained by extraction of the filtrate with NaOH solution. The total crude yield was 62%. Crystallization from water gave a pure sample: mp 187°; ir 3175 (NH), 1525 and 1350 (1370?) cm^{-1} (CNO_2); nmr (60 MHz, $CDCl_3$) 7.80 [s, 1, 5(3)-H] and 2.47 (s, 3, CH_3).

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.92; H, 4.07; N, 32.97.

3(5),4-Dinitro-5(3)-phenylpyrazole (2k). Rearrangement of 1k.—A 0.30-g portion of **1k** was dissolved in 5 ml of benzonitrile and thermolyzed at 140°; the resulting solution was worked up by extraction with NaOH solution. The crude yield was 0.24 g (80%). Crystallization from benzene gave an analytically pure sample: mp 149–150°; ir 3280 (NH), 1535 (m), 1370 and 1330 cm^{-1} (CNO_2); nmr (100 MHz, acetone) δ 7.9–7.7 (m, 2) and 7.7–7.5 (m, 3, aromatic).

Anal. Calcd for $C_9H_6N_4O_4$: C, 46.16; H, 2.58; N, 23.93. Found: 46.43; H, 2.72; N, 23.74.

Thermolysis of 1i.—A 2% solution of **1i** in benzonitrile was heated at 120°; the reaction was followed by tlc. Among other products, the rearrangement product 3(5)-nitro-4-phenylpyrazole (**2i**)[33] could be detected.

3(5),4-Dinitropyrazole (2j). Nitration of 2a with Mixed Acid.—Compound **2a** (1.5 g) was dissolved in 2.55 ml of concentrated sulfuric acid and nitrated by the method of Morgan and Ackerman[31] with 1.65 ml of nitric acid and 5.1 ml of sulfuric acid. The reaction mixture was poured on ice and, after saturation with NaCl, extracted with ether. Removal of the solvent gave 1.9 g (86%) of **2j** as white crystals from benzene: mp 87.5–88.5°; ir 3280 (NH), 1550, 1520, 1370, and 1340 cm^{-1} (NO_2); nmr (60 MHz, acetone) δ 8.71 [s, 5(3)-H]; mol wt, 158.0078 (calcd for $C_3H_2N_4O_4$, 158.0075).

Thermolysis of 1j.—The reaction mixture that was obtained when a solution of **1j** in benzonitrile (10%) was refluxed for 6 hr was worked up by extraction with NaOH solution. The oily liquid that was obtained appeared to be mainly a mixture of **2j** and **4a** (8:2, nmr analysis). When a solution of **1j** was heated for a longer time at a lower temperature (130°), other (unknown) products were formed.

3(5),4-Dinitro-5(3)-methylpyrazole (8).—Compound **2b** (0.80 g) was nitrated by the method of Morgan and Ackerman.[31] The reaction mixture was poured onto ice, neutralized with sodium carbonate, and extracted with ether, yield 0.78 g (72%). Crystallization from benzene gave an analytically pure sample: mp 120–121°; ir 3280 (NH), 1550, 1505, 1360, and 1330 cm^{-1} (NO_2); nmr (60 MHz, acetone) δ 2.67 (s, CH_3).

Anal. Calcd for $C_4H_4N_4O_4$: C, 27.91; H, 2.34; N, 32.56. Found: C, 28.33; H, 2.49; N, 32.30.

3,5-Dinitro-4-ethylpyrazole (7).—The reaction mixture that was obtained after nitration of 1.5 g of **2h** by the method of Morgan and Ackerman[31] was poured onto ice; the formed precipitate (unreacted **2h**) was removed by filtration; the filtrate was neutralized with sodium carbonate and extracted with ether to yield 0.48 g (23%) of **7**. The compound was purified by column chromatography[11] (silica gel H according to Stahl, chloroform–methanol–acetic acid, 80:20:0.5, as eluent) and crystallization from water: mp 170–171°; ir 3245 (NH), 1590 (?), 1545 and 1340 cm^{-1} (NO_2); nmr (100 MHz, hexadeuterioacetone) δ 3.19 (q, 2, CH_2) and 2.24 (t, 3, CH_3).

Anal. Calcd for $C_5H_6N_4O_4$: C, 32.26; H, 3.25; N, 30.10. Found: C, 32.71; H, 3.35; N, 30.26.

Nitration of 4-Nitropyrazole (4a).—This compound was treated with mixed acid by the same method that was used for the further nitration of **2a**. Work-up of the reaction mixture afforded the unreacted compound as the only product (tlc analysis).

Registry No.—**1a**, 7119-95-1; **1c**, 38859-25-5; **1d**, 38859-26-6; **1e**, 38859-27-7; **1f**, 38858-81-0; **1g**, 38858-82-1; **1j**, 35852-77-8; **1k**, 38858-84-3; **2a**, 26621-44-3; **2c**, 38858-86-5; **2d**, 38858-87-6; **2e**, 38858-88-7; **2f**, 38858-89-8; **2g**, 38858-90-1; **2h**, 31163-87-8; **2j**, 38858-92-3; **2k**, 38858-93-4; **4a**, 2075-46-9; **4c**, 38858-95-6; **4d**, 38858-96-7; **4e**, 38858-97-8; **6**, 38858-98-9; **7**, 38858-99-0; **8**, 38859-00-6; 3(5)-phenylpyrazole, 2458-26-6; 4-nitro-3(5)-(*p*-aminophenyl)pyrazole, 38859-02-8; 3(5)-methylpyrazole, 1453-58-3; 3(5)-(*p*-nitrophenyl)pyrazole, 20583-31-7; 4-methylpyrazole, 7554-65-6.

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(33) We wish to thank Dr. W. E. Parham, University of Minnesota, for providing a sample of this compound.

On the Reaction of Carbonyl Compounds with 3,5-Dihydroxy-4-phenylisoxazole. A Novel Type of Noncatalyzed Condensation and Carbon–Carbon Bond Formation

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3,5-Dihydroxy-4-phenylisoxazole reacts spontaneously with a variety of carbonyl compounds yielding with aromatic aldehydes *N*-arylmethylidene-4-phenylisoxazol-5-onium-3-enolates and with acetone a 1:2 condensation product. The latter undergoes reaction with alcohols giving 5-alkoxy-2-oxo-3-phenyl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazine. Crotonaldehyde, acrolein, and mesityl oxide reacted with the initial isoxazole. Structures and properties of the various products are studied.

The unusual physical properties of 3,5-dihydroxy-4-phenylisoxazole (**1**), prepared from ethyl α-phenylmalonate and hydroxylamine, have been described recently.[1] An interesting chemical property of this compound which is studied here is its reactivity toward carbonyl compounds. It reacts spontaneously either upon dissolution in the neat carbonyl compound or in solution, at room temperature. The stable red products which are obtained from aromatic aldehydes were briefly described in a recent communication[2] and were proved to be *N*-arylmethylidene-4-phenylisoxazol-5-onium-3-enolates (**2**). Additional data about these compounds are given in the Experimental Section below. The formation of **2** is probably initiated by the protonation of the aldehydic oxygen by the very acidic[1] enol of **1**, followed by the elimination of water. Another possible approach is a cyclic concerted mechanism (see Scheme I). In the case of benzaldehyde the re-

(1) G. Zvilichovsky, *Israel J. Chem.*, **9**, 659 (1971).

(2) G. Zvilichovsky, *Tetrahedron Lett.*, 2351 (1972).

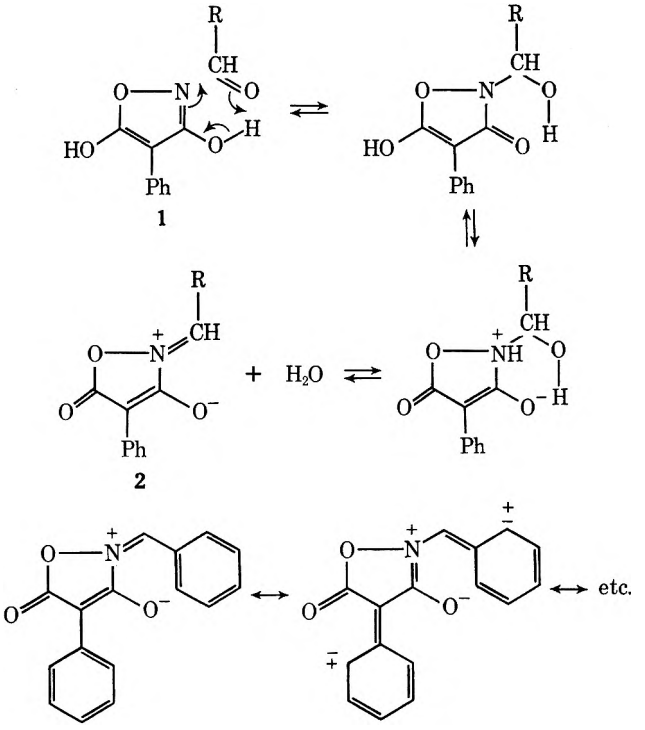
TABLE I

NMR DATA OF PRODUCTS DERIVED FROM ACETONE. δ VALUES AND RELATIVE INTEGRATION[a]

Compound no.	Solvent (time)[b]	CH_2	CH_3	$(CH_3)_2C$	OH
5	$CDCl_3$	2.92 s (1.6)	2.14 s (2.4)	1.54 s (4.8)	4.36 s (0.8)[c]
		2.36 s (0.4)	1.79 s (0.6)	1.40 s (1.2)	7.2 (0.2)
	Acetone-d_6	2.38 s (2.0)	1.79 s (3.0)	1.40 s (6.0)	7.2 (1.0)
	DMSO-d_6 (5 min)	2.55 s (2.0)	1.85 s (3.0)	1.38 s (6.0)	8.4 s (1.0)
	(10 min)[d]	2.55 s (1.9)	1.85 s (2.9)	1.38 s (5.7)	8.5 s (1.05)
			1.78 s (0.1)	1.87 d (0.3)[e]	
	(15 min)[d]	2.55 s (1.8)	1.85 s (2.7)	1.38 s (5.4)	8.9 s (1.1)
			1.78 s (0.3)	1.87 d (0.6)[e]	
	(25 min)[d]	2.55 s (1.6)	1.85 s (2.4)	1.38 s (4.8)	9.2 s (1.2)
			1.78 s (0.6)	1.87 d (1.2)[e]	9.2 s (1.2)
	(70 min)[d]	2.55 s (1.2)	1.85 s (1.8)	1.38 s (3.6)	9.6 s (1.4)
			1.78 s (1.2)	1.87 d (2.4)[e]	
	(20 hr)[d]	2.55 s (0.8)	1.85 s (1.2)	1.38 s (2.4)	10.0 s (1.6)
			1.78 s (1.8)	1.87 d (3.6)[e]	
	$CDCl_3$ + pyridine	2.92 s (2.0)	2.10 s (3.0)	1.48 s (6.0)	14.1 ($\overset{+}{N}H$)
	$CDCl_3$ + Et_3N	2.86 s (2.0)	2.05 s (3.0)	1.45 s (6.0)	10.2 ($\overset{+}{N}H$)
7, R = Et	$CDCl_3$	2.20 s (2.0)	1.60 s (3.0)	1.40 s (3.0)	1.0 t (OEt)
				1.34 s (3.0)	3.5 q (OEt)
7, R = Me	$CDCl_3$	2.22 s (2.0)	1.60 s (3.0)	1.40 s (3.0)	3.28 s (OMe)
				1.37 s (3.0)	

[a] The signals of the aromatic protons are not given in the table. In $CDCl_3$ 5 gave δ 7.20 s (4.0) and 7.20–7.60 m (1.0). In all other solvents a multiplet is observed. 7 gave a multiplet. [b] The time after the sample was dissolved. [c] This is the absorption of the methine proton of tautomer 5c. [d] A vinylic proton signal is also observed: δ 5.98 with increasing integration from 0.05 to 0.6. [e] This doublet is actually two singlets.

SCHEME I



action is reversible, and by addition of water it decomposes to the parent compounds. These red crystalline products (2) are stabilized by conjugation of the aldehydic component with the phenyl group at the 4 position, with a large number of resonance structures as shown for the benzaldehyde derivative (3). The stability of these zwitterionic compounds depends on the nature of the aldehyde; extended conjugation or electron-donating groups enhance their stability.[2] In the case of acetone, acrolein, or crotonaldehyde there is a more limited electron delocalization. Thus the zwitterionic analog of 2 becomes an active intermediate with a strongly electrophilic carbon, comparable to the carbon in phosgene immonium[3-5] or in the intermediate cyclopropanone imminium salt.[6]

It was mentioned previously[1] that 3,5-dihydroxy-4-phenylisoxazole (1) gives a yellow coloration with acetone. Attempts to isolate the colored product were unsuccessful. However, a new colorless product could be obtained in about 50% yield (5). The product gave analytical results of a condensation product of two molecules of acetone per molecule of 1, with the elimination of a molecule of water and has probably structure 5 (Scheme II). On hydrolysis it yields phenylacetic acid, excluding combination of any acetone molecule to any ring carbon, as phenylacetic acid is obtained *via* phenylmalonic acid by decarboxylation.

It appears that the strongly electrophilic carbon in 4 attacks the carbon of the ketone even in the absence of base. Evidence for the structure of 5 is also obtained from its spectral and chemical properties. The ir in the solid state shows a C=O absorption only at 1700 cm^{-1} which is probably due to the side-chain carbonyl group. The ring carbonyl absorption is absent similarly to the case of the parent compound as a result of tautomerism and hydrogen bonding.[1] The low frequency of the OH absorption (3210 cm^{-1}) also indicates hydrogen bonding in the solid state. The tautomeric equilibria of 5 are clearly seen in the nmr spectra (Table I).

The nmr absorption of the phenyl protons in the parent compound (1) consists of a multiplet rather than a singlet;[1] however, by determining the nmr spectrum of 5 in $CDCl_3$ a mixture of tautomers is observed. About 20% has a conjugated structure (5b), showing

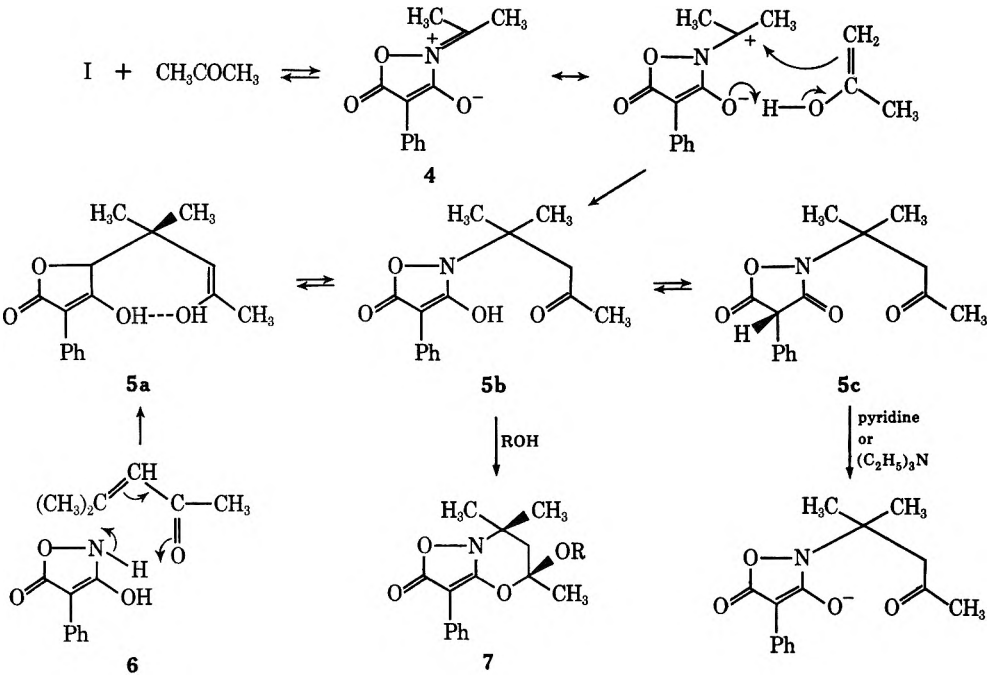
(3) H. G. Viehe and Z. Janosek, *Angew. Chem., Int. Ed.* Engl., **10**, 573 (1971); *Angew. Chem.*, **83**, 614 (1971).

(4) Z. Janosek and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, **10**, 574 (1971); *Angew. Chem.*, **83**, 615 (1971).

(5) H. G. Viehe, Z. Janosek, and M.-A. DeFrenne, *Angew. Chem., Int. Ed. Engl.*, **10**, 575 (1971); *Angew. Chem.*, **83**, 616 (1971).

(6) H. H. Wasserman and M. S. Baird, *Tetrahedron Lett.*, 3721 (1971).

SCHEME II



the aromatic multiplet, whereas about 80% give a singlet at δ 7.10 corresponding to structure **5c**. In addition there is a methine band at δ 4.35 which also arises from structure **5c**; this band is displaceable by D_2O. The side-chain bands indicate CH_2, CH_3CO, and $(CH_3)_2C$ groups at δ 2.92, 2.14, and 1.54, respectively. These bands are accompanied by bands of 20% intensity at δ 2.36, 1.79, and 1.40, respectively. Moreover, if structure **5c** is dominant in $CDCl_3$, the absorption of the ring carbonyl in the ir should be observed at higher frequencies, and, indeed, there are two carbonyl bands in chloroform at considerably higher frequency (1810 and 1730–1700 cm^{-1}) resembling cyclic anhydrides. Upon the addition of an organic base to the $CDCl_3$ solution, *e.g.*, pyridine or triethylamine, 100% of the enolic form is obtained resulting in a complete elimination of the aromatic singlet and in single peaks for each kind of the aliphatic protons of the side chain (see Table I). The enolic form is also favorable in acetone-d_6 as observed in the nmr spectrum (Table I), probably because of hydrogen bonding with molecules of the solvent. In DMSO-d_6 the conjugated enolic form exists; furthermore, it causes also enolization of the side-chain carbonyl. This enolization is slow and can be followed by changes in the nmr; it reaches a maximum of about 60% after 20 hr. In moist DMSO-d_6 the change is faster and there is also a shift upfield in the band of the acidic proton. Similar to what is observed in the semihydrate of the parent compound (**1**),[1] both the ring OH protons and the external OH protons give a single peak. During the enolization process this peak moves from δ 8.5 to 10.0 (in wet DMSO-d_6 it moves rather upfield). This enolization of the side chain is indicated by the decrease in the CH_2 protons band at δ 2.55 and the formation of a vinylic proton which absorbs at δ 5.98. The terminal methyl protons signal moves about 4 Hz upfield and the two geminal methyl groups become nonequivalent yielding two bands at δ 2.00 and 1.98 instead of one peak at δ 1.35. This is probably due to hydrogen bonding as shown in structure **5a**. Precipitation of **5a** from its DMSO solution and redissolution in $CDCl_3$ restores tautomer **5c**. This fact excludes any irreversible changes in DMSO and indicates proton tautomerization.

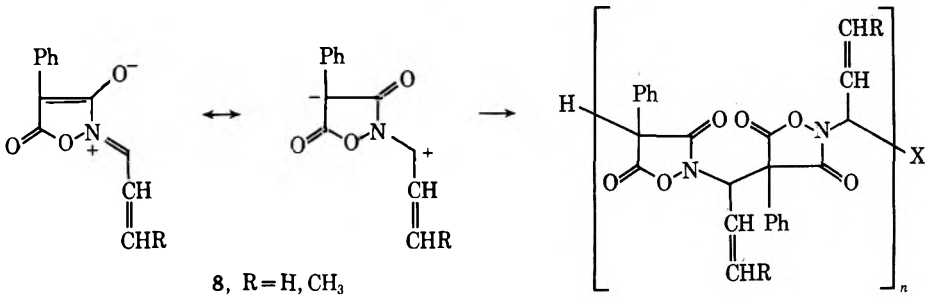
On a short heating of **5** in alcohols, *e.g.*, ethanol or methanol, a new heterocyclic compound was obtained. An attack of the alcoholic oxygen on the side-chain carbonyl is followed by a ring closure to a derivative of the unknown isoxazolo[3,2-*b*][1,3]oxazine bicyclic system (**7**). The nmr spectrum of **7** shows, as expected, a multiplet of the phenyl protons, indicating the conjugation of the phenyl group with the isoxazolone ring. The two geminal methyl protons are not equivalent in **7**, as they occur on either side of the plane of the ring system and as a result their signals are separated by 4 Hz in the ethoxy derivative (R = C_2H_5) at δ 1.33 and 1.38, respectively, and by a smaller difference in the methoxy derivative (R = CH_3).

A final proof for the structure of **5** was provided by the formation of an identical product by the reaction of **1** with mesityl oxide. The latter reaction represents another possible reaction of 3,5-dihydroxy-4-phenylisoxazole (**1**) with a carbonyl compound, *e.g.*, a noncatalyzed Michael addition (formulation **6**, Scheme II).

On the basis of the above findings it was easier to understand the reaction of 3,5-dihydroxy-4-phenylisoxazole (**1**) with crotonaldehyde or acrolein. Here again the stabilization of the immonium enolate species is too small and the aldehydic carbon becomes strongly electrophilic. By introducing crotonaldehyde to the solution of **1** in dry ether the red color which is formed initially disappears while a colorless precipitate deposits. This product was shown to have a polymeric structure **9** (Scheme III).

In the absence of an external active α carbon the electrophilic carbon attacks the nucleophilic carbon in intermediate **8**. The polymer contains successive saturated isoxazole-3,5-dione rings. This fact is well observed in the ir spectra where we find two carbonyl bands, one at as high frequency as 1825 cm^{-1} and a

SCHEME III



8, R=H, CH_3

9

second at 1730 cm^{-1} (see Table II), indicating the omission of tautomerism which results in a cyclic anhydride-like structure. The phenyl protons give a singlet in the nmr as expected from the nonconjugated structure of the polymer (**9**). The nmr spectra has a kind of a diffused feature. This arises not only from the polymeric nature of the compound but also from the presence of free radicals. It is difficult to explain the presence of two superimposed peaks at about $g = 2$ in the esr spectrum of **9**. One explanation is the resemblance of the carbon in the 4 position to that in certain malonic acid derivatives that undergo easy heterolytic fission.[7]

TABLE II

CARBONYL AND HYDROXYL ABSORPTION (cm^{-1})

Compd	Phase	CO	OH
1	Nujol	1680 weak	2500–2580
3	Nujol	1780, 1700	
5	Nujol	1700	3220
	$CHCl_3$	1810, 1700–1730	
	DMSO	1730	
7	Nujol	1735	
9	Nujol	1825, 1730	

Dimers (**9**, $n = 2$) could be obtained by carrying out the reaction in alcohols (X = OR) or in wet solvents (X = OH). Acrolein reacts with **1** similarly to crotonaldehyde.

Upon treatment of **1** with citral a very stable red product is obtained. This product could be obtained in a pure crystalline form, but contrary to its analogs of the aromatic series (**2**) it is soluble in aprotic nonpolar solvents. This was the only case in which it was possible to determine the nmr spectrum of a red isoxazolium enolate derivative. Citral consists of two isomers geranial and neral. The signals of the $^{+}N{=}CH$ protons of the two geometric isomers are at δ 8.15 and 8.20, respectively, and are coupled with the vinylic protons (J = 10 Hz). The aromatic protons of the phenyl group are split into two multiplets.

The above variety of unusual reactions of 3,5-dihydroxy-4-phenylisoxazole with carbonyl compounds and their synthetical applications are being investigated further. It seems that the unique chemical reactivity arises from the participation of the strongly acidic enol and can be classified as neighboring group effect in a nucleophilic reaction. The remarkably ready carbon–carbon bond formation is a result of the combination with the strong electron attraction of the isoxazolone system which is responsible for its unusual physical properties as well.

(7) H. A. P. de Jongh, C. R. H. I. de Jonge, H. J. M. Sinnige, W. J. de Klein, W. G. B. Huysmans, and W. J. Mijs, *J. Org. Chem.*, **37**, 1960 (1972).

Experimental Section

Melting points are uncorrected. Nmr spectra were determined with a Varian T-60 spectrometer. Visible and uv spectra with a Unicam SP 800A recording spectrophotometer.

Reaction of 3,5-Dihydroxy-4-phenylisoxazole with Acetone.—3,5-dihydroxy-4-phenylisoxazole (**1**) which was previously dried on P_2O_5 at 100° *in vacuo* (10 g) was dissolved with mild heating in acetone (15 ml) and kept at room temperature. After 12 hr an additional 15 ml of acetone was added and the precipitate was suspended in the reaction mixture. This was kept overnight at room temperature. The crystals were collected and recrystallized by dissolving in chloroform, filtering, and reprecipitating with petroleum ether (bp 40–60). The pure crystals of **5** are colorless (7.6 g, 48% yield), mp 138°.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09; mol wt 275.3. Found: C, 65.56; H, 6.13; N, 5.03; mol wt 275 (mass spectrum).

5-Alkoxy-2-oxo-3-phenyl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazine (**7**).—The diacetone derivative (**5**) (1 g) was heated to boiling in alcohol (20 ml). The clear solution which resulted was concentrated *in vacuo* to a small volume. Beautiful colorless crystals precipitated on cooling. The product (**7**) could be recrystallized from a small amount of alcohol.

Both in ethanol and methanol the yield was ~1 g (90–95%).

The 5-ethoxy derivative (**7**, R = C_2H_5) melted at 123°.

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62; mol wt 303.4. Found: C, 67.38; H, 6.80; N, 4.57; mol wt 303 (mass spectrum).

The 5-methoxy derivative (**7**, R = CH_3) melted at 135°.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84; mol wt 289.3. Found: C, 66.30; H, 6.80; N, 4.81; mol wt 289 (mass spectrom.).

The Reaction of 3,5-Dihydroxy-4-phenylisoxazole (**1**) **with Crotonaldehyde.**—Anhydrous 3,5-dihydroxyisoxazole (**1**) (5 g) was dissolved in dry ether (100 ml) and crotonaldehyde (1.8 ml) was added while shaking and cooling on ice. The red color which was initially formed disappeared and a colorless precipitate was formed. The polymer (**9**) was recrystallized from chloroform–petroleum ether (bp 40–60). It melted with decomposition at 230–240° (3.5 g, 54%).

Anal. Calcd for $(C_{13}H_{11}NO_3)_n$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.63; H, 4.43; N, 6.28.

On carrying the reaction in ethanol instead of ether a dimeric product was obtained (**9**, n = 1, X = OC_2H_5). It turns brownish at 150° and decomposes at 230° (4.5 g, 70%).

Anal. Calcd for $C_{28}H_{28}N_2O_7$: C, 66.66; H, 5.59; N, 5.55; C_2H_5O, 8.92. Found: C, 66.35; H, 5.45; N, 5.62; C_2H_5O, 8.89.

In methanol, a similar compound was obtained in about the same yield.

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.11; H, 5.34; N, 5.71. Found: C, 66.33; H, 5.20; N, 5.56.

An analogous compound but in a lower yield was obtained in butanol.

Anal. Calcd for $C_{30}H_{32}N_2O_7$: C, 67.66; H, 6.06; N, 5.26. Found: C, 68.37; H, 6.12; N, 5.01.

The Reaction of 3,5-Dihydroxy-4-phenylisoxazole (**1**) **with Acrolein.**—Anhydrous **1** was treated as above with acrolein instead of crotonaldehyde. In this case the red coloration of the

TABLE III

N-ALKYLIDENE- AND *N*-ARYLMETHYLIDENE-4-PHENYLISOXAZOL-5-ONIUM-3-ENOLATES (2)[a]

R	Registry no.	Method	Mp, °C (dec)	Yield, %	Visabsorption, λ_{max}, nm (ϵ),[b] in dioxane
C_6H_5	37118-32-4	B	215	45	480 (4,000)
CH=CHCH=C(CH₂)₄O	38896-39-8	A	198	55	484 (4,300)
$C_6H_5CH=CH$	37125-34-1	A	235	95	525 (5,000)
$2,3\text{-}(OMe)_2C_6H_3$	38896-41-2	A	220	60	468 (4,000)
$2,4\text{-}(OMe)_2C_6H_3$	38896-42-3	A	221	70	466 (4,300)
$3,4\text{-}(OMe)_2C_6H_3$	38896-43-4	A	216	45	468 (2,000)
$2\text{-}OHC_6H_4$	38896-44-5	B	204–205	35	475 (1,000)
$3\text{-}OMe\text{-}4\text{-}OHC_6H_3$	38896-45-6	B	208	40	460 (2,000)
$4\text{-}OMeC_6H_4$	38896-46-7	C[c]	218	85	466 (4,000)
$(CH_3)_2C=CH(CH_2)_2C(CH_3)=CH$	38896-47-8	C	104	80	485 (4,000)[d]
$4\text{-}NMe_2C_6H_4$	37118-33-5	A C[c]	233	100	408 (25,000)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in table. [b] The visible spectra were taken in dry dioxane; the values of the molar extinction coefficient are approximate because of the instability of these solutions, except the 4-dimethylaminobenzylidene derivative which is very slightly soluble in dioxane but the solution is stable in the dark. [c] Requires protection against daylight during preparation and storing. [d] This compound is considerably soluble in organic aprotic solvents like dioxane, tetrahydrofuran, or chloroform and gives quite stable solutions.

solution could not be observed, but the results were similar. The polymeric product was obtained in a low yield (15%), but the dimeric products were obtained in good yields (70–80%). Analytical results were satisfactory. Spectral properties were also similar to the crotonaldehyde products. A similar signal in the esr spectrum could be observed at $g \simeq 2$.

The Reaction of 3,5-Dihydroxy-4-phenylisoxazole (1) with Mesityl Oxide.—3,5-Dihydroxy-4-phenylisoxazole (1) (1.77 g) was dissolved by heating for 5 min in boiling mesityl oxide (8 ml). Alternatively 1 was dissolved in THF (4 ml) and after the addition of mesityl oxide (5 ml) the solution was boiled for 3 min. In both ways the reaction mixture was cooled in the freezer overnight, and the precipitate which deposited was collected and recrystallized from chloroform–petroleum ether (bp 40–60). The product melted at 140–142° (2 g, 87% yield). Ir, nmr, and elementary analysis were identical with the product which was obtained from 1 with acetone (see above). This product could be also converted into the isoxazolo[3,2-*b*][1,3]oxazine derivative 7.

***N*-Alkylidene- and *N*-Arylmethylidene-4-phenylisoxazol-5-onium-3-enolates (2). Method A.**—3,5-Dihydroxy-4-phenylisoxazole (1) semihydrate (1.86 g, 0.01 mol) was dissolved in tetrahydrofuran (30 ml) and the aldehyde (0.01 mol) added in tetrahydrofuran (15 ml). The solution was shaken for a few seconds and kept overnight at 4°. The crystals which separated were collected and dried over P_2O_5 at 100°. In the case of 4-dimethylaminobenzaldehyde the reaction was carried out in the dark and the product was dried and kept in the dark. The results are summarized in Table III.

Method B.—3,5-Dihydroxy-4-phenylisoxazole (1) semihydrate (1.86 g, 0.01 mol) was dissolved in tetrahydrofuran (30 ml) and the aldehyde (0.01 mol) was added in ether (15 ml). The red solution was shaken for a few seconds and petroleum ether (bp 40–60) or *n*-hexane (15 ml) was added. Upon keeping at 4° the red crystals separated. They were collected and treated as above. The results are summarized in Table III.

Method C.—3,5-Dihydroxy-4-phenylisoxazole (1) semihydrate (1.86 g, 0.01 mol) is dissolved in absolute ethanol (30 ml) and the aldehyde (0.01 mol) is added in absolute ethanol (30 ml). After being shaken for a few seconds the red crystals are allowed to settle for a few minutes and collected by filtration. Decomposition of the product occurs if the solution is kept too long. In the case of anisaldehyde and *p*-dimethylaminobenzaldehyde protection against daylight is essential during preparation and storing of the red product. The results are summarized in Table III.

Decomposition of *N*-Benzylidene-4-phenylisoxazol-5-onium-3-enolate by Water.—*N*-Benzylidene-4-phenylisoxazol-5-onium-3-enolate (**3**) (0.53 g) was stirred in tetrahydrofuran (5 ml) at 40° while water was added portionwise until the red solution turned almost colorless (about 0.4 ml of water). Chloroform (35 ml) was added and the mixture was cooled on ice for 3 hr. The white crystals (0.32 g) which separated were found identical by mp and ir with 3,5-dihydroxy-4-phenylisoxazole (1). The filtrate was concentrated *in vacuo* to 10 ml; a solution of 2,4-dinitrophenylhydrazine (0.5 g) in ethanol (25 ml), containing some drops of concentrated hydrochloric acid, was added; and the solution was cooled again for a few hours. 2,4-Dinitrophenylhydrazone of benzaldehyde (0.15 g) precipitated and was identified by mp and ir spectrum. A better yield of the 2,4-dinitrophenylhydrazone (0.3 g) could be obtained by adding the 2,4-dinitrophenylhydrazine to the decomposition mixture, before adding the chloroform, without isolation of (1).

TABLE IV

NMR DATA OF THE REDUCTION PRODUCT OF 2 WITH ZINC IN ACETIC ACID ($C_6H_5CH_2CONHCH_2Ar$)

Registry no.	Ar	Solvent	δ(C_6H_5)	δ(CH_2CO)	δ(NH)	δ(CH_2N)	δ(CH_3)
37125-35-2	$p\text{-}NMe_2C_6H_4$	$CDCl_3$	7.22 s (5)	3.43 s (2)	5.5 dif. (1)	4.20 d (2)	2.81 s (6)
		Acetone-d_6	7.26 s (5)	3.50 s (2)	dif.	4.20 d (2)	2.80 s (6)
		Acetone + D_2O	7.17 s (5)	3.41 s (2)		4.08 s (2)	2.70 s (6)
38896-50-3	$2,3\text{-}(OMe)_2C_6H_3$	$CDCl_3$	7.05 s (5)	3.43 s (2)	5.6 dif. (1)	4.20 d (2)	3.65 s (3), 3.56 s (3)
38896-51-4	$2,4\text{-}(OMe)_2C_6H_3$	Acetone-d_6	7.16 s (5)	3.43 s (2)	2.8 dif.	4.20 d (2)	3.65 s (6)

Reduction of *N*-(*p*-Dimethylaminobenzylidene)-4-phenylisoxazol-5-onium-3-enolate with Zinc Powder in Acetic Acid.—*N*-(*p*-Dimethylaminobenzylidene)-4-phenylisoxazol-5-onium-3-enolate (**2**, R = $p\text{-}NMe_2C_6H_4$) (2.0 g) was stirred in boiling acetic acid (70 ml) and zinc powder (4.5 g) was added portionwise until the solution became colorless (25 min). The solution was cooled to room temperature and filtered, and a solution of 5% sodium bicarbonate (500 ml) was added slowly while being cooled on ice. The solution was shaken vigorously to expel excess CO_2 and kept 24 hr at 4°. The solid which precipitated (1.6 g, 90%) was recrystallized twice from ethanol, mp 142°.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.57; N, 10.44. Found: C, 76.04; H, 7.80; N, 10.57.

Nmr data of this compound are summarized in Table IV.

Other derivatives of 2 are unstable in boiling acetic acid and therefore could not be reduced in the same way. Only in the cases of 2,3- and 2,4-dimethoxybenzylidene derivatives could poor yield of the same type of reduction product be obtained. They were not completely pure but their spectral properties were in agreement with their postulated structure (Table IV).

Registry No.—**1**, 36190-14-4; **5**, 38896-53-6; **7** (R = Et), 38896-54-7; **7** (R = Me), 38896-55-8; **9**, 38882-67-6; **9** (*n* = 1, X = OEt), 38896-56-9; **9** (*n* = 1, X = OMe), 38896-57-0; **9** (*n* = 1, X = OBu), 38896-58-1; acetone, 67-64-1; crotonaldehyde, 4170-30-3; mesityl oxide, 141-79-7.

The Stereochemistry of 2-Oxazoline Formation from Epoxides

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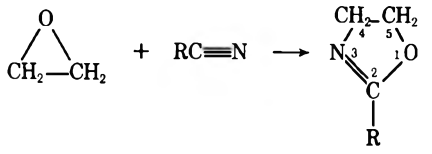
Received May 2, 1972

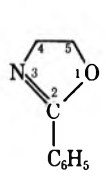
The stereochemistry of the ring-enlargement reaction of epoxides with nitriles in the presence of strong acids to give 2-oxazolines has been investigated. It is shown, mainly by nmr data, that the reaction proceeds with inversion and is 100% stereospecific; *e.g.*, *cis*- and *trans*-2,3-epoxybutane (**4** and **5**) with benzonitrile give exclusively *trans*-4,5-dimethyl-2-phenyl-2-oxazoline (**6b**) and *cis*-4,5-dimethyl-2-phenyl-2-oxazoline (**7b**), respectively. A number of new 2-oxazolines have been prepared, and their physical constants, derivatives, and nmr spectra are reported. The mechanism of the formation of the 2-oxazolines is discussed.

This paper deals with the acid-catalyzed ring opening of epoxides with nitriles to give 2-oxazolines[1] according to the following scheme (eq 1). Oda and

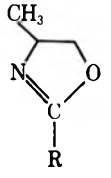


(1)

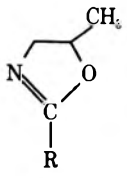
coworkers were the first to report this reaction.[2] Using ethylene oxide and benzonitrile with concentrated sulfuric acid as catalyst they obtained 2-phenyl-2-oxazoline (**1**) in 19% yield. Using propylene oxide and acetonitrile they obtained in 8% yield a mixture of the two positional isomers, consisting of 70% 2,4-dimethyl-2-oxazoline (**2a**) and 30% 2,5-dimethyl-2-oxazoline (**3a**). Using benzonitrile and propylene oxide a similar 70:30 mixture of 4-methyl-2-phenyl-2-oxazoline (**2b**) and 5-methyl-2-phenyl-2-oxazoline (**3b**)



1



2a, R = CH_3
b, R = C_6H_5



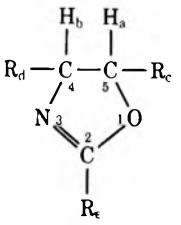
3a, R = CH_3
b, R = C_6H_5

was obtained. Yields in all these and similar reactions were low, between 5 and 21%.

Temnikova and coworkers performed additions to substituted styrene oxides with benzonitrile and acetonitrile using $SnCl_4$ as a catalyst.[3] Since none of these workers had investigated the stereochemistry and mechanism of this type of epoxide reaction, we undertook the present work.

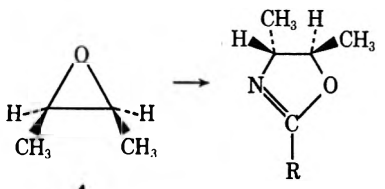
Results

Acetonitrile and benzonitrile were added to *cis*- and *trans*-2,3-epoxybutane (**4** and **5**, respectively) in the presence of concentrated sulfuric acid. In all cases the corresponding 2-oxazolines according to



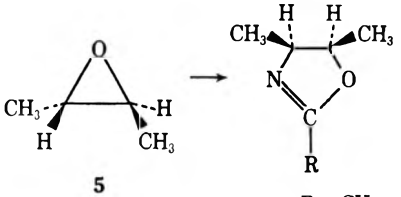
eq 1 were obtained, although generally in disappointingly low yield, as already found by Oda and coworkers.[2] The results are summarized in Table I.

Thus in the reaction of *cis*-2,3-epoxybutane (**4**) with acetonitrile, the oxazoline formed was *trans*-2,4,5-trimethyl-2-oxazoline (**6a**) exclusively. *trans*-2,3-Epoxybutane (**5**) on reaction with acetonitrile gave *cis*-2,4,5-trimethyl-2-oxazoline (**7a**) as the sole oxazoline isomer.



4

6a, R = CH_3
b, R = C_6H_5



5

7a, R = CH_3
b, R = C_6H_5

The stereospecificity of the reaction was best demonstrated by examination of the low-field part of the nmr spectra corresponding to the absorption bands of the 4 and 5 protons. For the crude reaction product from the cis epoxide **4**, namely the trans 2-oxazoline **6a**, absence of peaks in the region 4.16–4.75 ppm indicated that the cis 2-oxazoline **7a** was not present. Similarly, for cis 2-oxazoline **7a**, the product from the trans epoxide **5**, the absence of peaks in the region 3.18–3.68 ppm indicated that the trans 2-oxazoline **6a** was not present.

It was likewise shown that the cis epoxide **4**, when treated with benzonitrile, gave exclusively *trans*-4,5-dimethyl-2-phenyl-2-oxazoline (**6b**). This compound seems, on the basis of the melting point of its picrate salt, to be identical with a compound pre-

(1) For a recent review of oxazoline chemistry see J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

(2) R. Oda, M. Okano, S. Tokiura, and F. Mismui, *Bull. Chem. Soc. Jap.*, **35**, 1219 (1962).

(3) T. I. Temnikova and V. N. Yandovskii, *Zh. Org. Khim.*, **4**, 178 (1968); *Chem. Abstr.*, **68**, 78176 (1968); T. I. Temnikova and T. E. Zhesko, *Zh. Obshch. Khim.*, **33**, 3436 (1963); *Chem. Abstr.*, **60**, 1738c (1964).

TABLE I.—PHYSICAL PROPERTIES AND NMR SPECTRA OF 2-OXAZOLINES

Oxazoline	Yield, %	Bp, °C (mm)	Mp of picrate, °C	Chemical shifts, δ in CCl_4[a]				
				H_a	H_b	H_c	H_d	H_e
trans-2,4,5-Trimethyl-2-oxazoline (**6a**)	10	115–116	152–153	3.74–4.16 (pent.) J_{ac} = 5.9 J_{ab} = 6.0	3.18–3.68 (m) J_{bd} = 6.0 J_{ba} = 6.0 J_{be} = 1.5	1.27 (d)	1.15 (d)	1.83 (d) J_{eb} = 1.5
trans-4,5-Dimethyl-2-phenyl-2-oxazoline (**6b**)	5	116–118 (11)	133–134	3.91–4.23 (pent) J_{ac} = 5.5 J_{ab} = 6.0	3.41–3.86 (pent) J_{bd} = 6.0 J_{ba} = 6.0	1.35[b] (d)	1.21[b] (d)	7.55 + 7.83 (m)
cis-2,4,5-Trimethyl-2-oxazoline (**7a**)	17	120–122	136–137	4.28–4.75 (m) J_{ac} = 6.2 J_{ab} = 9.0	3.68–4.21 (m) J_{bd} = 6.6 J_{ba} = 9.0 J_{be} = 1.5	1.16 (d)	1.03 (d)	1.81 (d) J_{eb} = 1.5
cis-4,5-Dimethyl-2-phenyl-2-oxazoline (**7b**)	3	142–144 (29)	205–207	4.41–4.91 (oct) J_{ac} = 6.0 J_{ab} = 9.0	3.89–4.38 (oct) J_{bd} = 6.5 J_{ba} = 9.0	1.25[b] (d)	1.14[b] (d)	7.25 + 7.83 (m)
2,4-Dimethyl-2-oxazoline (**2a**) and			129–130 (**2a** only)		3.49–4.41 (m) J_{bd} = 6.0 J_{be} = 1.5		1.16 (d)	1.86 (d) J_{eb} = 1.5
2,5-Dimethyl-2-oxazoline (**3a**)	10	112–114 (mixture)		2.98–4.75 including H_d (m) J_{ac} = 5.8	J_{be} = 1.5	1.28 (d)	See H_a + H_b	1.85 (t) J_{eb} = 1.5

[a] With respect to tetramethylsilane as internal standard. *J* values are observed splitting values in hertz. [b] Two doublets superimposed into an unsymmetrical triplet.

pared by Strauss.[4] No mention of the stereochemical aspects of the compound was made, however. Similarly, the trans epoxide **5** gave the new compound *cis*-4,5-dimethyl-2-phenyl-2-oxazoline (**7b**) as the exclusive oxazoline.

Thus all reactions examined were found to proceed 100% stereospecifically with inversion to give the corresponding 2-oxazoline of inverted configuration.

Nmr Spectra.—All nmr data of the 2-oxazolines are summarized in Table I.

Our original assignment of the 4- and 5-methyl groups and protons was based on the use of the corresponding monomethyl compounds, 2,4-dimethyl-2-oxazoline (**2a**) and 2,5-dimethyl-2-oxazoline (**3a**). A 70:30 mixture of these compounds was prepared, using the method of Oda and coworkers,[2] and separated by gas chromatography. The structure of these two compounds was ascertained by independent synthesis.[2] It was found that the 4-methyl group in compound **2a** appeared clearly upfield in comparison with the 5-methyl group of oxazoline **3a**. Therefore, in the cases of the 4,5-dimethyl-2-oxazolines **6a**, **6b**, **7a**, and **7b** the upfield doublet was assigned to the 4-methyl group and the lower field doublet to the 5-methyl group. Similarly, the 4-methine proton absorbs at higher field than the 5 proton in all cases. All coupling constants are consistent with this assignment and the assignment agrees with the data reported for other 2-oxazolines.[5-8] All spectra were analyzed as X_3ABY_3 systems with $J_{AY} = J_{BX} = 0$.

In all examples studied the coupling constant $^3J_{HH}$ between the methyl group and the geminal proton was somewhat larger for the 4 position than for the 5 position. It has been found for other compounds that a neighboring π bond can decrease geminal coupling constants.[9] It is likely that the same effect, in our case the C=N double bond, can also decrease the doupling constant between geminal methyl group and proton.

Assignment of the Cis or Trans Configuration.—The assignment of the cis or trans configuration is based mainly upon the 4-H,5-H coupling constant. From Table I it is seen that the two cis compounds, **7a** and **7b**, have a 4-H,5-H coupling constant of 9.0 cps, whereas the corresponding two trans compounds, **6a** and **6b**, have a coupling constant of 6.0 cps. These values agree well with the values observed in other cis and trans 2-oxazolines of established structure. Generally, cis proton coupling is larger than trans proton coupling in five-membered rings, which cannot deviate appreciably from planarity as expected from the Karplus rule.[5,7,8,11,12]

(4) E. Strauss, *Chem. Ber.*, **33**, 2825 (1900).
(5) R. F. Lambert and C. E. Kristofferson, *J. Org. Chem.*, **30**, 3938 (1965).
(6) T. Nishiguchi, H. Tochio, A. Nebeya, and Y. Iwakura, *J. Amer. Chem. Soc.*, **91**, 5835 (1969); J. R. Carson, G. I. Poos, and H. R. Almond, *J. Org. Chem.*, **30**, 2225 (1965).
(7) T. A. Foglia, L. M. Gregory, and G. Maerker, *J. Org. Chem.*, **35**, 3779 (1970); T. A. Foglia and D. Swern, *ibid.*, **34**, 1680 (1969).
(8) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).
(9) Reference 10, p 273.
(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969.
(11) T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **36**, 1068 (1971).
(12) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969); ref 10, p 286 ff.

Further support for the assignment of the cis and trans configuration comes from a comparison of the chemical shifts at the 4 and 5 positions. The 4- and 5-methyl groups in all compounds examined absorb at *ca.* 0.1 ppm higher field in the cis isomers than in the corresponding trans isomers. On the other hand, the 4- and 5-methine protons absorb at *ca.* 0.5 ppm lower field in the cis 2-oxazolines than in the trans isomers. This effect can be attributed mainly to the diamagnetic anisotropy of the *C*-methyl bond and is found in many cis–trans isomer pairs of planar three- to five-membered ring compounds.[13] A methyl group has the tendency to shield a neighboring substituent in the cis position and to deshield a neighboring substituent in trans orientation. Thus, trans 4,5-methyl groups will mutually deshield each other so as to shift both methyl bands to lower field. At the same time the 4 and 5 protons will be shielded by the neighboring methyl groups and therefore shift upfield.[13]

Likewise, cis 4,5-methyl groups will mutually shield each other, causing the methyl bands to appear at higher field. The 4,5 protons will now be deshielded and therefore move to lower field. A more accurate treatment has to take into account the diamagnetic anisotropy of the C–H bonds of the methine protons[14] and the C–H bonds of the methyl groups as well as the rotation of the methyl groups.[15] This does not substantially change, however, the above conclusions.

All 2-methyl-2-oxazolines show a long-range coupling between the 2-methyl group and the 4 proton(s) of *ca.* 1.5 Hz, as has been reported for other 2-methyl-2-oxazolines and the similar 2-thiazolines.[8,16,17]

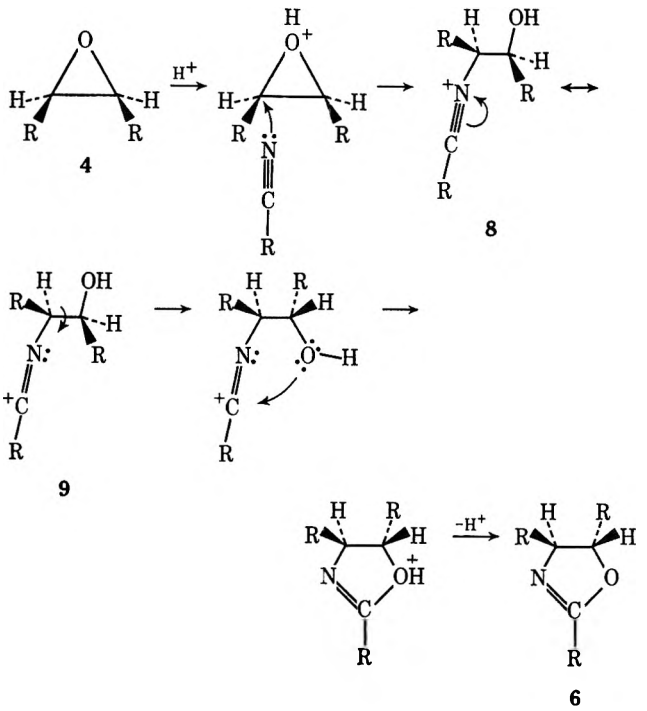
Infrared Spectra.—All 2-oxazolines show the strong band around 1665 cm^{-1} characteristic of the C=N stretch[6-8,18,19] and a strong band around 1040 cm^{-1} which can be assigned to one of the C–O–C stretching modes in agreement with Lundquist and Ruby.[19]

Discussion

The following general mechanism, illustrated by the reaction of the cis epoxide **4** to give the trans 2-oxazoline **6**, seems to account best for the observed results.

Thus the reaction involves one inversion on opening of the protonated epoxide ring by the nitrile to give the corresponding nitrilium ion **8**. This is followed by rotation around the C–C bond of the former epoxide ring and ring closure to give the 2-oxazoline of inverted configuration.

The above mechanism is completely analogous to the mechanism proposed by Helmkamp and coworkers[16] for the acid-catalyzed ring expansion of episulfides with nitriles to give 2-thiazolines (scheme below, O replaced by S). Here also complete stereospecificity



was found in all cases, with *cis*- and *trans*-2-butene episulfide (**4** and **5**, with O replaced by S) giving exclusively *trans*-2,4,5-trimethyl-2-thiazoline and *cis*-2,4,5-trimethyl-2-thiazoline, respectively (**6a** and **7a**, O replaced by S), upon reaction with acetonitrile in the presence of strong acids.

With respect to ring-expansion reactions of epoxides, the example best investigated with respect to the stereochemistry seems to be the reaction with xanthates to give 1,3-dithiolane-2-thiones ("cyclic trithiocarbonates"). Here Overberger and Drucker found also complete stereospecificity with Walden inversion in all examples studied.[20] All other ring expansions of epoxides[21] seem to proceed with predominant, if not exclusive, inversion, as do practically all epoxide ring-opening reactions.[22]

Experimental Section

General Procedures.—Infrared spectra were taken on a Perkin-Elmer 137 sodium chloride spectrophotometer. Methylene chloride was used as solvent.

Gas chromatography was done on a Varian Model 90P gas chromatograph. Most of the work was done with a 6-ft column of 15% Carbowax 20M on Gas-Chrom R.

Nmr spectra were taken on a Varian A-60 nuclear magnetic resonance spectrometer. Carbon tetrachloride was used as solvent and tetramethylsilane as internal standard.

The microanalyses were performed by the Hoffmann-La Roche Corp., Nutley, N. J., to whom we would like to extend our thanks.

***cis*- and *trans*-2,3-epoxybutane, 4 and 5,** respectively, were prepared essentially according to the method of Winstein and Lucas,[23] by addition of HOBr with *N*-bromosuccinimide to *cis*- and *trans*-2-butene, respectively, and elimination of HBr with aqueous NaOH, using, however, *N*-bromosuccinimide in place of *N*-bromoacetamide. The epoxides were found to be >99% pure

(13) Reference 10, p 234 ff.
(14) Reference 10, p 78 ff.
(15) J. Elguero and A. Fruchier, *Bull. Soc. Chim. Fr.*, 496 (1970).
(16) G. K. Helmkamp, P. J. Pettitt, J. R. Lowell, Jr., W. R. Inabey and R. G. Wolcott, *J. Amer. Chem. Soc.*, **88**, 1030 (1966); J. R. Lowell, Jr., and G. K. Helmkamp, *ibid.*, **88**, 768 (1966).
(17) J. Roggero and J. Metzger, *Bull. Soc. Chim. Fr.*, 1715 (1964).
(18) A. R. Katritzky and A. P. Aubler, "Physical Methods in Heterocyclic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, p 218; J. R. Carson, G. I. Poos, and H. R. Almond, Jr., *J. Org. Chem.*, **30**, 2225 (1965); H. L. Wehrmeister, *ibid.*, **26**, 3821 (1961); Stadtler Standard Infrared Spectra 21053-55.
(19) R. T. Lundquist and A. Ruby, *Appl. Spectrosc.*, **20**, 258 (1966).
(20) C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964).
(21) S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960); E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 3444 (1951).
(22) A. Rosowsky in A. Weissberger, Ed., "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, Interscience, New York, N. Y., 1964; R. J. Gritter in S. Patai, Ed., "The Chemistry of the Ether Linkage," Interscience, New York, N. Y., 1967, pp 381–411; R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).
(23) S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.*, **61**, 1576 (1939).

on the base of ir and nmr data and gas chromatographic analysis as originally assumed by Winstein and Lucas. *cis*- and *trans*-2,3-epoxybutane, **4** and **5**, each gave only one peak on gas chromatography on a 6-ft 15% Carbowax 20M on Gas-Chrom R column. A mixture of the two compounds was easily separated at 65°, the compounds having retention times of 4.8 and 3.6 min, respectively.

cis-**2,3-Epoxybutane** (**4**) had nmr $X_3AA'X_3'$ system; H_A = 2.60–2.94 (two overlapping octets); H_X = 1.19 (multiplet with predominating doublet); J_{AX} = 5.4 Hz (first-order analysis).[24]

trans-**2,3-Epoxybutane** (**5**) had nmr $X_3AA'X_3'$ system; H_A = 2.32–2.66 (multiplet); H_X = 1.21 (doublet); J_{AX} = 4.5 Hz (first-order analysis).

General Procedure for Reaction of Epoxides with Nitriles Similar to Procedure of Oda and Coworkers.[1]—A 30-ml portion of nitrile (distilled over phosphorus pentoxide) was added to a round-bottom flask and cooled in an ice bath; 15 ml of concentrated sulfuric acid was added slowly with stirring. A mixture of *ca.* 0.15 mol of the epoxide in 30 ml of the nitrile was added through the reflux condenser over a period of 1 hr. The mixture was then stirred for a period of 3 hr with the ice bath being allowed to melt at its own rate and then poured into 100 ml of ice water. This mixture was then extracted three times with 100 ml of ether and the ether was discarded. The aqueous phase was then neutralized with concentrated NaOH and filtered. Next it was made strongly basic with NaOH and extracted three times with 100 ml of ether. The three ether fractions were combined, dried over anhydrous magnesium sulfate, filtered, and distilled. The oxazoline was isolated by distillation through a short Vigreux column.

A number of attempts were made to seek conditions to improve the yield. These include the use of 60% perchloric acid, trifluoroacetic acid, and *p*-toluenesulfonic acid in place of the concentrated sulfuric acid, as well as no acid at all. All attempts, including the use of inverse addition, did not produce better yields.

2,4- and 2,5-Dimethyl-2-oxazolines (**2a** and **3a**).—The general procedure was followed using propylene oxide and acetonitrile. The mixture boiling at 112–114° was collected and separated by gas chromatography using a 6-ft column of 15% Carbowax 20M on Gas-Chrom R. Quantitative analysis showed the two isomers **2a** and **3a** to be in 70:30 proportion. The melting point of the picrate of the 2,4 isomer **2a** was 130° (lit.[2] mp 130–131°).

trans-**2,4,5-Trimethyl-2-oxazoline** (**6a**).—The general procedure was followed using 12.0 g (0.166 mol) of *cis*-2,3-epoxybutane (**4**). The reaction yielded 1.90 g (10%) of *trans*-2,4,5-trimethyl-2-oxazoline (**6a**), bp 115–116°, mp of picrate 152–153°.

trans-**4,5-Dimethyl-2-phenyl-2-oxazoline** (**6b**).—The general procedure was followed using 12.0 g (0.166 mol) of the cis epoxide **4** and benzonitrile as solvent. The reaction yielded 0.95 g (5%) of *trans*-4,5-dimethyl-2-phenyl-2-oxazoline, bp 116–118° (11 mm), mp of picrate 133–134°. *Anal.* Calcd for $C_{17}H_{16}N_4O_8$: C, 50.5; H, 3.99; N, 13.86. Found: C, 50.40; H, 4.18; N, 13.68.

cis-**2,4,5-Trimethyl-2-oxazoline** (**7a**).—This compound was prepared according to the general procedure using 12.0 g (0.166 mol) of *trans*-2,3-epoxybutane (**5**).

Distillation of the product yielded 3.30 g (17%) of *cis*-2,4,5-trimethyl-2-oxazone (**7a**), bp 120–122°, mp of picrate 136–137°. *Anal.* Calcd for $C_{12}H_{14}N_4O_8$: C, 42.11; H, 4.14; N, 16.37. Found: C, 42.19; H, 4.31; N, 16.29.

cis-**4,5-Dimethyl-2-phenyl-2-oxazoline** (**7b**).—The general procedure was followed using 12.0 g (0.166 mol) of *trans*-2,3-epoxybutane (**5**) and benzonitrile as solvent. The reaction yielded 0.60 g (3%) of *cis*-4,5-dimethyl-2-phenyl-2-oxazoline (**7b**), bp 142–144° (29 mm), mp of picrate 205–207°.

Registry No.—**2a**, 6159-23-5; **3a**, 6159-22-4; **4**, 1758-33-4; **5**, 21490-63-1; **6a**, 23336-75-6; **6a** picrate, 38898-94-1; **6b**, 38898-95-2; **6b** picrate, 38898-96-3; **7a**, 23236-41-1; **7a** picrate, 38898-98-5; **7b**, 36746-57-3; **7b** picrate, 38899-00-2; propylene oxide, 75-56-9.

Acknowledgments.—The authors wish to thank the Rutgers Research Council for financial support.

(24) Compare ref 10, p 224.

2,3-Dimethylcyclopropanecarboxylic Acids from 2,3-Dimethyloxiranes *via* the Wittig Reaction. Stereochemistry and Mechanism

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Triethyl phosphonoacetate anion reacted with (+)-(2*R*,3*R*)-2,3-dimethyloxirane to give predominantly (+)-(2*S*,3*S*)-2,3-dimethylcyclopropanecarboxylic acid and with *cis*-2,3-dimethyloxirane to give predominantly *cis*-2,3-dimethylcyclopropane-*trans*-carboxylic acid. Inversion of configuration must have occurred at both carbon atoms to account for these products. In each case minor amounts of stereoisomeric acids were produced. The results are discussed in terms of the overall mechanistic scheme.

The reaction of Wittig type reagents with epoxides to form cyclopropanecarboxylic acid derivatives has been well documented. Both carboethoxymethylenephosphoranes[1,2] and phosphonate anions[3-7] have been successfully utilized. Although certain aspects of the reaction pathway are well understood, there remains some disagreement concerning the overall mechanistic scheme.

Denney[1] postulated a stepwise decomposition of the intermediate **4** (process Y in Scheme I) to give **6** *via* an intramolecular SN2 displacement. This proposal was based on the observation that carboethoxymethylenetriphenylphosphorane reacted at 200° with cyclohexene oxide to form ethyl 7-norcaranecarboxylate and with optically active styrene oxide to form optically active *trans*-2-phenylcyclopropanecarboxylate. Denney's inversion mechanism has been supported by Tomoskozi[4] and Walborsky,[8] who established the absolute configuration of optically active *trans*-2-phenylcyclopropanecarboxylic acid.

In addition to the inversion mechanism the possibility of a competitive direct collapse of **4** (process X) either through a concerted process or through a zwit-

(1) D. B. Denney, J. J. Vill, and M. J. Boskin, *J. Amer. Chem. Soc.*, **84**, 3944 (1962).

(2) W. E. McEwen, A. Bladé-Font, and C. A. Vander Werf, *J. Amer. Chem. Soc.*, **84**, 677 (1962).

(3) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(4) I. Tomoskozi, *Tetrahedron*, **19**, 1969 (1963).

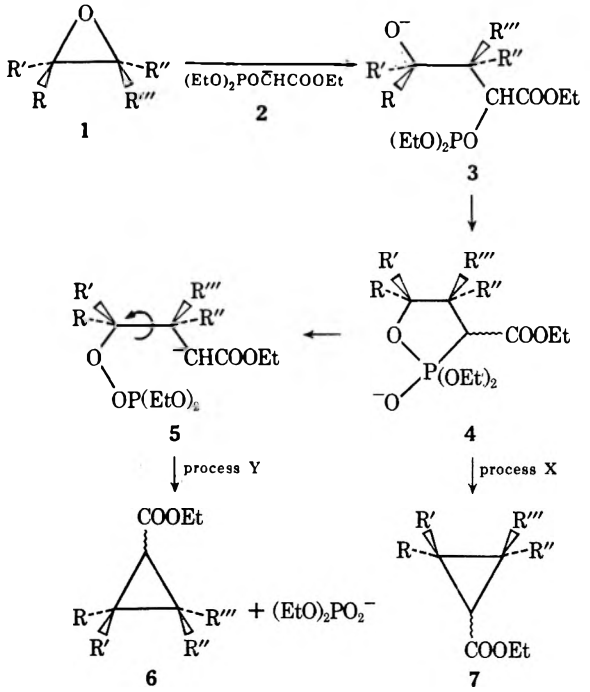
(5) I. Tomoskozi, *Tetrahedron*, **22**, 179 (1966).

(6) I. Tomoskozi, *Chem. Ind. (London)*, 689 (1965).

(7) N. C. Deno, W. E. Billips, D. LaVietes, P. C. Scholl, and S. Schneider, *J. Amer. Chem. Soc.*, **92**, 3700 (1970).

(8) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).

SCHEME I[a]



[a] The phosphonate anion 2 is depicted here since it was used in this investigation. The carboethoxymethylenephosphoranes presumably react in an analogous manner.

terion intermediate to yield 7 has been suggested.[4,8-10] Walborsky argued for the occurrence of the competitive direct collapse based on the low optical yields of *trans*-2-phenylcyclopropanecarboxylic acid that had been reported by other workers.[8]

In order to clarify the overall mechanistic scheme, the reaction of triethyl phosphonoacetate anion (2) with optically active *trans*-2,3-dimethyloxirane and with *cis*-2,3-dimethyloxirane was investigated. The use of these two epoxides was advantageous in that the product ratios of *trans*- to *cis*-2,3-dimethylcyclopropanecarboxylic acids that were formed could be directly related to the extent of occurrence of each of the two competing processes.

Results

Triethyl phosphonoacetate anion (2) reacted slowly with optically pure (+)-(2*R*,3*R*)-2,3-dimethyloxirane (**8**) to give after saponification a 16% yield of an optically active mixture of the isomeric 2,3-dimethylcyclopropanecarboxylic acids. Heating for 8 days at reflux was required. Also formed but not characterized was a considerable quantity of polymeric products which arose from self-condensation of 2 under the reaction conditions. Similar results were obtained with inactive **8**.

Assignment of the 2*S*,3*S* configuration to the major component **9a** was based on the high optical rotation[11] of the product mixture, $[\alpha]^{22}D$ +19.5°, corrected to +21.3° for the presence of the minor components. Structures of the *cis*-2,3-dimethyl-*cis*-cyclopropanecarboxylic acid **10** and the cis,trans isomer **11** were assigned by comparing their gas chromatographic retention times with those of authentic samples whose preparation and characterization are discussed below.

The anion 2 reacted with *cis*-2,3-dimethyloxirane (**12**) under milder conditions (24 hr at room temperature) to give after saponification an 18% yield of an isomeric mixture of 2,3-dimethylcyclopropanecarboxylic acids and only a small amount of polymeric products. Heating the reaction mixture for 48 hr at reflux increased the yield to 21%.

On standing the major component partially separated from the product mixture as a white solid, mp 79–80.5°. Spectroscopic methods proved less than diagnostic in establishing its structure, but a complete single-crystal X-ray analysis showed its stereochemistry to be cis,trans.[12] The racemic isomer **9** was identified by assuming its gas chromatographic retention time to be equal to that of **9a**. The all-cis acid **10** could not be readily isolated, but its structure was inferred from the following evidence. A fraction, bp 90.5–91.5° (7 mm), which contained 8% **10**, 87% **11**, and 5% **9** correctly analyzed for $C_6H_{10}O_2$. Its proton magnetic resonance spectrum was similar to that of pure **11** and did not contain any signals in the vinylic region. This ruled out the possibility of any ring-opened product. The isomeric mixture was converted to its ethyl ester, and then treated with sodium ethoxide in ethanol for 43 hr followed by hydrolysis. Gas chromatographic analysis of the resulting mixture showed the presence of **9** and **11** and only a trace of **10**. No additional components were evident. In the proton magnetic resonance spectrum the methyl doublet of **10** appeared 5 Hz upfield from that of **11**. These results, from at least three independent experiments in each case, are summarized in Table I.

TABLE I

PER CENT COMPOSITION OF PRODUCT MIXTURES FROM REACTION OF OXIDES WITH TRIETHYL PHOSPHONOACETATE ANION

2,3-Dimethyloxirane	2,3-Dimethylcyclopropanecarboxylic acid: trans (+)-9a	trans (±)-9	cis,cis 10	cis,trans 11
2*R*,3*R* (**8**)	93		6	1
cis (**12**)		4	6	90

Discussion

The forementioned results are consistent with Denney's inversion mechanism, since the major product formed in each case requires that its epoxide precursor undergo an even number of inversions. The synthesis of **9a** from **8** and **2** as described herein is superior to the previously reported preparation[11] in that the overall yield is comparable, the tedious process of resolution *via* diastereomers is eliminated, the optical purity is higher, and the absolute configuration is known.

Convincing evidence that the direct collapse of **4** is competing to some extent was the identification of the minor components formed in each of the two reactions. These are the expected products when the starting epoxides undergo ony one inversion, most likely to have occurred in the opening of the oxide ring. The virtually complete reversal of the relative proportions of **10** to **11** produced in each of the two

(9) S. Trippett, *Quart. Rev., Chem. Soc.*, **17**, 406 (1963).
(10) A. Maercker, *Org. React.*, **14**, 387 (1965).
(11) J. M. Walbrick, J. W. Wilson, Jr., and W. M. Jones, *J. Amer. Chem. Soc.*, **90**, 2895 (1968), prepared the enantiomer of **9a**, $[\alpha]^{25}D$ −10.0°, by resolution of the inactive acid **9**.
(12) A. T. McPhail and P. A. Luhan, *J. Chem. Soc., Perkin Trans. 2*, 2372 (1972).

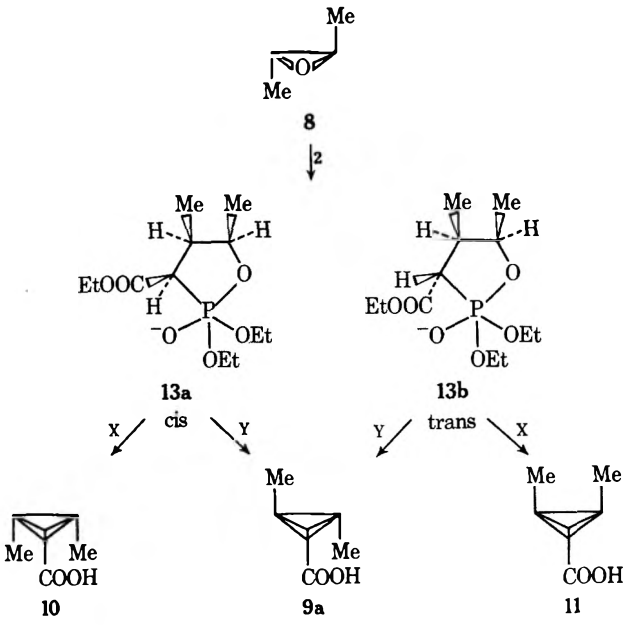
reactions would appear to rule out the existence of an intermediate common to the production of cis acids in each as well as ruling out their origin in contamination of the active oxide by the cis isomer. It is thus probable that the **10** and **11** produced from active oxide **8** and the (±)-**9** from the cis oxide **12** arose through a concerted collapse of the corresponding phosphonate esters **4**.[13]

Two factors must be considered in explaining the ratio of **10** to **11** produced *via* Scheme II: the relative amounts of **13a** and **13b** produced, and the relative probabilities of processes X (collapse) and Y (phosphonate opening, then rear-side attack) for each.

Given the results obtained we must conclude either that **13a** is produced in substantially greater amount than **13b**, or that the portion which follows path X (X/Y ratio) is substantially greater for the former than for the latter. The ratio of **10** to **11** produced from the cis oxide undoubtedly reflects steric control after the phosphonate ring is opened.

Finally, mention should be made of the low reactivity of **8** and **12** with the phosphonate anion **2**. This can be attributed to a steric effect, particularly in view of the reported high yields and facile reactions of **2** with other epoxides.[3,4,7] We have observed that **8** also reacts with other nucleophiles with difficulty. Despite this shortcoming, **8** has the possibility of being a useful precursor for the synthesis of other types of optically active compounds. We are currently investigating this possibility.

Scheme II



Experimental Section[14]

General Procedure for the Reaction of Triethyl Phosphonoacetate Anion (2) with 2,3-Dimethyloxirane.—To a stirred mixture of 9.65 g (0.23 mol) of 57% NaH in mineral oil and 25 ml of dry diglyme was added dropwise a solution of 44.8 g (0.20 mol) of triethyl phosphonoacetate in 25 ml of diglyme. After the evolution of hydrogen had ceased, a solution of 18.0 g (0.25 mol) of 2,3-dimethyloxirane was added. The mixture was stirred at the appropriate temperature. Upon completion of the reaction, a solution of 30 g of NaOH in 50 ml of water was added dropwise with cooling. The mixture was heated at reflux for 22 hr, cooled to room temperature, and diluted with 200 ml of water. The solution was washed with three 150-ml portions of ether, acidified with 50% H_2SO_4, and washed with four 75-ml portions of chloroform. The chloroform washings were dried (Na_2SO_4) and evaporated under reduced pressure to give a liquid residue. The residue was distilled to give a fraction, bp 75–95°, which was dissolved in 40 ml of 10% Na_2CO_3 and washed with four 25-ml portions of chloroform. The carbonate solution was acidified with 50% H_2SO_4 and washed with four 20-ml portions of chloroform. The later chloroform washings were dried (Na_2SO_4) and evaporated under reduced pressure to give a liquid mixture of 2,3-dimethylcyclopropanecarboxylic acids. The mixture could be further purified by distillation to give an analytical sample.

Reaction of 2 with (+)-(2*R*,3*R*)-2,3-Dimethyloxirane (8).—The reaction of 0.185 mol of **2** with 18.0 g (0.25 mol) of **8**[15,16] was carried out by heating at reflux over an 8-day period to give 3.65 g (16%) of an isomeric liquid mixture of 2,3-dimethylcyclopropanecarboxylic acids. Also isolated as the residue from the distillation was a considerable quantity of polymeric material which arose from self-condensation of **2**. This was verified by a separate experiment in which **2** was heated in the absence of **8** to give the same polymeric material. The isomeric mixture of 2,3-dimethylcyclopropanecarboxylic acids was distilled under reduced pressure to give an analytical sample: bp 84–87° (3.6 mm); $[\alpha]^{22}D$ +19.5° (c 0.2002, 95% ethanol); ir (neat) 2.9–4.3 (broad, –OH), 5.95 (C=O), 7.70, 8.14, 9.20, 9.37, and 10.7 μ (broad); nmr ($CDCl_3$) δ 12.06 (s, 1, CO_2H), 1.18 (d, J = 5.8 Hz), and 1.5–0.9 (m, 9).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.92; H, 8.80.

Vpc analysis of the cyclopropanecarboxylic acid mixture at 175° showed the presence of three components in the ratio of 6:93:1 in the order of increasing retention time. The major component was assigned as (+)-(2*S*,3*S*)-*trans*-2,3-dimethylcyclopropanecarboxylic acid (**9a**) on the basis of the high optical rotation of the mixture.[11] The two minor components were identified as *cis*-2,3-dimethyl-*cis*-cyclopropanecarboxylic acid (**10**) and *cis*-2,3-dimethylcyclopropane-*trans*-carboxylic acid (**11**) on the basis of their retention times.

Reaction of **2** with inactive **8** under the same reaction conditions gave similar results.

Reaction of 2 with *cis*-2,3-Dimethyloxirane (12).—From the reaction of 0.185 mol of **2** with 14.7 g (0.20 mol) of 12[16] at room temperature for 24 hr was obtained 3.8 g (18%) of an isomeric liquid mixture of 2,3-dimethylcyclopropanecarboxylic acids. Heating the reaction mixture at reflux for 38 hr increased the yields to 21%. Distillation of the isomeric mixture under reduced pressure gave an analytical sample: bp 88.5–94.0° (7 mm); ir (neat) 2.9–4.3 (broad, –OH), 5.95 (C=O), 7.65, 7.70, 7.80, 8.14, 9.25, and 10.6 μ (broad); nmr ($CDCl_3$) δ 11.62 (s, 1, CO_2H), 1.12 (d, J = 5.0 Hz), 1.03 (d, J = 5.0 Hz), and 1.7–0.7 (m, 9).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.00; H, 8.80.

Vpc analysis of the mixture at 175° showed the presence of three components in the ratio of 6:4:90 in order of increasing retention time. On standing, the major component partially crystallized from the mixture as a white solid: mp 79–80.5°; ir (Nujol) 2.9–4.3 (broad, –OH), 5.95 (C=O), 7.65, 7.70, 8.14, 9.25, and 10.6 μ (broad); nmr ($CDCl_3$) δ 11.75 (s, 1, CO_2H), 1.12 (d, J = 5.0 Hz), 1.8–0.9 (m, 9).

A complete single-crystal X-ray analysis determined its configuration as **11**.[12] The minor component **9** (4% of mixture) was assumed to display the same vpc retention time as the active isomer. The minor component **10** (6% of mixture) was identified on the basis of the spectral, vpc, and elemental analysis data.

(13) A zwitterionic intermediate has been proposed[8] for the case where the cationic center is benzylic, but would be less likely in the present case.

(14) Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman Model 137 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 using deuteriochloroform as a solvent and tetramethylsilane as an internal reference. Optical rotations were measured in a 0.1-dm cell with a Jasco Model ORD/UV5 recording spectropolarimeter. Concentrations are given in g/ml. Analytical gas–liquid partition chromatography was performed on a Hewlett-Packard Model 700 gas chromatograph using a 6 ft × 0.125 in. column containing 10% Carbowax 20M on 80–100 mesh Chromosorb W, acid washed and DMCS treated. Peak areas were obtained with a disk integrator. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

(15) H. J. Lucas and H. K. Garner, *J. Amer. Chem. Soc.*, **70**, 990 (1948).

(16) S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.*, **61**, 1576 (1939).

Preparation of Ethyl 2,3-Dimethylcyclopropanecarboxylates (Mixed Isomers) (14).—To 2.6 g (0.022 mol) of thionyl chloride was added dropwise a solution of 2.0 g (0.017 mol) of a mixture of 2,3-dimethylcyclopropanecarboxylic acids consisting of 4% **9**, 6% **10**, and 90% **11** in 5 ml of benzene. The reaction mixture was stirred at room temperature for 90 min and then heated at reflux for 90 min. After cooling to room temperature, 10 ml of absolute ethanol was added dropwise. The solution was evaporated under reduced pressure to give a liquid residue. Distillation gave 1.60 g (67%) of isomeric ethyl 2,3-dimethylcyclopropanecarboxylate (**14**): bp 53–56° (7 mm); ir (neat) 5.82 (C=O), 7.65, and 8.50 μ (COC); nmr ($CDCl_3$) δ 4.03 (m, 2, OCH_2CH_3, J = 7 Hz), 1.7–0.8 (m, 12).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.37; H, 9.99.

A solution containing 1.35 g of **14** and 0.015 mol of sodium ethoxide in 40 ml of absolute ethanol was heated at reflux for 43 hr. A solution of 10 g of NaOH in 15 ml of water was added dropwise, and the reflux was continued for 4 hr. The ethanol was removed under reduced pressure and the remaining aqueous solution was washed with three 15-ml portions of chloroform, acidified with 50% H_2SO_4, and washed with three additional 15-ml portions of chloroform. The latter chloroform washings were dried (Na_2SO_4) and evaporated under reduced pressure to give 1.0 g of 2,3-dimethylcyclopropanecarboxylic acids. Vpc analysis showed the presence of **9** and **11** and only a trace of **10**. No additional component was evident.

Registry No.—**2**, 38868-10-9; **8**, 1758-32-3; (±)-**9**, 20431-63-4; **9a**, 20431-72-5; **10**, 34669-52-8; **11**, 34669-51-7; **12**, 1758-33-4; **14**, 17214-87-8.

Acknowledgment.—The authors are grateful to Dr. A. T. McPhail and Mrs. P. A. Luhan for the X-ray crystallographic analysis.

Preparation and Applications of (Dialkylamino)methyloxosulfonium Methylides. Synthesis of Cyclopropanes and Oxiranes[1a]

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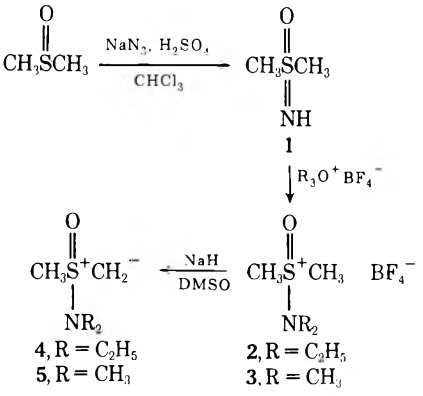
Received November 30, 1972

Dimethylsulfoximine, prepared from dimethyl sulfoxide, was dialkylated to give (*N*,*N*-dimethylamino)- and (*N*,*N*-diethylamino)dimethyloxosulfonium fluoroborate. Reaction of these salts with sodium hydride in a variety of aprotic solvents gave methylides. These ylides are effective as nucleophilic methylene transfer reagents; reactions with electrophilic alkenes yield cyclopropanes, while aldehydes and ketones react to give oxiranes.

In the past decade the chemistry of sulfur ylides has been an area of substantial interest.[2] The dimethylsulfonium and dimethyloxosulfonium methylides introduced by Corey and Chaykovsky are very useful synthetic reagents.[3] These ylides have been used to transfer a methylene group in a stepwise fashion across the double bond of a carbonyl or an electrophilic olefin to yield an epoxide or a cyclopropane, respectively. The transfer of more complex groups has also been achieved.[4]

The observation in this laboratory that ylides derived from (dimethylamino)alkylaryloxosulfonium fluoroborates[5] were capable of transferring alkylidene groups prompted us to undertake a study of the preparation and chemistry of an ylide derived from dimethylsulfoximine. This ylide would be accessible to the synthetic organic chemist and could serve as a model for ylides derived from other symmetrical dialkyl sulfoximines.

The first goal of this work was to prepare an ylide from dimethyl sulfoxide (DMSO) in as few steps as possible. Dimethylsulfoximine (**1**) could be prepared in 85% yield from DMSO using 1.1 equiv of hydrazoic acid, generated in a chloroform slurry from sodium azide and sulfuric acid.[6] The *N*,*N*-diethyl salt (**2**)[7] was chosen as the model ylide precursor. The choice of the *N*,*N*-diethyl derivative was prompted by the fact that triethyloxonium fluoroborate, the alkylating agent of choice, requires one less step in its preparation than trimethyloxonium fluoroborate. The dialkylation of the crude sulfoximine was accomplished in one flask using excess sodium carbonate as a base to give **2** in 81% yield. A similar procedure gave (dimethylamino)dimethyloxosulfonium fluoroborate (**3**) in 85% yield. Both salts were stable, white, crystalline solids.



(Diethylamino)methyloxosulfonium methylide (**4**) was readily prepared by dissolving the salt **2** in DMSO

(1) (a) Part XXXIX in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 19623). (b) National Science Foundation Graduate Trainee, 1968–1971.

(2) A. W. Johnson, "Ylid Chemistry," Academic Press, London and New York, 1966.

(3) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962); (b) *ibid.*, 3782 (1962); (c) *ibid.*, **86**, 1640 (1964); (d) *ibid.*, **87**, 1353 (1965); (e) H. Konig, *Fortschr. Chem. Forsch.*, **9**, 487 (1968).

(4) (a) E. J. Corey and W. Oppolzer, *J. Amer. Chem. Soc.*, **86**, 1899 (1964); (b) E. J. Corey, M. Jautelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967); (c) G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967); (d) *ibid.*, **33**, 1284 (1968); (e) G. B. Payne and M. R. Johnson, *ibid.*, **33**, 1285 (1968); (f) G. B. Payne, *ibid.*, **33**, 3517 (1968).

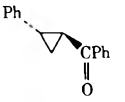
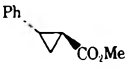
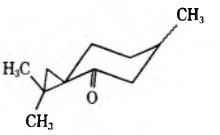
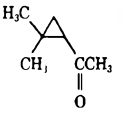
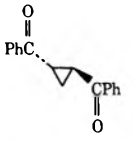
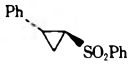
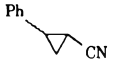
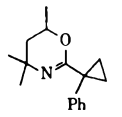
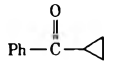
(5) (a) C. R. Johnson, E. R. Janiga, and M. Haake, *J. Amer. Chem. Soc.*, **90**, 3890 (1968); (b) C. R. Johnson, M. Haake, and C. W. Schroeck, *ibid.*, **92**, 6594 (1970).

(6) H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 2081 (1950).

(7) H. Schmidbaur and G. Kammel, *Chem. Ber.*, **104**, 3241 (1971), have recently described the preparation of salts **2** and **3** and the corresponding ylides **4** and **5**. Their interest was largely in the preparation and study of spectral properties.

TABLE I

CYCLOPROPANES

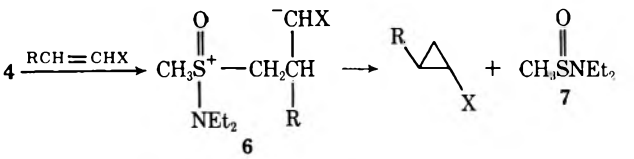
Substrate	Registry no.	Product	Registry no.	Yield, %
Benzalacetophenone	94-41-7		1145-92-2	93
Methyl cinnamate	103-26-4		5861-31-4	82
Pulegone	89-82-7		38709-59-0 (trans) 38709-60-3 (cis)	52
Mesityl oxide				62
2-Cyclohexenone	930-68-7		5771-58-4	60
trans-1,4-Diphenyl-2-butene-1,4-dione				62
Phenyl styryl sulfone	5418-11-1		21309-15-9	80
Cinnamonitrile	4360-47-8		5279-82-3 (cis) 5590-14-7 (trans)	49[a]
2-(1-Phenyl)vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine	38709-86-3		38709-65-8	75
α-Bromoacetophenone	70-11-1		3481-02-5	25

[a] Composition: 21% cis and 79% trans; in addition, β-methylcinnamonitrile (9%) was produced.

(distilled from calcium hydride) and adding it to a stirred slurry of sodium hydride in DMSO under a cover of nitrogen. After 10–15 min a clear solution of **4** was obtained. Ylide **4** was stable for extended periods at room temperature; it was found that at 52° the ylide had a half-life of approximately 40 hr. Solutions of the ylide were also prepared in dimethylformamide (DMF) and tetrahydrofuran (THF). Generation of the ylide **4** in THF required several hours owing to the heterogeneous nature of the reaction mixture. After the ylide was prepared in THF the fluoroborate salts could be filtered off and standardized solutions of **4** could be stored under nitrogen for several weeks in the refrigerator. In general, however, the ylide was prepared shortly before use. (Dimethylamino)methyloxosulfonium methylide (**5**) was prepared in the same manner as **4**.

DMSO was the solvent of choice in nearly all of the methylene transfer reactions. A qualitative kinetic study showed that the ylide reacted more rapidly in DMSO than in DMF. However, the major advantage of DMSO over other solvents lies in its greater solubility in water, allowing most of it to be easily removed by an aqueous wash. High water solubility also aided in the removal of the sulfinamide produced during the reaction. Chromatography over a short column of silica was found to be the most convenient method of product purification. Distillations were carried out when very volatile products were produced. Several methylene transfer reactions were run using both ylide **4** and ylide **5**; there was no notable difference in reactivity.

The ylide **4** was treated with a variety of α,β-unsaturated ketones, esters, sulfones, nitriles, and amides to give the corresponding cyclopropanes (Table I). These reactions are believed to occur stepwise *via* addition of the ylide to the substrate to give betaine **6** followed by ring closure with displacement of sulfinamide **7**.



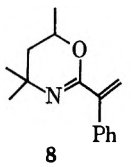
6

The rate of the ylide reactions with substrates of this nature seems to be dependent largely on the ease of betaine formation. Steric hindrance to attack by

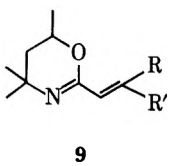
the ylide **4** was observed to slow the rate of reaction substantially; a rapid reaction occurred with 2-cyclohexenone while pulegone and mesityl oxide reacted at much slower rates. The stability of the betaine which is formed also seemed to influence the rate of these reactions. Qualitatively, there is a good correlation between the pK_a of an aliphatic sulfone, ketone, nitrile, or ester and the rate of reaction with substrates in which these groups stabilize the betaine. Phenyl styryl sulfone and benzalacetophenone reacted rapidly, while cinnamonitrile and methyl cinnamate required longer periods of time for complete reaction. Attempts to add the ylide to methyl styryl sulfone and cinnamide were not successful even after long periods of time and use of large excesses of ylide. (In the reaction medium these substrates may exist largely as their anions.)

The reaction of the ylide with benzalacetophenone was found to give a 93% yield of *trans*-1-benzoyl-2-phenylcyclopropane. The observation of the exclusive or predominant formation of trans cyclopropanes during the course of this study points toward the existence of the proposed betaine intermediate **6**.[8] A mixture of cis and trans cyclopropanes was obtained from cinnamonitrile; this suggests that because the cyano group is smaller than some of the other groups (benzoyl, carbomethoxy, or phenyl sulfone) investigated, the ring closure of the different betaine conformers can complete effectively.

During the course of this work Meyers and coworkers[9] reported the use of 4,4,6-trimethyl-5,6-trimethyl-5,6-dihydro-1,3-oxazines as precursors to a variety of aldehydes. It was found that the ylide **4** reacted smoothly with 2-(1-phenylvinyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (**8**) to give a 75% yield of the corresponding cyclopropane (Table I). The cyclopropyl compound was reduced with neutral sodium borohydride and hydrolyzed with oxalic acid to give an 81% yield of 1-phenylcyclopropanecarboxaldehyde.



8



9

Several other vinyloxazines (**9**) (R = alkyl or aryl) were prepared by dehydration of the corresponding alcohols. All of these vinyloxazines failed to react with the ylide **4**. In related work it was observed that the anion of dimethyl-*N*-*p*-toluenesulfonylsulfoximine[10] and dimethyloxosulfonium methylide also failed to add across the double bond of these oxazines. These failures only serve to emphasize the importance of the betaine stability in this type of ylide reaction. The phenyl group in the betaine formed as an intermediate in the addition of the ylide **4** and **8** afforded the stabilizing effect which was needed but was not available in the other systems.

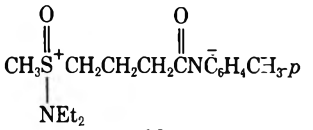
(8) C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, **93**, 5303 (1971).

(9) (a) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *ibid.*, **91**, 763 (1969); (b) A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *ibid.*, **91**, 765 (1969).

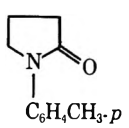
(10) C. R. Johnson and G. F. Katekar, *ibid.*, **92**, 5753 (1970).

Cyclopropyl phenyl ketone was prepared by the reaction of 3.3 equiv of the ylide **4** with α-bromoacetophenone; DMF was used as a solvent owing to the known affinity of DMSO to react with α-halo ketones to give glyoxals.[11] There was only a 25% yield of isolated product, but the reaction did demonstrate the ylide's ability to introduce two methylene groups by successive reactions; phenyl vinyl ketone is presumed to be an intermediate in this reaction. Earlier examples of this type of double methylene insertion reactions with dimethyloxosulfonium methylide had been observed by Bravo and coworkers.[12]

N-*p*-Tolyl-2-pyrrolidone (**11**) was observed as the major product from the reaction of the ylide **6** with *p*-acrylotoluidide. Konig and Metzger[13] reported a similar result when the dimethyloxosulfonium methylide was treated with this substrate. A logical mechanism to explain this observation involves proton transfer from nitrogen to carbon to give intermediate **10**, which then undergoes ring closure to the pyrrolidone **11**.



10



11

It was found that epoxides were formed in the reaction of the ylide with several aldehydes and ketones (Table II). As would be expected, aldehydes reacted more rapidly than ketones. In general, best results were obtained using a 30–100% excess of ylide coupled with short reaction times.

TABLE II
EPOXIDES

Substrate	Products	Yield, %
Benzaldehyde	C_6H_5—	57
p-Chlorobenzaldehyde	*p*-ClC_6H_4—	62
4-*tert*-Butylcyclohexanone		72
Heptanal	*n*-C_6H_{13}—	37
Cycloheptanone		42
4-Methylcyclohexanone		42

When **4** reacted with 4-*tert*-butylcyclohexanone only the *Z* epoxide was produced. Dimethyloxosulfonium methylide is reported to display a similar stereospecificity, while dimethylsulfonium methylide gave predominantly the *E* epoxide.[3d]

(11) N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, **81**, 4113 (1959).

(12) R. Bravo, G. Baudiano, C. Ticozzi, and A. Umani-Ronchi, *Tetrahedron Lett.*, 4181 (1968).

(13) H. Konig, H. Metzger, and K. Seelert, *Chem. Ber.*, **98**, 3712 (1965).

Experimental Section

General.—Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Boiling points are also uncorrected. The microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. The ir spectra were recorded on Perkin-Elmer infrared spectrophotometers, Models 137B and 621. The nmr spectra were taken on Varian spectrometers, Models A-60A and T-60, with a sweep width of 500 Hz; tetramethylsilane was used as the internal standard. Vapor phase chromatography was performed on F & M Models 5750 and 720 (thermal conductivity) chromatographs with 0.25-in. columns. The mass spectral data were obtained on either an Atlas CH4 or an AEI MS9 spectrometer mass. Many of the authentic samples used in comparisons had been previously prepared in our laboratory by ylide reactions.[6]

Dimethylsulfoximine (1).[6]—In a 2-l. flask equipped with a condenser, a mechanical stirrer, and an addition funnel, a mixture of 50 g (0.64 mol) of dimethyl sulfoxide, 46 g (0.71 mol) of sodium azide, and 570 ml of chloroform was cooled in an ice bath. Concentrated sulfuric acid (160 ml) was added to this slurry over a period of 1 hr. The mixture was slowly warmed to 42° and stirred at this temperature for 24 hr. After cooling, all the solids were dissolved in water, the chloroform layer was separated, and the aqueous layer was washed with two 150-ml portions of chloroform. The aqueous layer was made slightly alkaline using a 40% sodium hydroxide solution. The water was then removed on a rotary evaporator and the resulting salts were washed with 2 l. of warm ethanol. Removal of the ethanol and washing the ethanol-soluble salts with 500 ml of methylene chloride gave 51.5 g (87%) of the sulfoximine as a crystalline solid, nmr ($CDCl_3$) δ 3.10 (s, 6, CH_3), 2.84 (s, 1, NH).

(Diethylamino)dimethyloxosulfonium Fluoroborate (2).—In a 1-l. erlenmeyer flask fitted with a drying tube, 20.5 g (0.22 mol) of dimethylsulfoximine was dissolved in 300 ml of dry methylene chloride and cooled in a water bath. To this solution 45 g (0.24 mol) of triethyloxonium fluoroborate[14] was added as the reaction was stirred vigorously with a magnetic stirrer. After 15 min 110 g (1.04 mol) of anhydrous sodium carbonate was added and the reaction was allowed to stir for 3 hr. Then another 45 g of the triethyloxonium fluoroborate was added and the mixture was allowed to stir for 1 hr. The inorganic salts were removed and then washed with 3 l. of warm ethanol. The methylene chloride was removed and that material was added to the ethanol solution, which was reduced to about $^2/_3$ of its original volume. At this point cooling gave 44 g of the crude sulfoximine salt. Recrystallization from ethanol gave 42 g (81%), of salt **2**: mp 107–108°; ir (Nujol) 1250, 1140–1000 cm^{-1} (BF_4^-); nmr (DMSO-d_6) δ 4.05 (s, 6, CH_3), 3.86–3.44 (q, 4, CH_2), 1.42–1.18 (t, 6, CH_3).

Anal. Calcd for $C_6H_{16}BF_4NOS$: C, 30.40; H, 6.80. Found: C, 30.55; H, 6.98.

(Dimethylamino)dimethyloxosulfonium Fluoroborate (3).—A procedure, identical with that used to prepare **4** using trimethyloxonium fluoroborate as the alkylating agent, was followed. At the conclusion the carbonate salts were washed with 2 l. of warm methanol. Recrystallization from methanol gave 39 g (85%) of the salt **3**: mp 146–147°; ir (Nujol) 1240, 1140–1020 cm^{-1} (BF_4^-); nmr (DMSO-d_6) δ 4.0 (s, 6, SMe), 3.06 (s, 6, NMe).

Anal. Calcd for $C_4H_{12}BF_4NOS$: C, 22.98; H, 6.17. Found: C, 23.25; H, 5.89.

(Diethylamino)methyloxosulfonium Methylide (4). A. Preparation in DMSO.—In a 50-ml three-necked flask equipped with a stirrer, an additional funnel, a gas inlet tube, and a serum stopper was placed 11 mmol of sodium hydride (as a 59.4% dispersion in mineral oil), and 5 ml of DMSO (distilled from calcium hydride) under a cover of nitrogen. To this, 2.60 g (11 mmol) of (diethylamino)dimethyloxosulfonium fluoroborate (**2**) in 12 ml of DMSO was added through the addition funnel over a period of 15 min with good stirring. There was a vigorous evolution of hydrogen, and the mixture was kept at room temperature with the aid of a water bath. After a few minutes a clear solution was obtained. An identical procedure can be used to prepare (dimethylamino)methyloxosulfonium methylide (**5**).

B. Preparation in THF.—The same apparatus as described above was used. The sodium hydride and the fluoroborate were placed in the flask as dry solids. The THF (distilled from sodium dispersion) was then introduced into the reaction flask all at once, and the heterogeneous mixture was stirred for several hours while being kept in room temperature with a water bath. The inorganic salts could be filtered off under nitrogen and a solution of the ylide **4** could be stored in a refrigerator for several weeks. In most cases no effort was made to remove the inorganic salts, and the ylide solution was used soon after its preparation.

Methylene Transfer Reactions.—In general, the reaction mixtures were poured into 100 ml of water and the product was extracted three times with 50-ml portions of ether. The ether solution was dried over magnesium sulfate and evaporated at reduced pressure. Chromatography over an 18 × 0.5 in. column of silica gel eluting first with 100 ml of pentane followed by benzene gave the desired products in a high state of purity. In several cases when the product was very volatile the crude product was purified by a short-path distillation.

***trans*-1-Benzoyl-2-phenylcyclopropane.**—To a stirring solution of ylide **4** (11 mmol) in 17 ml of DMSO was added a solution of 2.08 g (10 mmol) of benzalacetophenone in 8 ml of DMSO over a period of 10 min. The mixture was allowed to stir at room temperature for 4 hr. Work-up and chromatography yielded 2.08 g (94%) of an oil which solidified upon standing. The infrared spectrum was identical with that of a known sample: ir (film) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.27–7.1 (m, 10, aryl), 3.0–2.45 (m, 2, COH and CH), 2.0–1.2 (two m, 2, CH_2).

Methyl *trans*-2-Phenylcyclopropylcarboxylate.—Ylide **4** (12 mmol) was prepared in 17 ml of DMSO. A solution of 1.62 g (10 mmol) of methyl cinnamate in 8 ml of DMSO was added over a period of 30 min. The reaction mixture was allowed to stir for 48 hr at room temperature. Work-up and chromatography gave 1.45 g (82.5%) of the cyclopropyl ester. The product was one component by glpc analysis on a 8 ft × 0.25 in., 20% DEGS on C-W column at 180°: ir (film) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.5–6.0 (m, 5, aryl), 3.67 (s, OCH_3), 2.7–2.3 (m, 1, $CHCO_2$), 2.1–1.1 (m, 3, $CHCH_2$).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.70; H, 6.93.

Cyclopropyl Phenyl Ketone.—Ylide **4** (31 mmol) was prepared in 28 ml of DMF at 0°. α-Bromoacetophenone (1.92 g, 9.65 mmol) in 20 ml of DMF was added over a period of 30 min. The reaction was stirred in an ice bath for 12 hr and at room temperature for 6 hr. Work-up and chromatography gave 0.35 g (25%) of the cyclopropyl ketone. The infrared spectrum and glpc behavior were identical with that of an authentic sample; nmr ($CDCl_3$) δ 8.2–7.2 (2, m, 5, aryl), 2.9–2.4 (m, 1, OCCH), 1.4–8.0 (m, 4, cyclopropyl).

Reaction of the Ylide with Cinnamonitrile.—The ylide **4** (20 mmol) was prepared in 20 ml of DMSO. Cinnamonitrile (1.29 g, 10 mmol) was added and the reaction was stirred at 50° for 24 hr. The reaction mixture was poured into ice water and extracted with ether. The ether was dried with magnesium sulfate and evaporated. After work-up the crude product was chromatographed over silica gel to give 0.83 g (58%) of product. Glpc analysis (10 ft × 0.25 in., 15% DEGS on Diaport S at 210°) indicated the presence of three components, A, B, and C, with retention times of 10.5, 13.2, and 18.7 min in a ratio of 16:66:18. These three components could be separated by tedious chromatography on silica gel or by preparative glpc using a 6 ft × 0.75 in., 20% DEGS on Chromosorb W column.

Component A had ir (film) 2225, 1610, 1570, 790, 755 cm^{-1}; nmr ($CDCl_3$) δ 8.35 (s, 5, aryl), 5.54 (q, 1, J = 1.1 Hz, CH), 2.4 (d, 3, J = 1.1 Hz, CH_3). On the basis of the spectral evidence component A was assumed to be β-methylcinnamonitrile. A (200 mg) was stirred in 10 ml of 2 *N* sodium hydroxide in an oil bath at 100° for 24 hr. After cooling the mixture to room temperature it was diluted with 15 ml of water and washed with ether. The water layer was acidified and extracted with ether. The ether was dried and evaporated to give 194 mg of a solid, mp 96–97°. This compares well with mp 98° for β-methylcinnamic acid.[15]

Component B could be obtained as a crystalline solid: mp 51–52° from ether–pentane; ir (film) 2250, 1610, 1500, 1460, 1400, 750, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.5–6.9 (m, 5, aryl), 2.8–2.4 (m, 1, CHCN), 1.7–1.4 (m, 3). Hydrolysis of B in 2 *N* NaOH gave *trans*-2-phenylcyclopropanecarboxylic acid, indicating that B is the corresponding nitrile.

(14) (a) H. Meerwein, *Org. Syn.*, **46**, 113 (1966); (b) *ibid.*, **46**, 120 (1966).

(15) L. Kh. Vinograd and N. S. Vul'fson, *J. Gen. Chem. USSR*, **29**, 2656 (1959).

Component C could be obtained as a crystalline solid: mp 37° from ether–pentane; ir (film) 2250, 1610, 1500, 1460, 760, 730, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.3 (s, 5, aryl), 3.3–2.8 (m, 1, CHCN), 2.0–1.1 (m, 3). Basic hydrolysis of C in 2 *N* NaOH at reflux for 48 hr gave *cis*-2-phenylcyclopropanecarboxylic acid. These data indicate that C is *cis*-2-phenylcyclopropanecarbonitrile.

Reaction of Ylide 4 with *p*-Acrylotoluidide.—The ylide 4 was prepared by stirring 4.40 g (186 mmol) of 2 and 0.446 g (186 mmol) of sodium hydride in 16 ml of DMSO. A solution of 2.0 g (124 mmol) of *p*-acrylotoluidide in 8 ml of DMSO was added and the reaction mixture was allowed to stir for 24 hr at room temperature. After work-up the product was chromatographed over alumina and eluted with benzene to give 1.07 g (50%) of *N*-*p*-tolyl-2-pyrrolidone (11) and 190 mg (9%) of a material assigned the structure 3-(3′-*N*-*p*-tolyl-2-pyrrolidone)-*N*-*p*-tolylpropionamide. Both compounds were crystalline solids, mp 86–87° (lit.[16] mp 88–89°) and 190–191°, respectively. *N*-*p*-Tolyl-2-pyrrolidone had ir ($CHCl_3$) 1680, 1505, 1390, 1300 cm^{-1}; nmr ($CDCl_3$) δ 7.4–6.9 (2 d, 4, aryl), 3.86–3.50 (t, 2, OCH_2), 2.77–1.67 (m, 4, ring), 2.36 (s, 3, CH_3). 3-(3′-*N*-*p*-Tolyl-2-pyrrolidone)-*N*-*p*-tolylpropionamide had ir ($CHCl_3$) 3430, 1660, 1520 cm^{-1}; nmr ($CDCl_3$) δ 7.6–6.9 (m, 8, aryl), 4.5–4.1 (t, 2, $COCH_2$), 2.8–1.7 (m, 13).

Reaction of the Ylide 4 with Pulegone.—Ylide 4 (11.5 mmol) was prepared in 15 ml of DMSO. A solution of 1.52 g (10 mmol) of pulegone in 10 ml of DMSO was added and the reaction mixture was stirred at room temperature for 48 hr. Following work-up, chromatography of the crude product over silica gel gave 0.87 g (52%) of a 60:40 mixture of the diastereomeric cyclopropanes, ir (film) 1710 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.28; H, 10.99.

2-(1-Phenyl)cyclopropyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine.—The ylide 4 (15 mmol) was prepared in 15 ml of DMSO. A solution of 2.17 g (9.45 mmol) of 2-(1-phenyl)vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine[17] in 10 ml of DMSO was added and the reaction was allowed to stir at 50° for 60 hr. Work-up gave 2.3 g of crude product which was distilled (76–84°, 0.3 mm) using a short-path distillation apparatus to give 1.74 g (75% of product which solidified on standing: ir (film) 1660 cm^{-1} (C=N); nmr ($CDCl_3$) δ 7.45–7.0 (m, 5, aryl), 4.3–3.8 (m, 1, OCH), 1.9–0.8 (m, 16).

Preparation of 1-Phenylcyclopropanecarboxaldehyde.—The 2-(1-phenyl)cyclopropyloxazine (1.72 g, 7.1 mmol) was dissolved in 20 ml of 50:50 THF–ethanol and cooled in an acetonitrile–Dry Ice bath at −45°, and 300 mg (7.95 mmol) of sodium borohydride in 1.5 ml of basic water was added slowly with periodic checks to maintain the pH as close to 7 as possible using 9 *N* HCl. After the addition of the sodium borohydride the reaction was allowed to stir for an additional 1 hr before the mixture was poured into water. The water was made basic with 40% NaOH and extracted with ether. The ether was washed with saturated NaCl, dried over potassium carbonate, and evaporated to give 2 g of crude product. Hydrated oxalic acid (11.8 g) was dissolved in 30 ml of water, which was heated to a boil in a small distillation apparatus equipped with an additional funnel. The crude tetrahydrooxazine was dissolved in ether and added slowly. The water was allowed to distil over until it was no longer cloudy. The distillate was dissolved in pentane, the solution was dried, and the pentane was evaporated to give 0.86 g (81%) of the desired aldehyde, ir (film) 1705 cm^{-1} (C=O).

***trans*-1-(Phenylsulfonyl)-2-phenylcyclopropane.**—To a solution of ylide 4 (6 mmol) in 15 ml of DMSO was added over a period of 30 min a solution of 1.22 g (5 mmol) of phenyl styryl sulfone in 10 ml of DMSO. The reaction was allowed to stir for 24 hr. Work-up and chromatography yielded 1.06 g (82%) of a crystalline solid: mp 93–94° (lit.[18] mp 95–96°); ir (film) 1300, 1150 cm^{-1}; nmr ($CDCl_3$) δ 8.1–6.9 (m, 10, aryl), 3.1–2.4 (m, 2), 2.05–1.2 (m, 2).

3-Norcaranone.—Ylide 4 (11 mmol) was prepared in 18 ml of DMSO. To this solution was added 0.96 g (10 mmol) of 2-cyclohexenone in 7 ml of DMSO and the reaction was allowed to stir for 3 hr at room temperature. Isolation of the crude product in the standard manner followed by chromatography over a short column of silica gel, eluting with pentane, followed by 50:50 methylene chloride–benzene, gave 0.63 g (57%) of 3-norcaranone: ir (film) 1690 cm^{-1}; nmr ($CDCl_3$) δ 2.7–1.45 (m, 8, cyclohexyl), 1.4–0.8 (m, 2, cyclopropyl).

Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.39. H, 9.25.

1-Methylene-4-methylcyclohexane Oxide.—Ylide 4 (13 mmol) was prepared in 17 ml of DMSO. To this solution was added 1.12 g (10 mmol) of 4-methylcyclohexanone in 5 ml of DMSO. The reaction was stirred at 50° for 8 hr. Standard work-up and chromatography gave 0.52 g (42%) of the epoxide: ir (film) 920, 840, 770 cm^{-1}; nmr ($CDCl_3$) δ 2.81 (s, 2, OCH_2), 2.2–0.8 (m, 12).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.8. Found, C, 76.21; H, 11.12.

1-Octene Oxide.—The ylide 4 (15 mmol) was prepared in 25 ml of DMSO. The ylide solution was warmed to 50° and 1.14 g (10 mmol) of heptanal in 20 ml of DMSO was added over a period of 90 min. The reaction was allowed to stir for an additional 2 hr at 50°. Following work-up, the crude product was chromatographed over silica gel eluting first with pentane and then pentane–ether. Bulb-to-bulb distillation gave 0.462 g (36.5%) of the epoxide. The infrared spectrum was identical with that of an authentic sample: nmr ($CDCl_3$) δ 3.2–2.4 (m, 3, $CHCH_2$), 1.8–0.7 (m, 15, alkyl).

Styrene Oxide.—Ylide 4 (13 mmol) was prepared in 17 ml of DMSO. A solution of 1.06 g (10 mmol) of benzaldehyde in 8 ml of DMSO was added over a period of 30 min. The reaction was allowed to stir for 1 hr at room temperature and 2 hr at 50°. The reaction mixture was poured into ice water and extracted with ether. The ether was dried over magnesium sulfate and evaporated; the residue was distilled at 80° (5 mm) to give 0.684 g (57%) of colorless styrene oxide, whose infrared spectrum was identical with that of an authentic sample.

***p*-Chlorostyrene Oxide.**—Following a similar procedure to that used for styrene oxide, *p*-chlorostyrene oxide was produced in 62% yield from *p*-chlorobenzaldehyde. Work-up and chromatography yielded 0.96 g (62%) of *p*-chlorostyrene oxide. The infrared spectrum of the product was identical with that of an authentic sample.

(*Z*)-1-Methylene-4-*tert*-butylcyclohexane Oxide.—A solution of ylide 4 (13 mmol in 17 ml of DMSO) was warmed to 50° and 1.54 g (0.010 mol) of 4-*tert*-butylcyclohexanone in 8 ml of DMSO was added over a period of 30 min. The reaction was stirred at this temperature for 4 hr. The crude product was chromatographed over silica gel to give 1.24 g (72%) of the *Z* epoxide, whose infrared spectrum was identical with that of an authentic sample: ir (neat) 920, 855, and 800 cm^{-1}; nmr ($CDCl_3$) δ 2.61 (s, 2, CH_2), 2.0–1.8 (m, 9, ring), 0.88 (s, 9, *t*-Bu).

Methylenecycloheptane Oxide.—Ylide 4 (26 mmol in 20 ml of DMSO) was warmed to 50° and 1.46 g (0.013 mol) of cycloheptanone in 10 ml of DMSO was added over a period of 20 min. The reaction mixture was stirred overnight at 50°. Chromatography of the crude product over silica gel gave 0.69 g (42%) of the oxirane. An infrared spectrum was identical with that of an authentic sample; nmr ($CDCl_3$) δ 2.58 (s, 2, OCH_2), 1.67 (s, 12, ring).

Registry No.—**1**, 1520-31-6; **2**, 36501-44-7; **3**, 36501-42-5; **4**, 38421-38-4; **11**, 3063-79-4; dimethyl sulfoxide, 67-68-5; sodium azide, 26628-22-8; triethyloxonium tetrafluoroborate, 368-39-8; trimethyloxonium tetrafluoroborate, 420-37-1; β-methylcinnamonitrile, 14368-40-2; *p*-acrylotoluidide, 7766-36-1; 3-(3′-*N*-*p*-tolyl-2-pyrrolidone)-*N*-*p*-tolylpropionamide, 38709-70-5; 1-methylene-4-methylcyclohexene oxide, 38709-71-6; 4-methylcyclohexanone, 589-92-4; 1-octene oxide, 2984-50-1; heptanal, 111-71-7; (*Z*)-1-methylene-4-*tert*-butylcyclohexane oxide, 7787-78-2; 4-*tert*-butylcyclohexanone, 98-53-3; methylenecycloheptane oxide, 185-85-3; cycloheptanone, 502-42-1.

(16) P. Lipp and F. Caspers, *Ber.*, **58**, 1011 (1925).

(17) A sample of the oxazine was kindly supplied by Professor A. I. Meyers.

(18) W. E. Truce and V. R. Badiger, *J. Org. Chem.*, **29**, 3277 (1964).

Preparation and Reactions of Stabilized (Dialkylamino)methyloxosulfonium Methylides. Synthesis of 1,3-Oxathiole 3-Oxides[1a]

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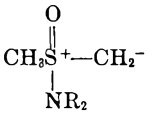
(Dimethylamino)- and (diethylamino)oxosulfonium methylide were treated with acid chlorides, anhydrides, and isocyanates to produce carbonyl-stabilized (dialkylamino)methyloxosulfonium methylides. Stabilized ylides were also prepared by reaction of the simple methylides with methanesulfonyl chloride and ethyl phenylpropiolate. (Dimethylamino)methyloxosulfonium benzoylmethylide and (dimethylamino)methyloxosulfonium acetylmethylide were alkylated at the carbonyl oxygen with trialkyloxonium salts to produce substituted (dialkylamino)methyl(2-alkoxyvinyl)oxosulfonium fluoroborates; the stereochemistry about the carbon–carbon double bond was ascertained by nmr. Acyl-stabilized methylides in this series were found to undergo a unique reaction, catalyzed by cupric sulfate, to yield 5-substituted 1,3-oxathiole 3-oxides.

A wide variety of sulfonium ylides stabilized by strong electron-withdrawing groups on the α carbon have been prepared; the chemistry of these compounds has been the subject of a number of studies.[2] Although these ylides transfer alkylidene groups to only the most reactive of substrates, they have been observed to undergo several interesting rearrangement and decomposition reactions.

The preparation of ylides **1** and **2** are described in the accompanying paper.[3] Here we describe the preparation of a number of stabilized ylides derived from **1** and **2** and compare their chemistry with that of other stabilized sulfonium ylides.

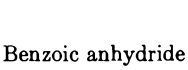
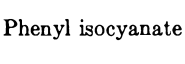
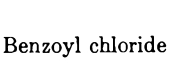
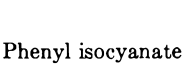
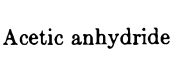
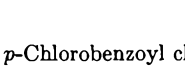
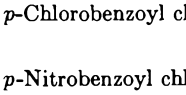
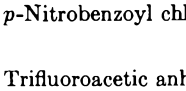
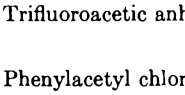


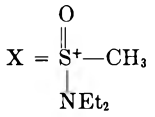
1, R = Me
2, R = Et

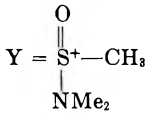
Preparation of Ylides.—Table I outlines the different stabilized ylides which were prepared; in most of these cases no effort to maximize the yield was made. In the preparation of these stabilized ylides at least 2 equiv of methylide is required, since the product is more acidic than the starting material. In general, the stabilized ylides displayed a fair shelf life; some decomposition was noted when stored for several months at room temperature. The dimethylamino ylide **1** was found to give products with superior crystalline properties, and following this observation only ylide **1** was used in the preparation of stabilized ylides.

Stabilized ylides **3**–**14** were prepared by reaction of the appropriate substrate with either **1** or **2** in THF at 0°. In the case of the benzoyl ylides, use of the less reactive anhydride as substrate rather than the acid chloride yielded a more manageable product mixture, at least when the diethylamino ylide was used. Several attempts to prepare a formyl-stabilized derivative were unsuccessful. While **12** could be prepared by reaction of **1** with mesyl chloride, *p*-nitrobenzenesulfonyl chloride gave no identifiable product.

TABLE I
STABILIZED YLIDES

Substrate	Stabilized ylide	No.	Yield, %
Benzoic anhydride		3	53
Phenyl isocyanate		4	83
Benzoyl chloride		5	60
Phenyl isocyanate		6	75
Acetic anhydride		7	65
p-Chlorobenzoyl chloride		8	65
p-Nitrobenzoyl chloride		9	82
Trifluoroacetic anhydride		10	31
Phenylacetyl chloride		11	52
Methanesulfonyl chloride	$CH_2SO_2\bar{C}HY$	12	58
Ethyl phenylpropiolate	$EtO_2CCH{=}CPh\bar{C}HX$	13	38
Ethyl phenylpripolate	$EtO_2CCH{=}CPh\bar{C}HY$	14	55

X = 

Y = 

The formation of **13** and **14** parallels that of similar reactivity observed when dimethyloxosulfonium methylide was used.[4] Thus, in these systems proton transfer of the initial adduct takes precedence over cyclopropene formation.[5]

O-Alkylation of Stabilized Ylides.—It has been reported by Bestmann[6] that carboethoxymethylenetriphenylphosphorane could be successfully O-alkylated with thiethyloxonium fluoroborate. A variety of stabilized sulfur ylides had previously been C-alkylated with methyl iodide, and the O-alkylation of dimethylsulfonium benzoylmethylide with trimethyl-

(1) (a) Part XL in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 19623). (b) National Science Foundation Graduate Trainee, 1968–1971.

(2) (a) A. W. Johnson and R. T. Amel, *J. Org. Chem.*, **34**, 1240 (1969); (b) H. Nazaki, D. Tunemoto, S. Matubana, and K. Kondo, *Tetrahedron*, **23**, 545 (1967); (c) K. W. Ratts and A. H. Yao, *J. Org. Chem.*, **31**, 1689 (1966); (d) B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 138 (1967); (e) W. E. Truce and G. D. Madding, *Tetrahedron Lett.*, 386 (1966); (f) G. B. Payne, *J. Org. Chem.*, **33**, 3517 (1968).

(3) C. R. Johnson and P. E. Rogers, *ibid.*, **38**, 1793 (1973).

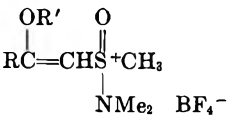
(4) C. Kaiser, B. M. Trost, J. Beeson, and J. Weinstock, *ibid.*, **30**, 3972 (1965).

(5) E. J. Corey and M. Jautelat, *J. Amer. Chem. Soc.*, **89**, 3912 (1967).

(6) H. J. Bestmann, R. Saalfrank, and J. P. Snyder, *Angew. Chem., Int. Ed. Engl.*, **8**, 216 (1969).

oxonium fluoroborate has been reported.[7] For these reasons it seemed that it would be worthwhile to O-alkylate several of the acylides prepared in this study.

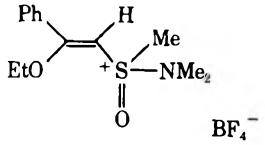
Using trimethyl- and triethyloxonium fluoroborate it was possible to O-alkalylate the benzoyl- and acetyl-stabilized ylides **5** and **7**. The reactions were performed at 0° in methylene chloride in the presence of excess sodium carbonate. In all the cases studied,



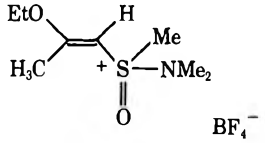
15, R = Ph; R′ = Et
16, R = Ph; R′ = Me
17, R = Me; R′ = Et
18, R = Me; R′ = Me

mixtures of diastereomeric vinyl salts were obtained; in several cases these isomers could be separated by fractional crystallization.

It seems valid to assume that the *Z* isomer of **15** and **16** should be the more favored thermodynamically, because a phenyl group has a larger steric requirement than either an ethoxy or a methoxy group. For similar reasons the *E* isomer of **17** and **18** should be favored.



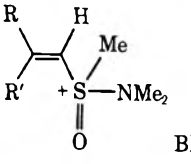
15 *Z* diastereomer



17 *E* diastereomer

Using the values of Pascuel, Meier, and Simon,[8] approximate shifts of the vinyl proton in each of these systems were estimated. These calculations indicated that the vinyl proton of the *Z* isomer of **15** and **16** would appear further downfield than that of the *E* isomer, and that the vinyl proton of the *E* isomer of **17** and **18** appear at lower field than that of the *Z* isomer (Table II).

TABLE II
VINYL ETHER SALTS

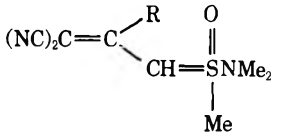


Compd	Isomer	R	R′	% at equil	Calcd vinyl shift	Obsd vinyl shift
15	*Z*	Ph	OEt	68	4.37	3.71
15	*E*	OEt	Ph	32	4.12	3.56
16	*Z*	Ph	OMe	73	4.37	3.74
16	*E*	OMe	Ph	27	4.12	3.52
17	*Z*	Me	OEt	12	3.74	3.36
17	*E*	OEt	Me	88	3.93	3.56
18	*Z*	Me	OMe	10	3.74	3.42
18	*E*	OMe	Me	90	3.93	3.64

Pure isomers or mixtures of different composition than that at equilibrium were stirred in methylene chloride in the presence of sodium carbonate. In all four systems it was found that after an extended period of time the isomer with the least shielded vinyl proton dominated. On this basis structural assignments were made.

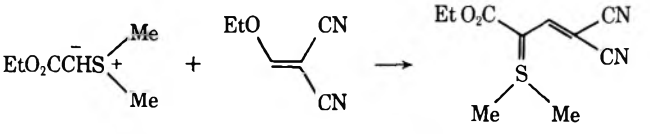
These vinyl ether salts were treated with the anions of several active methylene compounds; it was hoped that this would represent a route to substituted cyclopropyl ethers.[9,10] Initial efforts were made using diethyl and dimethyl malonate. Sodium alkoxides were used as bases, and the reactions were first run at room temperature and later at 50°. Nmr spectra of the crude products offered no evidence for the existence of cyclopropanes. These spectra did indicate that methyl benzoate was present when sodium methoxide was used as a base in reactions with phenylvinyl ethers. It was also noted that in the presence of a sodium methoxide the salt **15** was converted to **16**.

Salts **15** and **17** were found to react smoothly with the anion of malononitrile to give, as expected, the stabilized ylides **19** and **20**, respectively, rather than



19, R = Ph
20, R = Me

cyclopropane. A third allylide identified only on the basis of its nmr spectrum was obtained from the reaction of **15** and methyl cyanoacetate. Payne has observed the formation of allylide **22** in the reaction of



22

(dimethylsulfuranylidene)acetate (**21**) with ethoxymethylenemalononitrile.[2f] There are obvious similarities between Payne's system and the one under study.

It appears that steric factors prevented the addition of the anions of diethyl and dimethyl malonate to the β carbon. Electron donation by the ether oxygen may have also reduced the electrophilic nature of that carbon. The smaller anions derived from malononitrile and methyl cyanoacetate were able to overcome these obstacles, but the elimination of a molecule of alcohol rather than sulfinamide was the reaction pathway followed.

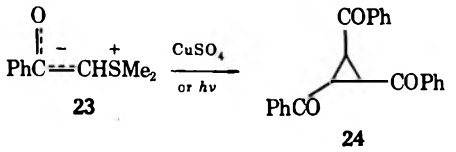
Conversion to 1,3-Oxathiole 1-Oxides.—In a study of dimethylsulfonium phenacylide, Trost[2d] observed that it was stable in refluxing benzene, chloroform, or cyclohexene. He found, however, that tribenzoylcyclopropane (**24**) was obtained in high yield when

(7) S. H. Smallcombe, R. J. Holland, R. H. Fish, and M. C. Caserio, *Tetrahedron Lett.*, 5987 (1968).

(8) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

(9) (a) J. Gosselck, L. Beress, and H. Schenk, *Angew. Chem., Int. Ed. Engl.*, **5**, 596 (1966); (b) J. Gosselck, H. Albrecht, F. Dost, H. Schenk, and G. Schmidt, *Tetrahedron Lett.*, 995 (1968); (c) J. Gosselck and G. Schmidt, *ibid.*, 2615 (1969); (d) G. Schmidt and J. Gosselck, *ibid.*, 3445 (1969).

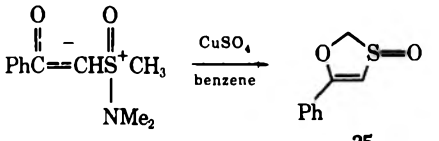
(10) C. R. Johnson and J. P. Lockard have reported [*Tetrahedron Lett.*, 4589 (1971)] that (dimethylamino)phenyl(2-phenylvinyl)oxosulfonium fluoroborate undergoes reactions with active methylene compounds to give cyclopropanes. Gosselck and coworkers[9] had shown that simple vinyl sulfonium salts reacted with the anions of active methylene compounds to give cyclopropanes.



23 24

a solution of the ylide was refluxed in cyclohexene in the presence of excess anhydrous copper sulfate. This cyclopropane was also obtained on irradiation of a benzene solution of the ylide with an Hanovia high-pressure mercury lamp using a Pyrex filter. On this basis it was suggested that benzoylcarbene was a common intermediate in both reactions.

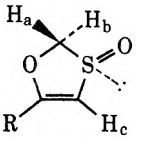
A very different result was observed when the benzoyl-stabilized ylide **5** was stirred with 2 equiv of anhydrous cupric sulfate in cyclohexene or benzene. A crystalline solid identified as 5-phenyl-1,3-oxathiole 3-oxide (**25**) was obtained in high yield.



5 25

It was found that several other acylides also rearranged cleanly to the corresponding 1,3-oxathiole 3-oxides. In the examples studied, the stabilized ylides were stirred in refluxing benzene, cyclohexene, or toluene for approximately 33 hr in the presence of 2 equiv of cupric sulfate. The 1,3-oxathiole 3-oxides (**25**, **26**, **27**) could be isolated as crystalline solids, while **28** and **29** were isolated as oils. These sulfoxides were stable at room temperature, but were decomposed quickly by traces of acid (Table III).

TABLE III
1,3-OXATHIOLE 3-OXIDES

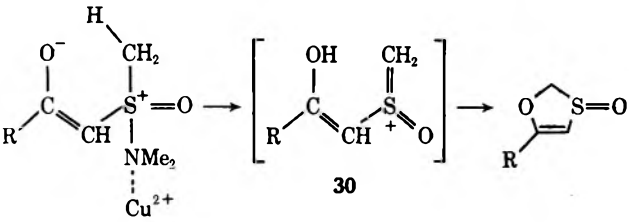


Compd	R	Yield, %	Nmr, ppm (J, Hz) H_a[a]	H_b[a]	H_c[b]
25	Ph	84	5.63 (11)	5.1 (11)	6.75
26	*p*-ClPh	80	5.54 (12)	5.0 (12)	6.65
27	*p*-NO_2Ph	79	5.65 (12)	5.1 (12)	6.95
28	CH_3	80	5.35 (12)	4.9 (12)	6.05
29	$PhCH_2$	64	5.25 (12)	4.8 (12)	6.00

[a] Doublets. [b] Singlets.

The infrared spectra of these compounds all displayed a sulfoxide absorption in the 1020–1040-cm^{-1} region. The nmr spectra of this ring system were very characteristic. In all cases the vinyl proton appeared as a singlet at approximately δ 6.0–6.8, while the diastereotopic protons on the carbon flanked by the sulfoxide and ether appeared as AB quartets between δ 4.5 and 5.0. The doublet at lower field was assigned to the proton cis to the sulfoxide oxygen.[11] The mass spectrum of **25** showed a parent ion of *m/e* 180 and displayed major peaks corresponding to the loss of oxygen and formaldehyde. Peaks assumed to be the phenacylium ion, phenylacetylene, and the tropylium ion were also observed. Similar mass spectral fragmentation patterns were shown by all the examples studied.

The role of the cupric ion may be that of coordination with the dimethylamino group to improve its "leaving group" ability. When the acyl group contained electron-withdrawing substituents, somewhat elevated temperatures were required to effect the cyclization. It is our present hypothesis that these reactions proceed in concerted fashion to give an intermediate sulfur-stabilized carbonium ion (**30**), which undergoes cyclization. Regardless of the mechanism, these reactions show a characteristic of a Pummerer reaction—a sulfur is reduced and an adjacent carbon is oxidized.[12] In Pummerer reactions, which are more typical at the "sulfin" oxidation stage, carbonium ions stabilized by an adjacent sulfur are believed to be key intermediates. A close analogy to the present reaction is from the work of Ratts and Yao[13] in which acyl-stabilized ylides (**31**) were found to rearrange to enol ethers (**32**) in refluxing water.



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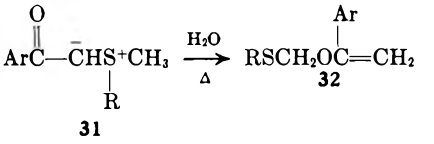

31 32

In the case of **5**, refluxing in aqueous solution resulted principally in hydrolysis to benzoic acid, but traces of oxathiole could be detected by nmr.

A survey of the literature revealed no previous examples of 1,3-oxathiole 3-oxides. Several examples of this ring system at the sulfide and sulfone oxidation stages have been reported.[14] Several attempts were made to oxidize **25** using peracetic acid, hydrogen peroxide, sodium metaperiodate, 1-chlorobenzotriazole,[15] and Collins reagent.[16] The media of the first three attempts were acidic, and under these conditions the oxathiole ring decomposed The Collins procedure yielded some recovered starting material, but an nmr of the crude product showed no peaks which might be assigned to the sulfone. The nmr of the crude product from the attempted oxidation with 1-chlorobenzotriazole in methanol indicated that Cl and MeO had added across the double bond. Sodium borohydride will reduce alkoxysulfonium salts to sulfides.[17] However, several attempts to prepare the methoxysulfonium salt of the

(11) R. G. D. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).

(12) C. R. Johnson and W. G. Phillips, *ibid.*, **91**, 682 (1969).

(13) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **33**, 70 (1968).

(14) (a) K. Dickore, *Justus Liebigs Ann Chem.*, **671**, 139 (1964); (b) K. Nozaki, M. Yakaku, and Y. Hayashi, *Tetrahedron Lett.*, 2303 (1967); (c) G. Ottmann, G. D. Vickers, and H. Hooks, *J. Heterocycl. Chem.*, **4**, 527 (1967); (d) K. Hirai, *Tetrahedron Lett.*, 1137 (1971); (e) W. Drenth and H. J. DeGruitjen, *Recl. Trav. Chim. Pays-Bas*, **89**, 379 (1970).

(15) W. D. Kingsbury and C. R. Johnson, *Chem. Commun.*, 365 (1969).

(16) (a) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); (b) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4000 (1970).

(17) C. R. Johnson and W. G. Phillips, *ibid.*, **32**, 3233 (1967).

oxathiole failed because trace amounts of acid present in the alkylating agents catalyzed the decomposition of the ring.

Experimental Section[18]

(Diethylamino)methyloxosulfonium (*N*-Phenylcarbamoyl)-methylide (4).—The ylide 2[3] (9.7 mmol) in 20 ml of THF was cooled in an ice bath and 1.0 g (8.4 mmol) of phenyl isocyanate was added in 5 ml of THF. The reaction was allowed to warm to room temperature and stir for 24 hr. The solvent was evaporated at reduced pressure and the residue was stirred with methylene chloride. The salts were filtered off and the methylene chloride was evaporated.[19] The crude product was chromatographed over a short column of alumina eluting with 50:50 benzene–chloroform to give 1.85 g (83%) of 4 as a crystalline solid: mp 114° (benzene–pentane); ir ($CHCl_3$) 3420, 1630, 1580, 1320 cm^{-1}; nmr ($CDCl_3$) δ 7.7–7.0 (m, 6, aryl and NH), 3.8 (s, 1, CH), 3.65–3.2 (q, 4, NCH_2), 3.31 (s, 3, SCH_3), 1.45–1.05 (t, 6, CH_3).

Anal. Calcd for $C_{13}H_{20}N_2O_2S$: C, 58.18; H, 7.51. Found: C, 58.45; H, 7.72.

(Dimethylamino)methyloxosulfonium (*N*-Phenylcarbamoyl)-methylide (6).—The ylide 1 (18.5 mol) in 30 ml of THF was cooled in an ice bath and 2.0 g (0.0168 mol) of phenyl isocyanate in 10 ml of THF was added over a period of 30 min. The crude product[19] was a crystalline solid, and recrystallization from benzene–pentane gave 3.1 g (75%) of 6: mp 146–147°; ir ($CHCl_3$) 3430, 1630, 1590 cm^{-1}; nmr ($CDCl_3$) δ 7.9–6.8 (m, 6, aryl and NH), 3.64 (s, 1, CH), 3.28 (s, 3, SCH_3), 2.88 (s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71. Found: C, 55.03; H, 6.99.

(Diethylamino)methyloxosulfonium Benzoylmethylide (3).—The ylide 2 (0.044 mol) in 100 ml of THF in a 250-ml three-necked flask equipped with a mechanical stirrer was cooled in an ice bath and 4.52 g (0.02 mol) of benzoic anhydride in 30 ml of THF was added over the period of 1 hr. The reaction was allowed to warm to room temperature and stirred for 4 hr. The crude product[19] was stirred with 500 ml of ether, which was decanted from a small amount of insoluble material and reduced to ½ its volume, and on cooling 2.7 g (53%) of a crystalline solid, mp 90.5–91°, was obtained: ir ($CHCl_3$) 1590, 1550, 1370 cm^{-1}; nmr ($CDCl_3$) δ 8.0–7.2 (2 m, 5, aryl), 4.9 (s, 1, CH), 3.6–3.15 (q, 4, NCH_2), 3.54 (s, 3, SCH_3), 1.35–1.05 (t, 6, CCH_3).

Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56. Found: C, 61.68; H, 7.64.

The ylide 3 was also prepared from 2 (15 mmol) and benzoyl chloride (7 mmol) in THF at 0°. The product (66% as a yellow oil) had spectral properties identical with those of 3 (above) and could be obtained in crystalline form from ether–pentane.

(Dimethylamino)methyloxosulfonium Benzoylmethylide (5).—The ylide 1 in 120 ml of THF was cooled in an ice bath and 8.0 g (0.0592 mol) of benzoyl chloride in 20 ml of THF was added over the period of 30 min. The reaction was allowed to warm to room temperature and was stirred for a total of 5 hr. The crude product[19] was stirred with 1 l. of ether, which was decanted from a small amount of insoluble material, and then reduced to ½ its volume. On cooling, 8.0 g (60%) of a crystalline solid, mp 80–81°, was obtained: ir ($CHCl_3$) 1585, 1540, 1370 cm^{-1}; nmr ($CDCl_3$) δ 8.0–7.2 (2 m, 5, aryl), 4.83 (s, 1, CH), 3.44 (s, 3, SCH_3), 2.77 (s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71. Found: C, 58.62; H, 6.93.

(Dimethylamino)methyloxosulfonium Acetylmethylide (7).—The ylide 1 (65 mmol) in 80 ml of THF was cooled in an ice bath and 3 g (0.0296 mol) of acetic anhydride in 20 ml of THF was added over the period of 1 hr. The crude product[19] was stirred with 300 ml of ether which was decanted from a small amount of insoluble material and then on cooling yielded 3.2 g (65%) of crystalline product: mp 46–46.5°; ir ($CHCl_3$) 1575, 1375 cm^{-1}; nmr ($CDCl_3$) δ 4.52 (s, 1, CH), 3.4 (s, 3, SCH_3), 2.92 (s, 6, NCH_3), 1.97 (s, 3, CCH_3).

Anal. Calcd for $C_6H_{13}NO_2S$: C, 44.15; H, 8.03. Found: C, 43.87; H, 8.31.

The ylide 1 was also treated with acetyl chloride. The crude product was chromatographed over alumina eluting first with methylene chloride and then chloroform to give 58% of a yellow oil which gave spectra identical with those of ylide 7 (above). The use of acetic anhydride is preferred, since it seems to give a cleaner product.

(Dimethylamino)methyloxosulfonium *p*-Chlorobenzoylmethylide (8).—The ylide 1 (68.5 mmol) in 80 ml of THF was cooled in an ice bath and *p*-chlorobenzoyl chloride (5.4 g, 31 mmol) in 20 ml of THF was added over a period of 30 min. The reaction was stirred for 6 hr at 0° and then allowed to warm to room temperature overnight. The crude product[19] was dissolved in 200 ml of ether, filtered, and cooled to give, with periodic additions of pentane, 5.2 g (65%) of a crystalline solid: mp 61–62°; ir (KBr) 1590, 1545, 1390, 1350, 1170, 1070, and 835 cm^{-1}; nmr ($CDCl_3$) δ 7.9–7.3 (q, 4, aryl), 4.85 (s, 1, CH), 3.54 (s, 3, SCH_3), 2.99 (s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{14}ClNO_2S$: C, 50.86; H, 5.43. Found: C, 50.67; H, 5.55.

(Dimethylamino)methyloxosulfonium *p*-Nitrobenzoylmethylide (9).—The ylide 1 was treated with *p*-nitrobenzoyl chloride in the manner described above for 8. The crude product was recrystallized from benzene–pentane to give 82% of a yellow solid: mp 108–109.5°; ir (KBr) 1550, 1520, 1340, 1170, 1080, and 890 cm^{-1}; nmr ($CDCl_3$) δ 8.2–7.8 (q, 4, aryl), 4.9 (s, 1, CH), 3.6 (s 3, SCH_3), 2.95 (s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 522. Found, C. 48.67; H, 5.34.

(Dimethylamino)methyloxosulfonium Trifluoroacetylmethylide (10).—The 1 (68.5 mmol) was treated with trifluoroacetic anhydride (30 mmol). The crude product was dissolved in ether and on cooling and the addition of pentane 1.9 g (31%) of 10 as a crystalline solid, mp 41.5–43°, was obtained: ir (KBr) 1600, 1250, 1180, 1090, 935, and 890 cm^{-1}; nmr ($CDCl_3$) δ 4.8 (s, 1, CH), 3.54 (s, 3, SCH_3), 3.0 (s, 6, NCH_3).

Anal. Calcd for $C_6H_{10}F_3NO_2S$: C, 33.18; H, 4.64. Found: C, 33.07; H, 4.71.

(Dimethylamino)methyloxosulfonium Phenacetylmethylide (11).—A solution of the ylide 1 (68.5 mmol) was treated with phenylacetyl chloride (4.8 g, 31 mmol) at 0°. The crude product[19] was taken up in ether and with periodic additions of pentane 3.8 g (52%) of a crystalline solid, mp 60–61°, was obtained: ir (KBr) 1570, 1370, 1180, 1090, and 930 cm^{-1}; nmr ($CDCl_3$) δ 7.3 (s, 5, aryl), 4.1 (s, 1, CH), 3.48 (s, 2, CH_2), 3.37 (s, 3, SCH_3), 2.82 (s, 6, NCH_3).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.44; H, 7.16.

(Dimethylamino)methyloxosulfonium Methanesulfonylmethylide (12).—A solution of the ylide 1 in 80 ml of THF solution was cooled in an ice bath, and 2.6 g (0.226 mol) of methanesulfonyl chloride in 15 ml of THF was added. The reaction was allowed to stir at 0° for 5 hr and then warmed to room temperature overnight. A crystalline solid (2.6 g, 58%), mp 80.5–81.5°, was obtained from benzene–pentane: ir (KBr) 1280, 1200, 1110, 1020, and 950 cm^{-1}; nmr ($CDCl_3$) δ 3.83 (s, 1, CH), 3.18 (s, 3, SCH_3), 3.08 (s, SO_2CH_3), 3.0 (s, 6, NCH_3).

Anal. Calcd for $C_5H_{13}NO_3S_2$: C, 30.13; H, 6.58. Found: C, 30.34; H, 6.82.

(Diethylamino)methyloxosulfonium (3-Carboethoxy-2-phenyl)-allylide (13).—The ylide 2 in 10 ml of THF was cooled to 0° and ethyl phenylpropiolate (1.0 g, 5.6 mmol) in 4 ml of THF was added over a period of 10 min. The reaction mixture was stirred overnight. The crude product[19] was chromatographed on silica gel eluting first with benzene and then with chloroform to give 0.720 g (38%) of a yellow oil. A crystalline solid, mp 98–99°, was obtained from chloroform–hexane: ir ($CHCl_3$) 1665, 1520, 1150, 1100, 995 cm^{-1}; nmr ($CDCl_3$) δ 7.67–7.15 (m, 5, aryl), 5.93 (s, 1, CH), 4.82 (s, 1, CH), 4.4–3.97 (q, 2, OCH_2), 3.43–2.75 (m, 4, NCH_2), 1.46–1.08 (t, 3, CH_3), 0.96–0.70 (t, 6, CH_3).

Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.97. Found: C, 63.47; H, 7.95.

(Dimethylamino)methyloxosulfonium (3-Carboethoxy-2-phenyl)allylide (14).—The ylide 1 was treated with ethyl phenylpropiolate. Recrystallization from ether–pentane yielded 55% of a solid: mp 89–91°; ir ($CHCl_3$) 1650, 1525, 1240 cm^{-1}; nmr ($CDCl_3$) δ 7.6–7.16 (m, 5, aryl), 5.8 (s, 1, CH), 4.78 (s, 1, CH), 4.34–3.92 (q, 2, OCH_2), 2.94 (s, 3, SCH_3), 1.4–1.1 (t, 3, CH_3).

Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.16. Found: C, 60.97; H, 7.08.

Reaction of Ylide 5 with Triethyloxonium Fluoroborate.—A solution of 3.0 g (13.3 mmol) of the benzoyl-stabilized ylide 5

(18) For general details see Experimental Section of ref 3.

(19) In the preparation of stabilized ylides, all of the crude products were isolated in the manner described for 4.

was dissolved in 100 ml of methylene chloride and stirred in an ice bath under a cover of nitrogen. Triethyloxonium fluoroborate (7.5 g, 0.037 mol) was added and the reaction was allowed to stir. After 30 min, tlc indicated that some starting material was present. The reaction was kept alkaline by the addition of 4.0 g (0.037 mol) of sodium carbonate. One hour later, 2.5 g of triethyloxonium fluoroborate was added, and the reaction was allowed to stir for 3 hr. The reaction mixture was poured into 100 ml of water, which was extracted with 250 ml of methylene chloride. The methylene chloride was dried and removed at reduced pressure to give 4.1 g (90%) of crude product. A mixture of two isomers was obtained from this reaction, but the ratio of the two isomers varied from reaction to reaction. These two isomers could be separated by fractional crystallization, and on the basis of nmr spectra, structural assignments were made. (*Z*)-(Dimethylamino)methyl(2-ethoxy-2-phenylvinyl)oxosulfonium fluoroborate (**15-*Z***) had mp 108.5–110°; ir (Nujol) 1705 (w), 1690 (w), 1650 (s), 1140–1020 cm^{-1} (BF_4^-); nmr ($CDCl_3$) δ 7.5 (s, 5, aryl), 6.18 (s, 1, vinyl), 4.64–4.18 (q, 2, CH_2), 3.5 (s, 3, SCH_3), 2.8 (s, 6, NCH_3), 1.66–1.30 (t, 3, CH_3).

Anal. Calcd for $C_{13}H_{20}BF_4NO_2S$: C, 45.77; H, 5.91. Found: C, 45.54; H, 6.13.

(*E*)-(Dimethylamino)methyl(2-ethoxy-2-phenylvinyl)oxosulfonium fluoroborate (**15-*E***) had mp 63–64°; ir (Nujol) 1700 (w), 1690 (m), 1655 (m), 1140–1020 cm^{-1} (BF_4^-); nmr ($CDCl_3$) δ 7.6 (s, 5, aryl), 5.94 (s, 1, vinyl), 4.4–4.0 (q, 2, CH_2), 3.77 (s, 3, SCH_3), 3.12 (s, 6, NCH_3), 1.58–1.07 (t, 3, CH_3).

Anal. Calcd for $C_{13}H_{20}BF_4NO_2S$: C, 45.77; H, 5.91. Found: C, 46.01; H, 5.95.

Reaction of Ylide 5 with Trimethyloxonium Fluoroborate.—Ylide **5** was treated with trimethyloxonium fluoroborate in a manner similar to that described above using triethyloxonium fluoroborate to give 1.25 g (85%) of a mixture of two vinyl ether fluoroborate salts. This mixture could not be separated, but it was possible on the basis of later work to assign a structure to each isomer. (*Z*)-(Dimethylamino)methyl(2-methoxy-2-phenylvinyl)oxosulfonium fluoroborate (**16*Z***) had nmr ($CDCl_3$) δ 7.5 (s, 5, aryl), 6.24 (s, 1, vinyl), 4.17 (s, 3, OCH_3), 3.57 (s, 3, SCH_3), 2.74 (s, 6, NCH_3).

(*E*)-(Dimethylamino)methyl(2-methoxy-2-phenylvinyl)oxosulfonium fluoroborate (**16-*E***) had nmr ($CDCl_3$) δ 7.53 (s, 5, aryl), 5.93 (s, 1, vinyl), 3.95 (s, 3, OCH_3), 3.78 (s, 3, SCH_3), 3.1 (s, 6, NCH_3).

Anal. (as mixture) Calcd for $C_{12}H_{18}BF_4NO_2$: C, 44.06; H, 5.54. Found: C, 43.82; H, 5.50.

Reaction of Ylide 7 with Triethyloxonium Fluoroborate.—A mixture (50% yield) of two isomeric vinyl ether fluoroborate salts was obtained. This mixture could never be completely separated, but on the basis of the nmr spectrum, structural assignments could be made. (*Z*)-(Dimethylamino)methyl(2-ethoxy-2-methylvinyl)oxosulfonium fluoroborate (**17-*Z***) had nmr ($CDCl_3$) δ 5.77 (s, 1, vinyl), 4.64–4.27 (q, 2, OCH_2), 3.60 (s, 3, SCH_3), 3.07 (s, 6, NCH_3), 2.32 (s, 3, CCH_3), 1.6–1.3 (t, 3, CH_2CH_3).

(*E*)-(Dimethylamino)methyl(2-ethoxy-2-methylvinyl)oxosulfonium fluoroborate (**17-*E***) had nmr ($CDCl_3$) δ 5.98 (s, 1, vinyl), 4.4–4.0 (q, 2, OCH_2), 3.62 (s, 3, SCH_3), 3.10 (s, 6, NCH_3) 2.32 (s, 3, CCH_3), 1.6–1.3 (t, 3, CH_2CH_3). The mixture was converted to the tetraphenylborate salt by exchange with sodium tetraphenylborate.

Anal. (as mixture of monohydrated tetraphenylborate salts). Calcd for $C_{32}H_{40}BNO_3S$: C, 72.58; H, 7.61. Found: C, 72.56; H, 7.87.

Reaction of Ylide 7 with Trimethyloxonium Fluoroborate.—The components of this mixture could never be completely separated. (*Z*)-(Dimethylamino)methyl(2-methoxy-2-methylvinyl)oxosulfonium fluoroborate (**18-*Z***) had nmr ($CDCl_3$) δ 5.67 (s, 1, vinyl), 4.04 (s, 3, OCH_3), 3.60 (s, 3, SCH_3), 3.04 (s, 6, NCH_3), 2.32 (s, 1, CCH_3). (*E*)-(Dimethylamino)methyl(2-methoxy-2-methylvinyl)oxosulfonium fluoroborate (**18-*E***) had nmr ($CDCl_3$) δ 5.94 (s, 1, vinyl), 3.97 (s, 3, OCH_3), 3.64 (s, 3, SCH_3), 3.10 (s, 6, NCH_3), 2.32 (s, 3, CCH_3).

Anal. (as mixture of tetraphenylboroate salts). Calcd for $C_{31}H_{36}BNO_2S$: C, 74.84; H, 7.29. Found: C, 74.36; H, 7.44.

(Dimethylamino)methyloxosulfonium (3,3-Dicyano-2-phenyl)allylide (19).—A solution of 100 mg (1.47 mmol) of malononitrile was stirred in 7 ml of methanol under a cover of nitrogen; 1.5 ml (1.5 mmol) of 1 *M* sodium methoxide was added. Over a period of 10 min, 480 mg (1.46 mmol) of salt **16** dissolved in 10 ml of methanol was added. The reaction mixture was allowed to stir at room temperature for 5 hr, and then was worked up by pouring it into water and extracting with methylene chloride. The methylene chloride was dried and evaporated to give 390 mg of crude product. The ylide **19** (300 mg, 75%) as a crystalline solid, mp 180–184° dec, was obtained from methylene chloride–pentane: ir ($CHCl_3$) 2200, 1460, 1430, 980, 830 cm^{-1}; nmr ($CDCl_3$) δ 7.43 (s, 5, aryl), 5.0 (s, 1, CH), 3.48 (s, 3, SCH_3), 2.58 (s, 6, NCH_3).

Anal. Calcd for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53. Found: C, 61.25; H, 5.67.

(Dimethylamino)methyloxosulfonium (3,3-Dicyano-2-methyl)allylide (20).—In a similar manner malononitrile anion and salt **17** gave **20** (59%): mp 146–147°; ir ($CHCl_3$) 2170, 1480, 990 cm^{-1}; nmr ($CDCl_3$) δ 4.74 (s, 1, CH); 3.11 (s, 3, SCH_3), 2.97 (s, 6, NCH_3), 2.3 (s, 3, CCH_3).

Anal. Calcd for $C_9H_{13}N_3OS$: C, 51.16; H, 6.20. Found: C, 50.94; H, 6.34.

(Dimethylamino)methyloxosulfonium (3-Carbomethoxy-3-cyano-2-phenyl)allylide.—A solution of 150 mg (1.5 mmol) of methyl cyanoacetate was stirred in 10 ml of methanol with 1.6 mmol of sodium methoxide. The vinyl salt **15** (500 mg, 1.5 mmol) was dissolved in 3 ml of methanol and added. The reaction mixture immediately darkened and was allowed to stir at room temperature for 24 hr. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride was dried and evaporated. The residue was taken up in a small amount of methylene chloride and 140 mg (30%) of a crystalline solid, mp 205–206°, was obtained following the addition of pentane: ir (KBr) 2200, 1660, 1450, and 1120 cm^{-1}; nmr ($CDCl_3$) δ 7.45 (s, 5, aryl), 6.6 (s, 1, CH), 3.85 (s, 3, OCH_3), 3.0 (s, 3, SCH_3), 2.6 (s, 6, NCH_3).

Equilibration of Salts 15-*Z* and 15-*E*.—A solution of 100 mg (0.294 mmol) of pure **15-*E*** was stirred in 5 ml of methylene chloride with 100 mg (0.95 mmol) of sodium carbonate at room temperature for 5 days. The reaction mixture was poured into water and extracted with methylene chloride. Nmr analysis of the product indicated that 32% of the product was **15-*E*** and 68% was **15-*Z***. When a pure sample of **15-*Z*** was subjected to similar equilibrating conditions, an identical product mixture was obtained.

Equilibration of Other Salts.—In a manner similar to that described above for **15** the equilibrium composition for other salts were found to be as follows: **16**, 27% *E* and 73% *Z*; **17**, 88% *E* and 12% *Z*; **18**, 90% *E* and 10% *Z*.

5-Phenyl-1,3-oxathiole 3-Oxide (25).—Anhydrous cupric sulfate (2.8 g, 0.0175 mol) was added to a solution of 2.0 g (8.9 mmol) of the benzoyl-stabilized ylide **5** in 60 ml of benzene. The reaction mixture was stirred at 80° for 30 hr. The copper salts were filtered off and washed with 75 ml of methylene chloride. The solvent was evaporated and 1.34 g (84%) of **25** as a crystalline solid, mp 108–109°, was obtained from benzene–pentane: ir (KBr) 1605, 1565, 1060, and 1020 cm^{-1} (s); nmr ($CDCl_3$) δ 8.0–7.3 (m, 5, aryl), 6.75 (s, 1, vinyl), 5.63 (d, 1, J = 11 Hz, CHSO), 5.1 (d, 1, J = 11 Hz, CHSO).

Anal. Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47. Found: C, 59.71; H, 4.58.

5-*p*-Chlorophenyl-1,3-oxathiole 3-Oxide (26).—The *p*-chlorobenzoyl stabilized ylide **8**, 1.0 g (3.85 mmol), was stirred with 1.23 g (7.7 mmol) of anhydrous cupric sulfate in 50 ml of toluene at 110° for 30 hr. At this time the copper salts were filtered off and washed with 100 ml of dichloromethane. The solvent was evaporated to give 0.69 g (80%) of **26** as a crystalline solid: mp 122–123° (benzene–pentane); ir (KBr) 1590, 1550, 1470, 1390, 1320, and 1070–1020 cm^{-1} (s); nmr ($CDCl_3$) δ 7.9–7.3 (q, 4, aryl), 6.65 (s, 1, vinyl), 5.54 (d, 1, J = 12 Hz, CHSO), 5.0 (d, 1, J = 12 Hz, CHSO).

Anal. Calcd for $C_9H_7ClO_2S$: C, 50.36; H, 3.29. Found: C, 50.59; H, 3.52.

5-*p*-Nitrophenyl-1,3-oxathiole 3-Oxide (27).—A solution of 1.0 g (3.7 mmol) of the *p*-nitrobenzoyl stabilized ylide **9** in 50 ml of toluene was stirred with 1.2 g (7.4 mmol) of anhydrous cupric sulfate. After 30 hr at 110° the copper salts were filtered off and washed with 100 ml of methylene chloride. The solvent was evaporated and 0.66 g (79%) of **27** was obtained as a crystalline solid: mp 169–170° (methylene chloride–pentane); ir (KBr) 1580, 1540, 1340, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 8.5–7.8 (q, 4, aryl), 6.95 (s, 1, vinyl), 5.65 (d, 1, J = 11 Hz, CHSO), 5.10 (d, 1, J = 11 Hz, CHSO).

Anal. Calcd for $C_9H_7NO_4S$: C, 48.00; H, 3.13. Found: C, 48.29; H, 3.33.

5-Methyl-1,3-oxathiole 3-Oxide (**28**).—A solution of 0.5 g (3.06 mmol) of the acetyl-stabilized ylide **7** was stirred with 0.98 g (6 mmol) of anhydrous copper sulfate at 70° for 36 hr. The insoluble salts were filtered off and washed with methylene chloride to give 300 mg (80%) of **28**: ir (film) 1620, 1050–1030 cm^{-1}; nmr ($CDCl_3$) δ 6.05 (s, 1, vinyl), 5.35 (d, 1, J = 12 Hz, CHSO), 4.9 (d, 1, J = 12 Hz, CHSO), 2.2 (s, 3, CH_3). This product displayed a mass spectrum in accord with the assigned structure.

Registry No.—**1**, 38709-75-0; **2**, 38421-38-4; **3**, 38709-77-2; **4**, 38709-78-3; **5**, 38709-79-4; **6**, 38709-80-7; **7**, 38709-81-8; **8**, 38709-82-9; **9**, 38709-83-0; **10**, 38709-84-1; **11**, 38709-85-2; **12**, 38709-87-4; **13**, 38709-88-5; **14**, 38709-89-6; **15**-*Z*, 38708-52-0; **15**-*E*, 38708-53-1; **16**-*Z*, 38708-54-2; **16**-*E*, 38708-55-3; **17**-*Z*, 38780-33-5; **17**-*E*, 38708-56-4; **17**-*Z* tetraphenylborate salt, 38811-40-4; **17**-*E* tetraphenylborate salt, 38704-60-8; **18**-*Z*, 38708-57-5; **18**-*E*, 38708-58-6; **18**-*Z* tetraphenylborate salt, 38704-61-9; **18**-*E* tetraphenylborate salt, 38704-62-0; **19**, 38709-90-9; **20**, 38709-91-0; **25**, 38709-92-1; **26**, 38709-93-2; **27**, 38709-94-3; **28**, 38709-95-4; **29**, 38709-96-5; phenyl isocyanate, 103-71-9; benzoic anhydride, 93-97-0; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; *p*-chlorobenzoyl chloride, 122-01-0; trifluoroacetic anhydride, 407-25-0; phenylacetyl chloride, 103-80-0; methanesulfonyl chloride, 124-63-0; ethyl phenylpropiolate, 2216-94-6; triethyloxonium tetrafluoroborate, 368-39-8; trimethyloxonium tetrafluoroborate, 420-37-1; sodium tetraphenylborate, 143-66-8; (dimethylamino)methyloxosulfonium (3-cyano-3-carbomethoxy-2-phenyl)allylide, 38709-99-8.

Conformationally Rigid Organosulfur Molecules. Derivatives of 4-Thiatricyclo[4.2.1.$0^{3,7}$]nonane and 4-Thiatricyclo[4.3.1.$0^{3,7}$]decane[1]

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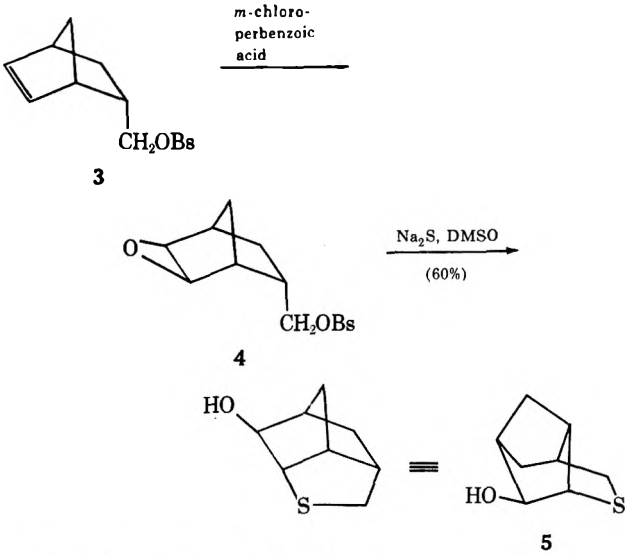
The reaction of sodium sulfide with the epoxy brosylates **4** and **12** provided *exo*-2-hydroxy-4-thiatricyclo[4.2.1.$0^{3,7}$]nonane (**5**) and *exo*-2-hydroxy-4-thiatricyclo[4.3.1.$0^{3,7}$]decane (**13**), respectively. Compound **5** has been oxidized to the corresponding hydroxy sulfone **14**, to sulfoxides **15a** and **15b**, and to keto sulfide **17**. Reduction of the latter compound with sodium borohydride gave the endo hydroxy sulfide **16**. Reduction of **17** by hydrazine and base yielded sulfide **18**. Compound **13** was converted to the keto sulfide **19**, which upon reduction with sodium borohydride gave the epimeric alcohol **20**.

Conformationally rigid organosulfur molecules provide substrates which are useful in studies pertaining to stereochemistry and intramolecular interactions.[2,3] Examples of systems presently available for such studies are sulfides **1**[4] and **2**.[5] We now report several additions, namely *exo*-2-hydroxy-4-thiatricyclo[4.2.1.$0^{3,7}$]nonane (**5**) and *exo*-2-hydroxy-4-thiatricyclo[4.3.1.$0^{3,7}$]decane (**13**) along with several derivatives.

1 **2**

The synthesis of compound **5** is outlined in Scheme I. The reaction of sodium sulfide with epoxy brosylate **4** is thought to lead to intermediate **6** by initial displacement of the brosyl group. This postulate is supported by experiments of Gray and Heitmeier,[6] which demonstrated that exo norbornyl epoxides are resistant to opening on treatment with lithium aluminum hydride. From intermediate **6** C–O cleavage could occur at either C_2 or C_4, leading to either sulfide alcohol **5** or **7**, respectively. Studies of Dreiding models indicated that attack at C_2 would involve more strain than attack at C_4; therefore, *a priori*, sulfide alcohol **5** was expected to be the product of this reaction. In fact, a stable, waxy solid was obtained in 60% yield, which, upon acetylation followed by desulfurization, afforded *exo*-2-acetoxy-5-*endo*-methylbicyclo[2.2.1]heptane (**8**). Sulfide alcohol **7** would have led to *exo*-2-acetoxy-*endo*-6-methylbicyclo[2.2.1]heptane (**9**).

SCHEME I
SYNTHESIS OF
exo-2-HYDROXY-4-THIATRICYCLO[4.2.1.$0^{3,7}$]NONANE (**5**)[a]



[a] Bs = *p*-bromobenzenesulfonyl.

(1) Part XLI in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 19623).

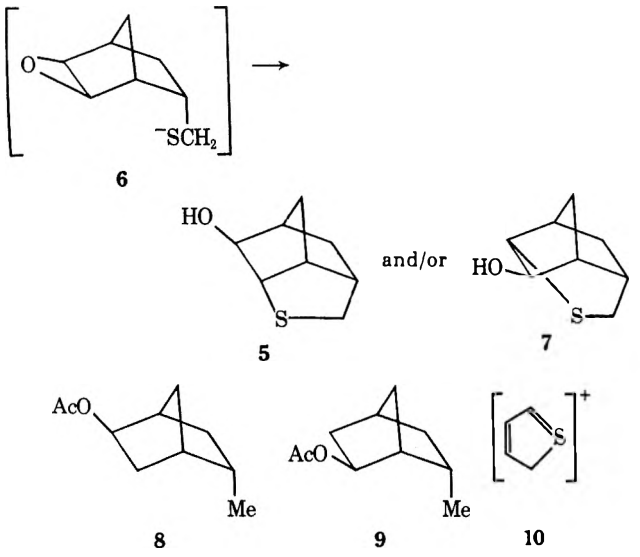
(2) For reviews of this subject, see N. J. Leonard, *Rec. Chem. Progr.*, **17**, 24, (1956); L. N. Ferguson and J. C. Nadi, *J. Chem. Educ.*, **42**, 529 (1965).

(3) L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **89**, 6659 (1967); L. A. Paquette, G. V. Meehan, and L. D. Wise, *ibid.*, **91**, 3231 (1969).

(4) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1662 (1966).

(5) C. R. Johnson, J. E. Keiser, and J. C. Sharp, *ibid.*, **34**, 860 (1969).

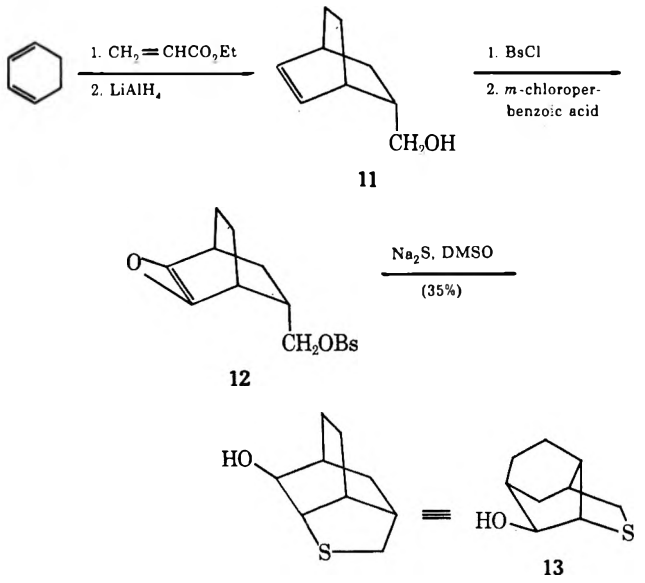
(6) A. Gray and D. Heitmeier, *ibid.*, **34**, 3253 (1969).



Further evidence supporting structure **5** was furnished by mass spectral data. A strong ion (52%) at *m/e* 85 assumed to be **10** indicates that the sulfur is bound in a five-membered ring, whereas the sulfur atom is contained in a six-membered ring, and would not be expected to fragment in such a way that would produce the *m/e* 85 ion.[7]

The preparation of compound **13** is outlined in Scheme II. Treatment of epoxy brosylate **12** with

Scheme II
Preparation of
exo-2-Hydroxy-4-thiatricyclo[4.3.1.0^{3,7}]decane (**13**)



sodium sulfide also furnished a waxy, crystalline solid (35%). The ir and nmr spectra were very similar to those of **5** and the mass spectrum displayed an intense ion (51%) at *m/e* 85. Similar ring closures involving nucleophilic attack by carbon,[8] oxygen,[9a] or nitrogen[9b] produced products corresponding to "frontal" closure.

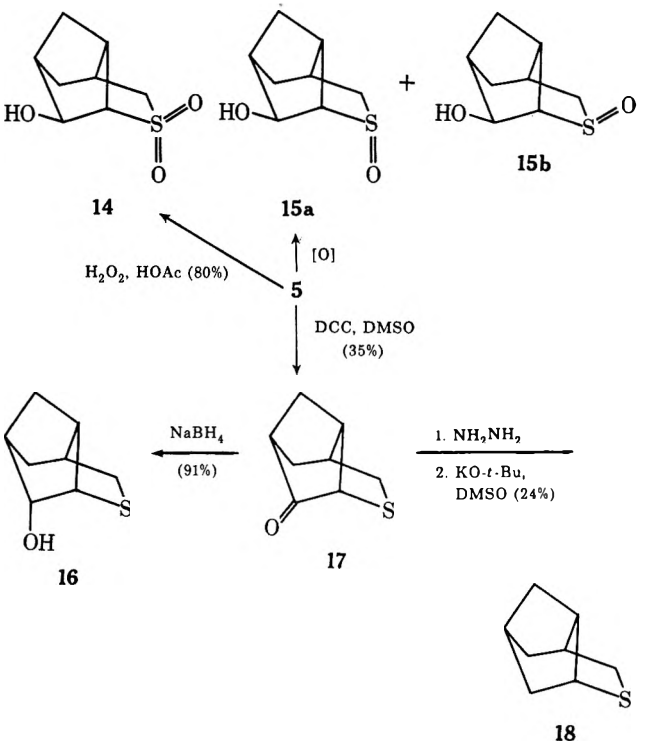
(7) For another example see C. R. Johnson and F. Billman, *J. Org. Chem.*, **36**, 855 (1971).

(8) R. R. Sauers, R. A. Parrent, and S. B. Demale, *J. Amer. Chem. Soc.*, **88**, 2257 (1966); R. R. Sauers, R. M. Hawthorne, and B. I. Dentz, *J. Org. Chem.*, **32**, 4071 (1967).

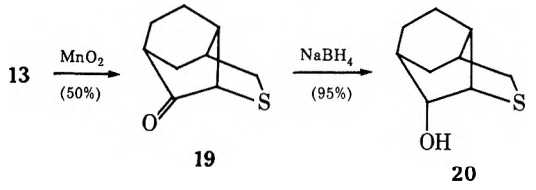
(9) (a) P. O. Hoch, G. Stratton, and J. Coulson, *ibid.*, **34**, 1912 (1969); (b) R. E. Banks, L. E. Birks, and R. N. Haszeldine, *J. Chem. Soc. C*, 201 (1970).

Summaries of chemical transformations achieved starting with the target compounds **5** and **13** are found in Schemes III and IV, respectively.

Scheme III
Transformations of Compound **5**



Scheme IV
Transformations of Compound **13**



The oxidation of **5** to sulfone **14** was found to proceed readily with hydrogen peroxide in acetic acid. The use of other reagents, such as *m*-chloroperbenzoic acid, ozone, or hydrogen peroxide in acetone, resulted in incomplete oxidation, yielding mixtures of sulfoxides and sulfone. Sulfide alcohol **5** was oxidized to an isomeric mixture of sulfoxide alcohols **15** by treatment with a variety of oxidizing agents (see Experimental Section). Separation of this isomeric mixture into the endo (**15a**) and exo (**15b**) isomers was accomplished by preparative gas chromatography after prior silyation[10] of the hydroxyl group; all attempts to separate these isomers by tlc or elution chromatography failed. The stereochemical assignments were made on the basis of the syn-axial effect,[11] which summarily states that, if a pair of isomeric sulfoxides exists in which a proton is syn-axial with the electron pair in one isomer and with the SO bond in the other isomer, the proton that is syn

(10) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(11) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 759 (1966); A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 881 (1967); A. B. Foster, T. D. Inch, H. M. Qadir, and J. M. Webber, *ibid.*, 1086 (1968); C. R. Johnson and W. O. Siegl, *Tetrahedron Lett.*, 1879 (1969).

axial with the SO bond is invariably downfield. Hence, the assignment of stereochemistry of isomeric sulfoxides **15a** and **15b** is possible by observing the chemical shift of the CHOH proton.

The first isomer eluted from glpc, after hydrolysis back to the alcohol sulfoxide, displayed a broadened singlet at δ 4.60 for the CHOH proton. This peak was not affected by sample dilution, eliminating the possible absorption of the hydroxyl proton at this position. The second isomer eluted was found to have the CHOH absorption more upfield and contained under the envelope of ring protons. The chemical shift of the CHOH proton in **5** is δ 3.64. Thus, the first isomer to be eluted is assigned the structure **15a** and the second **15b**. This result could be rationalized by assuming that the exo sulfoxide **15b** would bind to the column more strongly than would **15a** owing to diminished steric hindrance of the exo sulfoxide isomer.[12]

Sulfide ketone **19** was prepared from **13** in moderate yield by treatment with "activated" manganese dioxide[13] in hexane–pentane (1:1, v/v). Conversely, sulfide alcohol **5** was resistant to oxidation by these conditions for reaction times of up to 3 weeks. The problem became one of selective oxidation of the hydroxyl group without concomitant oxidation at sulfur. Jones' reagent and chromium trioxide in pyridine were found to be unsatisfactory. Keto sulfide **17** was prepared in moderate yield (35%), however, by oxidation *via* the Pfitzner–Moffatt method.[14]

Reduction of keto sulfides **17** and **19** furnished exclusively endo-hydroxyl derivatives **16** and **20**. The ir (CCl_4) showed hydroxyl absorption at 3400 cm^{-1} which was not shifted to higher frequency upon dilution. The exo alcohols **5** and **13** each possess two absorptions appearing at 3600 and 3450 cm^{-1}. The 3450-cm^{-1} absorption is found to decrease upon dilution relative to the 3600-cm^{-1} absorption. The alcohol sulfides **16** and **20** are, therefore, assumed to contain fairly strong intramolecular hydrogen bonding to sulfur.

Conversion of the sulfide ketone **17** to sulfide **18** was achieved by reduction *via* the Cram modification of the Wolff–Kishner reduction.[15]

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and were uncorrected. Infrared spectra were measured with a Perkin-Elmer Model 21 grating spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Analytical vapor phase chromatography was performed on an F & M 5750 using 0.25-in. columns. Preparative glpc was conducted on an F & M 776 Prepmaster Jr. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. The mass spectra were measured on Atlas CH4 or AEI MS9 mass spectrometers.

5-(*p*-Bromobenzenesulfonoxymethyl)bicyclo[2.2.1]hept-2-ene (3).—To 50 g (0.40 mol) of a mixture of exo and endo alcohols[16] of 5-(hydroxymethyl)norbornene in an ice bath was added 110 g (0.43 mol) of brosyl chloride. After the solution was stirred at 0° for 0.5 hr the temperature was allowed to rise to room temperature; stirring was continued for 17 hr. The solution was then poured into 2 l. of water previously cooled to 0° and the heterogeneous mixture was stirred for 5 hr. The resulting mixture was extracted with ethyl ether (3 × 250 ml), and the extracts were combined and washed with a 10% aqueous solution of hydrochloric acid (3 × 100 ml) and a saturated sodium bicarbonate solution (3 × 100 ml) and dried ($MgSO_4$). Evaporation of the ether gave a clear oil which crystallized on standing to produce 100 g (73%) of a white solid, mp 62–68°.

Anal. Calcd for $C_{14}H_{15}BrO_3S$: C, 48.98; H, 4.40. Found: C, 49.13; H, 4.62.

6-(*p*-Bromobenzenesulfonoxymethyl)-3-oxatricyclo[3.2.1.0^{2,4}]-octane (4).—A solution of 20 g (0.059 mol) of **3** dissolved in 50 ml of benzene was added dropwise over a 20-min period to 14 g (0.07 mol) of *m*-chloroperbenzoic acid dissolved in 500 ml of benzene and cooled to 0°. The reaction mixture was stirred for 14 hr, during which time the mixture was allowed to warm to room temperature. The reaction mixture was washed with a 10% sodium hydroxide solution and water, and after drying ($MgSO_4$) the solvent was evaporated to give 19.9 g (95.6%) of a white, crystalline solid, mp 89–90°. This material was used without further purification in the following reaction.

***exo*-2-Hydroxy-4-thiatricyclo[4.2.1.0^{3,7}]nonane (5).**—A 2-l. three-necked flask was equipped with a mechanical stirrer and a Y joint to which was connected a condenser and an addition funnel; the remaining neck was fitted with a second addition funnel. Gas inlet–outlet equipment was assembled and the system was purged with nitrogen. Dimethyl sulfoxide (200 ml) was added to the reaction vessel and the solution was heated to 60°. Then 19 g (0.053 mol) of **4** dissolved in 200 ml of dimethyl sulfoxide and 16.8 g (0.07 mol) of sodium sulfide nonahydrate dissolved in dimethyl sulfoxide–water (500:30 ml, v/v) were simultaneously added over a 3-hr period. The reaction was allowed to stir for 24 hr at a temperature between 60 and 70°, after which time the reaction mixture was concentrated to 100 ml, diluted with 500 ml of water, and extracted with methylene chloride (5 × 200 ml), and the combined extracts were washed with water (5 × 200 ml) and dried ($MgSO_4$). Evaporation of the methylene chloride yielded an oily gum which was purified by chromatography over silica gel (0.05–0.20 mm, E. Merck, Darmstadt) using ethyl ether as the eluent. The yield was 4.9 g (60%) of a waxy solid, mp 136–137°. The mass spectrum showed a parent ion at the calculated molecular weight of 156.

Anal. Calcd for $C_8H_{12}OS$: C, 61.49; H, 7.74. Found: C, 61.34; H, 7.64.

***exo*-2-Hydroxy-4-thiatricyclo[4.2.1.0^{3,7}]nonane 4-Oxides (15).**—Oxidation of sulfide **5** with *tert*-butyl hypochlorite[17] in anhydrous methanol at −78° gave a 62% yield of a mixture, mp 182–195°, composed of **15a** (15%) and **15b** (85%). A sample of the mixture was purified for analysis by vacuum sublimation at 110° (0.1 Torr).

Anal. Calcd for $C_8H_{12}O_2S$: C, 55.78; H, 7.02. Found: C, 56.04; H, 7.23.

Oxidation of **5** with sodium metaperiodate[18] in aqueous methanol at 0° gave 44% of a mixture, mp 188–194°, which contained 34% of **15a** and 66% of **15b**. Oxidation of **5** with 1-chlorobenzotriazole[19] in anhydrous methanol at −78° gave 66% of a solid, mp 188–194°, composed of 33% **15a** and 67% **15b**.

Separation of Sulfoxide Isomers 15a and 15b.—The silyl ethers were prepared according to the method of Sweeley, Bentley, Makita, and Wells.[10] Thus, 0.10 g of isomeric sulfoxide mixture **15** was dissolved in 2 ml of dry pyridine to which was added 0.4 ml of hexamethyldisilazane followed by 0.2 ml of trimethylsilyl chloride. A white precipitate immediately formed and was allowed to settle. Injections were made on an F & M Prepmaster Jr. 776 using a 6 ft × 0.75 in. 15% FFAP column operating at 210° with a nitrogen flow rate of 300 ml/min. The first isomer, the trimethylsilyl ether of **15a**, had a retention time of 9 min; the retention time of the second isomer, the trimethylsilyl ether of **15b**, was 16 min. The compound were washed from their traps with methanol and stirred overnight in an aqueous methanolic solution. Extraction with methylene chloride, drying ($MgSO_4$), and evaporation produced 0.01 g of **15a**, mp 205–208°, and 0.04 g of **15b**, mp 198–200°. The ir spectra of each isomer was undistinguishable from the ir spectrum of the isomeric mixture **15**.

***exo*-2-Hydroxy-4-thiatricyclo[4.2.1.0^{3,7}]nonane 4,4-Dioxide (14).**—To 0.312 g (2 mmol) of **5** dissolved in 25 ml of glacial acetic acid was added 1.36 g (12 mmol) of hydrogen peroxide (30%).

(12) W. O. Siegl and C. R. Johnson, *J. Org. Chem.*, **35**, 3657 (1970).

(13) J. Attenburrow, A. F. B. Camerson, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jones, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(14) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965).

(15) D. J. Cram, M. Sayhun, and G. Knox, *ibid.*, **84**, 1734 (1962).

(16) K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938).

(17) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(18) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(19) W. D. Kingsbury and C. R. Johnson, *Chem. Commun.*, 365 (1969).

The reaction mixture was stirred for 12 hr, then diluted with 40 ml of water and extracted with methylene chloride. Evaporation afforded 0.30 g (80%) of a white solid: mp 190–192°; ir ($CHCl_3$) 1300, 1120 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_{12}O_3S$: C, 51.05; H, 6.43. Found: C, 50.85; H, 6.67.

4-Thiatricyclo[4.2.1.0^{3,7}]nonan-2-one (17).—To 0.93 g (4.3 mmol) of dicyclohexylcarbodiimide in a 25-ml round-bottom flask was added a solution of **5** prepared as follows. A 0.174-g (1.1 mmol) portion of **5** was dissolved in 3 ml of dimethyl sulfoxide and added to another solution containing 3 ml of benzene, 0.14 ml of dry pyridine, and 0.06 ml of trifluoroacetic acid. The reaction mixture was stirred for 3 days, after which time 15 ml of benzene was added and the salts were filtered. The benzene solution was thoroughly washed with water and dried ($MgSO_4$). Evaporation of the benzene produced an oil which was purified by chromatography over silica gel (0.05–0.20 mm, E. Merck, Darmstadt) using methylene chloride as the eluent. The resulting white solid, 0.061 g (35%), had mp 128–129°; ir ($CHCl_3$) 1745 cm^{-1} (CO); mass spectrum parent ion at *m/e* 154 (calcd, 154). An analytical sample was prepared by sublimation at 35° (0.05 Torr).

Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54. Found: C, 62.21; H, 6.63.

4-Thiatricyclo[4.2.1.0^{3,7}]nonane (18).—To 0.57 g (3.7 mmol) of sulfide ketone **17** was added 10 ml of 85% hydrazine hydrate and the resulting solution was refluxed for 20 hr. Extraction with ethyl ether, drying ($MgSO_4$), and evaporation of the solvent afforded 0.38 g (61.5%) of the hydrazone as a white solid, mp 84–86°. The ir indicated that all of the ketone had reacted. Without further purification this solid was added to a solution of 1.14 g (7.6 mmol) of potassium *tert*-butoxide in 3 ml of dimethyl sulfoxide over a period of 2 hr.[15] Nitrogen gas was evolved immediately and the solution turned reddish orange. After addition was complete the reaction mixture was allowed to stir for an additional 1 hr; 20 ml of water was added; and the resulting solution was extracted with ethyl ether and dried ($MgSO_4$). Evaporation of the ethyl ether produced a yellow oil from which 0.20 g (39%) of a white solid, mp 109–111°, could be isolated by sublimation (40°, 0.5 mm). High-resolution mass spectroscopy showed the molecular weight to be 140.063736 compared to the calculated molecular weight of 140.065957.

6-(*p*-Bromobenzenesulfonoxymethyl)-3-oxatricyclo[3.2.1.0^{2,4}]nonane (12).—To 54 g (0.389 mol) of the alcohol **11**[20,21] dissolved in 200 ml of pyridine and cooled to 0° was added 110 g (0.43 mol) of brosyl chloride. After the solution was stirred at 0° for 30 min the temperature was allowed to reach room temperature and the reaction mixture was stirred for 17 hr. The solution was then poured into 2 l. of water at 0° and stirred for 5 hr. The resulting heterogeneous mixture was extracted with ethyl ether (3 × 250 ml), and the ether extracts were combined and washed with a 10% hydrochloric acid solution (3 × 100 ml) and a saturated sodium bicarbonate solution (3 × 100 ml), and dried ($MgSO_4$). Evaporation of the ethyl ether afforded 124 g (88.5%) of the brosylate as a white solid, mp 76–77°.

This product was epoxidized using the identical conditions as previously outlined for the epoxidation of **3**. Thus from 20 g (0.056 mol) of the starting brosylate **12**, 20.7 g (97%) of a white solid was isolated, mp 85–90°. This product was used in the following reaction without further purification.

***exo*-2-Hydroxy-4-thiatricyclo[4.3.1.0^{3,7}]decane (13).**—The apparatus was arranged as described in the preparation of **5**. Thus 20.7 g (0.0554 mol) of epoxy brosylate **12** dissolved in 150 ml of dimethyl sulfoxide was treated with 18.0 g (0.075 mol) of sodium sulfide nonahydrate dissolved in dimethyl sulfoxide–water (200:50, v/v) to give 3.0 g (31.6%) of a white solid, mp 165–168°. Sublimation at 110° (0.1 mm) produced an analytical sample. The mass spectrum had a parent ion at *m/e* 170 which corresponds to the calculated molecular weight.

Anal. Calcd for $C_9H_{14}OS$: C, 63.48; H, 8.29. Found: C, 63.30; H, 8.30.

4-Thiatricyclo[4.3.1.0^{3,7}]decan-2-one (19).—To 0.3 g (1.75 mmol) of **13** dissolved in 100 ml of a 1:1 (v/v) pentane–hexane solution was added 6.0 g "active" manganese dioxide[13] and this mixture was allowed to stir for 1 week. The manganese dioxide was then filtered and the hexane–pentane was evaporated, leaving 0.14 g (50%) of a white solid, mp 110–112°, ir ($CHCl_3$) 1710 cm^{-1} (CO). Sublimation (110°, 0.5 Torr) produced an analytical sample. The mass spectrum showed a parent ion at *m/e* 168 (calcd 168).

Anal. Calcd for $C_9H_{12}OS$: C, 64.35; H, 7.19. Found: C, 64.53; H, 7.36.

Sodium Borohydride Reductions of Ketones 17 and 19.—To 1.0 mmol of ketone dissolved in 20 ml of anhydrous methanol cooled to 0° was added 0.038 g (1.0 mmol) of sodium borohydride. Stirring for 12 hr followed by evaporation of the methanol gave a solid which was stirred in methylene chloride for 1 hr and filtered. Evaporation of the methylene chloride afforded a white solid in each case. Compound **16**, mp 181–184°, was produced in 91% yield; compound **20**, mp 171–173°, was obtained in 95% yield.

***exo*-2-Acetoxy-4-thiatricyclo[4.2.1.0^{3,7}]nonane.**—To 0.312 g (2.0 mmol) of **5** dissolved in 6 ml of benzene, 4 ml of hexane, and 0.2 ml of pyridine at 0° was added 0.180 ml (2.7 mmol) of acetyl chloride. This solution was stirred at 0° for 5 hr and then placed in the refrigerator (−5°) overnight. The mixture was then poured over ice–water and stirred for 2 hr. The aqueous solution was extracted with ethyl ether (3 × 50 ml), and the ether extracts were combined and washed with a 10% aqueous hydrochloric acid solution (3 × 20 ml), a saturated aqueous sodium hydrogen carbonate solution (3 × 50 ml), and water (3 × 50 ml) and dried ($MgSO_4$). Evaporation of the ether furnished 0.28 g (90%) of a clear liquid, ir (film) 1740, 1240–1220, 1020, 1000 cm^{-1}. The acetate was used without further purification in the next step.

Desulfurization of Acetate of 5.—To the acetate prepared above was added 10 ml of absolute ethyl alcohol and *ca.* 3 g (one teaspoon) of 5-day-old Raney nickel (W-2). This mixture was stirred for 15 hr and filtered. Evaporation of the ethanol gave 0.12 g (43% based on crude acetate) of a clear liquid. The ir of this liquid is identical with that of authentic *exo*-2-acetoxy-*endo*-5-methylbicyclo[2.2.1]heptane (**8**).[22]

Registry No.—**3**, 4802-32-8; **4**, 38858-17-2; **5**, 38906-64-8; **5** acetate, 38974-09-3; **11**, 15181-03-0; **12**, 38858-19-4; **13**, 38858-20-7; **14**, 38858-21-8; **15a**, 38858-22-9; **15b**, 38858-23-0; **16**, 38858-24-1; **17**, 38868-12-1; **18**, 29625-41-0; **19**, 38868-14-3; **20**, 38858-25-2; *exo*-5-(hydroxymethyl)-2-norbornene, 13360-81-1; *endo*-5-(hydroxymethyl)-2-norbornene, 15507-06-9; *m*-chloroperbenzoic acid, 937-14-4.

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Carbonyl Stretching Frequencies and Transmission of Electronic Effects in 1-Phenyl-3-(5-aryl-2-furyl)propenones and 1-Phenyl-3-(5-aryl-2-thienyl)propenones

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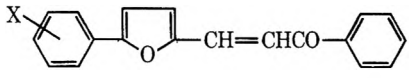
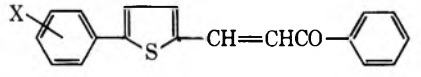
The s-cis and s-trans carbonyl stretching frequencies of a series of *trans*-1-phenyl-3-(5-aryl-2-furyl)propenones (I) and *trans*-1-phenyl-3-(5-aryl-2-thienyl)propenones (II) have been measured in carbon tetrachloride and chloroform solutions. Statistically significant linear free-energy relationships were obtained between ν(C=O) and σ^+ constants; poorer correlations using σ values were obtained in all cases. The data were also treated using the Swain–Lupton F and R constants, and poorer correlations than noted with σ^+ were obtained. The influence of the conformation on the transmission of electronic effects is discussed and compared with that in analogous systems. The parameters of the linear free-energy relationships for series I and II were compared with those for a series of *trans*-1-phenyl-3-arylpropenones (III). Using the slopes of ν(C=O) *vs.* σ^+ correlations in series I–III the transmissive factors for the furan and thiophene rings were calculated and related to data published earlier. The determined order of transmission for the intervening groups was furan > thiophene > benzene.

In preceding work[2-6] we have investigated, using linear free-energy relationships between the carbonyl stretching frequencies and substituent constants, the transmission of electronic effects and the influence of conformation on this transmission in a series of substituted chalcones and other α,β-unsaturated ketones. Furthermore, we used[7-10] the correlations between the carbonyl stretching frequencies and substituent constants for quantitative study of the transmission of electronic effects by the furan and thiophene bridges in several systems.

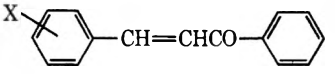
Continuing our investigations of linear free-energy relationships of α,β-unsaturated ketones and of transmission of electronic effects by various intervening groups, we have measured the carbonyl stretching frequencies of a series of *trans*-1-phenyl-3-(5-aryl-2-furyl)propenones (I) and *trans*-1-phenyl-3-(5-aryl-2-thienyl)propenones (II) and compared the results with those for a series of *trans*-1-phenyl-3-arylpropenones (III) (chalcones) reported earlier.[1,2]



I



II



III

Results and Discussion

Carbonyl Stretching Frequencies.—The carbonyl stretching frequencies measured in CCl_4 and $CHCl_3$ solutions for a series of *trans*-1-phenyl-3-(5-aryl-2-furyl)propenones (I) and *trans*-1-phenyl-3-(5-aryl-2-thienyl)propenones (II) are listed in Tables I and II, respectively. The carbonyl region of the spectra of these compounds is similar in shape to that of the analogous region of the spectra of substituted chalcones.[2,3] On the basis of this analogy and the solvent

TABLE I

1-PHENYL-3-(5-ARYL-2-FURYL)PROPENONES (I)[a]

Compd	X	In CCl_4 $\nu_{s\text{-}cis}$	In CCl_4 $\nu_{s\text{-}trans}$	In $CHCl_3$ $\nu_{s\text{-}cis}$
1	4-OCH_3	1666.0	1642.5	1660.0
2	4-CH_3	1667.5	1644.5	1661.0
3	4-H	1668.5	1645.5	1662.0
4	4-Cl	1668.5	1646.5	1662.5
5	4-Br	1669.0	1647.0	1662.5
6	3-Cl	1669.5	1647.0	1663.5
7	3-Br	1670.0	1648.0	1663.5
8	3-NO_2	1670.5	1649.5	1664.0
9	4-NO_2	1671.5	*b*	1665.0

[a] Frequencies are given in cm^{-1}. [b] Not available because of low solubility of compound in CCl_4.

TABLE II

1-PHENYL-3-(5-ARYL-2-THIENYL)PROPENONES (II)[a]

Compd	X	In CCl_4 $\nu_{s\text{-}cis}$	In CCl_4 $\nu_{s\text{-}trans}$	In $CHCl_3$ $\nu_{s\text{-}cis}$	In $CHCl_3$ $\nu_{s\text{-}trans}$
10	4-OCH_3	1664.5	1645.0	1658.0	1633.0
11	4-CH_3	1665.0	1646.0	1658.5	1634.5
12	3-CH_3	1666.0	1647.0	1659.5	1636.0
13	4-H	1666.0	1647.0	1660.0	1636.0
14	4-Cl	1666.5	1647.0	1660.0	1636.5
15	4-Br	1667.0	1647.5	1660.5	1636.5
16	3-Cl	1667.5	1648.0	1661.0	1638.0
17	4-NO_2	1668.0	1649.5	1662.0	1639.0

[a] Frequencies are given in cm^{-1}.

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sensitivity of the bands (see below) we assign the intense, higher frequency band to the C=O stretching mode of the s-cis conformer ($\nu_{s\text{-cis}}$) and the lower frequency band of much weaker intensity to the C=O stretching mode of the s-trans conformer ($\nu_{s\text{-trans}}$) (see Tables I and II). As was the case for chalcones,[2,3,11] the s-cis conformation, as assessed from band intensities, predominates in the equilibrium mixture. Since the s-trans carbonyl stretching frequencies of chalcones measured in $CHCl_3$ have not been reported previously, we include them in Table III for the sake

TABLE III

1-PHENYL-3-ARYLPROPENONES (III) IN $CHCl_3$

Compd	X	$\nu_{s\text{-trans}}$, cm^{-1}
18	4-$N(CH_3)_2$	1627.0
19	4-OCH_3	1635.0
20	4-CH_3	1639.5
21	4-H	1643.5
22	4-F	1643.0
23	4-Cl	1644.0
24	3-Cl	1645.0
25	4-CN	1646.0
26	3-NO_2	1646.0
27	4-NO_2	1648.0

of comparison with data of compounds of series I and II. In the spectra of 1-phenyl-3-(5-aryl-2-thienyl)-propenones (II) in $CHCl_3$ both the $\nu_{s\text{-cis}}$ and $\nu_{s\text{-trans}}$ bands appear. However, in the case of 1-phenyl-3-(5-aryl-2-furyl)propenones (I) in $CHCl_3$ only the s-cis band is clearly observable. In some cases on the lower frequency side of the $\nu_{s\text{-cis}}$ band a small pronounced shoulder occurs, probably corresponding to the carbonyl band of the s-trans conformer. This may be due to a low concentration of the s-trans conformer in the equilibrium mixture or to the overlapping of the weak $\nu_{s\text{-trans}}$ band with the higher frequency wing of an intense ν(C=C) band in the 1600 cm^{-1} region. For these reasons this report describes for series I in $CHCl_3$ only the s-cis carbonyl stretching frequencies.

Comparison of the $\nu_{s\text{-cis}}$ frequencies of compounds in series I with those of series II (see Tables I and II) shows that exchange of the furan ring for the thiophene ring causes a frequency decrease of 1.5–3.5 cm^{-1} in both solvents. This is similar to the case of 1-phenyl-3-(2-furyl)propenones and 1-phenyl-3-(2-thienyl)-propenes[12] as well as of other unsaturated carbonyl compounds[7-10] containing furan and thiophene rings, respectively. On the other hand, the $\nu_{s\text{-trans}}$ frequencies of compounds of series II are 0.5–2.5 cm^{-1} higher than those of series I.

When comparing the data from Tables I and II with that for chalcones III[2,3] (see Table III), we found that the insertion of the furan or thiophene intervening group in the chalcone system produces a significant decrease in both the $\nu_{s\text{-cis}}$ and $\nu_{s\text{-trans}}$ frequency similar to the other previously described cases.[7-10]

In passing from CCl_4 to $CHCl_3$ we observe a decrease of 6.0–6.5 cm^{-1} in the $\nu_{s\text{-cis}}$ frequency of compounds in both series I and II. However, in the case of the $\nu_{s\text{-trans}}$ frequency the same decrease is 10.0–12.0 cm^{-1}. This is similar to the chalcones III,[2,3] where the CCl_4–$CHCl_3$ solvent effect is roughly two times more efficient for $\nu_{s\text{-trans}}$ frequency than for $\nu_{s\text{-cis}}$ frequency. Hayes and Timmons[11] found that the carbonyl bands of s-trans conformers of several α,β-unsaturated ketones were more solvent sensitive than those of corresponding s-cis conformers.

Linear Free-Energy Relationships.—In earlier work[2,3] we have treated statistically the linear free-energy relationships between the carbonyl stretching frequencies and σ as well as σ^+ constants for chalcones III. It was found[3] that the statistically most significant relationships were obtained using Brown and Okamoto's σ^+ values.

As expected, the $\nu_{s\text{-cis}}$ as well as the $\nu_{s\text{-trans}}$ frequencies of compounds in series I and II correlate well with substituent constants (see Table IV). For comparison we have included in Table IV the results of the statistical treatments for the chalcones III. Treatment of each of the 11 data sets with σ resulted in a poorer correlation than was obtained with σ^+. The correlation with σ^+ implies that in compounds of series I and II there operates a significant resonance interaction between the substituent and the carbonyl group even though it is separated by a large intervening group containing a double bond and a heterocyclic ring. The correlations for the $\nu_{s\text{-trans}}$ frequencies are in each case statistically more significant than those for the corresponding $\nu_{s\text{-cis}}$ frequencies.

The data were also treated employing the two-parameter approach described by Swain and Lupton.[13] We have previously noted that generally carbonyl stretching frequency data were correlated less satisfactorily by the two-parameter approach than by the use of σ^+ with the Hammett expression.[3,5] In each of the 11 data sets listed in the tables, correlations with σ^+ are superior to those employing the two-parameter method.[14] The values of % R for the 11 data sets do not vary within the calculated error.[14] The significance of % R[6,15] as well as the theoretical significance of the two-parameter approach has been questioned.[15] The results of the correlations of the 11 data sets recorded here lend support to the questioning of the utility of the Swain–Lupton approach.[15] In view of the poor correlations obtained in this work and the questions that have been raised about the approach, it seems inappropriate at this time to attempt to draw conclusions based upon the two-parameter linear free-energy relationship.

Influence of Conformation on Transmission.—Previous work has suggested that the effect of conformation on transmission in α,β-unsaturated ketones is largely a function of the relative coplanarity of the system.[2,5] It is expected that the steric requirements of I–III and consequently the relative coplanarity of the s-cis and s-trans isomers do not differ greatly from those previously studied. The observed $\rho_{s\text{-cis}}/\rho_{s\text{-trans}}$ ratios for I–III are generally in accord with those observed previously and support the expected view that steric factors are not particularly important.

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TABLE IV
RESULTS OF STATISTICAL TREATMENT USING σ^+ CONSTANTS[a]

Series	Conformer	Solvent	n	ρ	s_ρ	i	s_i	s	r	$\bar{r}$
I	s-cis	CCl_4	9	3.32	0.19	1668.5	0.1	0.3	0.989	0.980
I	s-trans	CCl_4	8	4.74	0.27	1646.0	0.1	0.3	0.990	0.990
I	s-cis	$CHCl_3$	9	3.13	0.17	1662.2	0.1	0.2	0.990	0.987
II	s-cis	CCl_4	8	2.49	0.25	1666.2	0.0	0.3	0.970	0.971
II	s-trans	CCl_4	8	2.82	0.18	1647.0	0.0	0.2	0.989	0.990
II	s-cis	$CHCl_3$	8	2.72	0.23	1659.8	0.0	0.3	0.980	0.982
II	s-trans	$CHCl_3$	8	3.99	0.19	1636.0	0.0	0.2	0.993	0.989
III[b]	s-cis	CCl_4	10	5.62	0.48	1673.7	0.3	1.1	0.972	
III[b]	s-trans	CCl_4	10	7.20	0.34	1654.2	0.2	0.8	0.991	
III[c]	s-cis	$CHCl_3$	21	6.18	0.25	1666.7	0.0	0.6	0.985	
III	s-trans	$CHCl_3$	10	8.23	0.50	1641.9	0.0	1.2	0.985	

[a] n = number of points; ρ = slope; s_ρ = standard deviation of ρ; i = intercept; s_i = standard deviation of i; s = standard deviation; r = correlation coefficient; $\bar{r}$ = arithmetic mean of the correlation coefficients for series I and III and series II and III, respectively. [b] Data taken from ref 2. [c] Data taken from ref 3.

The one exception in these ratios, for which there is no obvious explanation, is that of II obtained from the data arising from measurements in carbon tetrachloride solution.

Transmissive Factors for the Furan and Thiophene Rings.—As it was shown[7,10] the ν(C=O) *vs.* σ and ν(C=O) *vs.* σ^+ linear free-energy relationships with compounds containing a heterocyclic bridge between a substituted benzene ring and carbonyl group can be used in a quantitative study of the transmission of electronic effects by the given heterocyclic bridges. Similar to our earlier approach,[7] we have selected here the most significant free-energy relationships for calculation of transmissive factors. This selection was carried out on the basis of the highest value of the arithmetic means of the correlation coefficients $\bar{r} = (r_I + r_{III})/2$ and $\bar{r} = (r_{II} + r_{III})/2$ for the series of compounds I, II, and III, respectively. Following this procedure $\nu_{s\text{-cis}}$ *vs.* σ^+ and $\nu_{s\text{-trans}}$ *vs.* σ^+ correlations were chosen, since the $\bar{r}$ values in these cases are higher than those for $\nu_{s\text{-cis}}$ *vs.* σ and $\nu_{s\text{-trans}}$ *vs.* σ relationships (see Table IV).

Using data in Table IV we calculated the transmissive factors of the electronic effects for the 2,5-furylene and 2,5-thienylene bridges [π'(Fu)and π'(Thi)] from the equations

$$\pi'(\text{Fu}) = \rho_{II}/\rho_{III} \quad (1)$$

$$\pi'(\text{Thi}) = \rho_{II}/\rho_{III} \quad (2)$$

where ρ_I, ρ_{II}, and ρ_{III} are the slopes of the selected $\nu_{s\text{-cis}}$ *vs.* σ^+ or $\nu_{s\text{-trans}}$ *vs.* σ^+ linear free-energy relationships for the series of compounds I, II, and III, respectively. The transmissive factors π'(Fu) and π'(Thi) in both solvents, CCl_4 and $CHCl_3$, have been calculated using eq 1 and 2. The values obtained here are in agreement with those published earlier.[7-10] Since the transmissive factors determined from the linear free-energy relationships for the five various systems (this work and that previously reported[7,8]) are in good mutual agreement they are expressed as mean transmissive factors, $\bar{\pi}'$(Fu) and $\bar{\pi}'$(Thi).[16]

CCl_4 $\bar{\pi}'$(Fu) 0.64 ± 0.10 $\bar{\pi}'$(Thi) 0.44 ± 0.08

$CHCl_3$ $\bar{\pi}'$(Fu) 0.47 ± 0.06 $\bar{\pi}'$(Thi) 0.42 ± 0.06

It follows from the comparison of the $\bar{\pi}'$ values that the transmission by the furan ring is significantly sensitive to the solvent used. However, the transmission by the thiophene ring is practically independent of the CCl_4–$CHCl_3$ solvent change. The cause of this was suggested earlier[7-10] as hydrogen bonding interaction between the furan ring oxygen atom and the chloroform molecules. Comparing the $\bar{\pi}'$(Fu) and $\bar{\pi}'$(Thi) values in nonhydrogen-bonding CCl_4 solvent with the value of $\bar{\pi}'$(Ph) = 0.27 ± 0.03 (transmissive factor for 1,4-phenylene bridge),[17] we observe, as noted in our previous work,[10] that the transmission by the intervening groups decreases in the order furan, thiophene, benzene. Interestingly, this is the order in which the delocalization energies of the systems increase.

Experimental Section

Infrared Frequencies.—The ir stretching frequencies for all compounds of series I–III were determined on a Zeiss UR 20 three-prism spectrometer operated in the expanded scale mode at scan rates of 10 cm^{-1} min. The wavenumber scale of the instrument was calibrated using the spectra of a standard mixture of indene, camphor, and cyclohexanone.[18] The solvents CCl_4 and $CHCl_3$, both spectral grade, were purified and dried in the manner used before.[18] The concentrations of solutions were chosen to give absorption between 70 and 75%. NaCl cells with path lengths of 0.5, 1.0, and 2.5 mm were used. The carbonyl stretching bands of the s-trans conformers of compounds of series I and II, similar to the chalcones,[2,3] usually appeared as a shoulder on the lower frequency side of the intense $\nu_{s\text{-cis}}$ bands. Therefore, similar to the approach[2] previously reported, the frequency determination was done after graphic resolution of the overlapping bands. All frequencies reported were obtained from averaging three different scans, the maximum scattering of which was 0.5 cm^{-1}.

Calculations.—The Hammett correlations were made with σ constants reported by McDaniel and Brown,[19] and σ^+ constants published by Brown and Okamoto[20] were used. The least-squares treatments were computed on a Regnezentralen Gier digital computer using standard statistical relations.[21] The two-

(16) The microfilm edition of this journal contains the π'(Fu) and π'(Thi) values calculated from each data set together with π'(Fu) and π'(Thi) values reported in our previous papers[7-10] which were used to calculate $\bar{\pi}$ values recorded here. These will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-1807.

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parameter relationships were computed using an IBM 7094 computer (*cf.* ref 6).

Compounds Studied.—The 1-phenyl-3-(5-aryl-2-furyl)propenones (I) and 1-phenyl-3-(5-aryl-2-thienyl)propenones (II) were prepared by condensation of acetophenone with 5-aryl-2-furfuraldehydes and 5-aryl-2-thiophenecarboxaldehydes, respectively, following the procedure described earlier.[22,23] All compounds were recrystallized from appropriate solvents[22,23] until constant melting point was obtained. The 1-phenyl-3-arylpropenones (III) were obtained by condensation of acetophenone with substituted benzaldehydes according to previous reports.[24,25] The chalcones were recrystallized from ethanol and the purity was checked by tlc on Al_2O_3 or SiO_2 (Silufol). The melting points of all compounds agreed well with those described.[22-25]

Registry No.—**1**, 38899-16-0; **2**, 38899-17-1; **3**, 38899-18-2; **4**, 38899-19-3; **5**, 38899-20-6; **6**, 38898-73-6; **7**, 38898-74-7; **8**, 38898-75-8; **9**, 38898-76-9; **10**, 38898-77-0; **11**, 38898-78-1; **12**, 38898-79-2; **13**, 38898-80-5; **14**, 38898-81-6; **15**, 38898-82-7; **16**, 38898-83-8; **17**, 38898-84-9; **18**, 22965-98-6; **19**, 22252-15-9; **20**, 22252-14-8; **21**, 614-47-1; **22**, 22966-07-0; **23**, 22252-16-0; **24**, 22966-13-8; **25**, 22966-17-2; **26**, 24721-24-2; **27**, 2960-55-6; furan, 110-00-9; thiophene, 110-02-1.

Acknowledgments.—We wish to thank Associate Professor Š. Toma for samples **18–27**.

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Synthesis and Spectral Properties of N-Sulfated and/or O-Sulfated Amino Alcohols

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N-Sulfated and/or O-sulfated amino alcohols and 2-deoxy-2-sulfoamino-D-glucose were synthesized and their nmr and ir spectra were measured for the analysis and structural elucidation of sulfated polysaccharides. N-Sulfation of alkylamines and amino alcohols results in a downfield shift of the signal of the proton attached to the carbon atom bearing the amino group by 0.21–0.48 ppm, while O-sulfation results in a downfield shift of the proton attached to the carbon atom bearing *O*-sulfate by 0.36–0.65 ppm. Some discussions are made on the effect of N-sulfation of 2-deoxy-2-amino-D-glucose on H-1 and H-2. Comparison of ir spectra of these sulfate esters revealed two characteristic absorptions (1420–1450 and 1200–1220 cm^{-1}) in *N*-sulfates.

In recent years, some reports have appeared on the structural elucidation of natural mucopolysaccharides[1-3] and synthetic sulfated polysaccharides[4] by using nmr spectra. In general, nmr spectra of these compounds are fairly complicated even by using a high-resolution nmr spectrograph, but the chemical shift of the proton attached to the carbon atom bearing the *O*-sulfate and *N*-sulfate group, and that on the adjacent carbon atom, give important clues for spectral analyses of these compounds. As a model compound for sulfated sugars, we synthesized N-sulfated and/or O-sulfated cyclic and acyclic amino alcohols, and their nmr spectra were measured to examine the effect of N- or O-sulfation on the chemical shift of the proton attached to the carbon atom bearing the sulfate group and that on the adjacent carbon.

Although ir spectra of *O*-sulfates have been reported,[5] those due to *N*-sulfate have hardly been documented.[6,7] Therefore, ir spectra of the synthesized compounds were also measured to examine the absorptions characteristic of the *N*-sulfate group.

Results and Discussion

Cyclic and acyclic alkylamine and amino alcohol sulfates were synthesized systematically. Analytical data for amino alcohol sulfates are given in Table I.

Since it is difficult to avoid contamination of *O*-monosulfate in acyclic *N,O*-disulfates by the method of Reitz and others,[8] we modified the method of Wolfrom and Juliano[9] to synthesize *N,N,O*-trisulfates, and their mild acid hydrolysis afforded *N,O*-disulfates in a comparatively good yield. On the other hand, cyclic *N,O*-disulfates are invariably accompanied with *O*-monosulfates, and trisulfate is not formed even on modification of the reaction conditions. Trans and cis cyclic *N,O*-disulfates were isolated by repeated recrystallization in 19.5 and 22.1% yield, respectively.

The starting 2-aminocyclohexanol was obtained by low-pressure hydrogenation of 2-acetaminophenol over rhodium catalyst, which was used in hydrogenation of alkoxyaniline,[10] separation of trans and cis compounds from the resultant product by chromatography over silica gel, and acid hydrolysis. These trans and cis compounds were identified by nmr spectra. This is simpler and gives a better yield than by the known definitive synthesis of trans[11] and cis[12] compounds.

Dodgson[6] obtained the potassium salt of 2-deoxy-2-sulfoamino-D-glucose by sulfation of 2-deoxy-2-amino-D-glucose with pyridine–sulfur trioxide. We used the same reagents and obtained 2-deoxy-2-sulfoamino-D-glucose as its sodium salt as needle crystals by recrystallization from methanol–water.

Nmr spectra of acyclic alkylamine and amino alcohol sulfates are summarized in Table II. As will

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Table I

Constants of Amino Alcohol Sulfates

Registry no.	Compd			Yield,[a] %	Mp, °C Obsd	Mp, °C Lit.	N Calcd	N Found	S Calcd	S Found
38911-08-9	$HOCH_2CH_2NHSO_3Na$			22.3	136–137		8.59	8.21	19.60	19.38
	$^-O_3SOCH_2CH_2NH_3^+$			44.7	274–277	277–279[b]				
	$NaO_3SOCH_2CH_2NHSO_3Na$			54.4	212–215	220–221[c]				
38974-12-8	$NaO_3SOCH_2CH_2N(SO_3Na)_2$			72.3	212–215		3.81	3.81	26.19	25.87
	$HOCH_2CH_2CH_2NHSO_3Na$			18.2	141–142	*d*				
	$^-O_3SOCH_2CH_2CH_2NH_3^+$			76.6	234–236	226–227.5[b]				
38911-09-0	$NaO_3SOCH_2CH_2CH_2NHSO_3Na$			27.1	234–236		5.02	4.92	22.97	23.23
38911-10-3	$NaO_3SOCH_2CH_2CH_2N(SO_3Na)_2$			51.1	198–201		3.67	3.71	25.23	25.76
	$(CH_2)_4CHOR_1CHNHR_2$									
	R_1	R_2								
38899-01-3	H	SO_3Na	trans	41.5	232 dec		6.45	6.56	14.75	14.57
	SO_3^-	H_2^+	trans	27.2	300 dec	300 dec[b]				
38899-02-4	SO_3Na	SO_3Na	trans	19.5	211 dec		4.39	4.26	20.09	19.63
38899-03-5	H	SO_3Na	cis	39.9	251 dec		6.45	6.35	14.75	14.71
	SO_3^-	H_2^+	cis	25.6	295 dec	289–290[e] dec				
38899-04-6	SO_3Na	SO_3Na	cis	22.1	186–187		4.39	4.17	20.09	19.84
38899-05-7	2-Deoxy-2-sulfoamino-D-glucose (Na)[f]			34.1	235 dec		4.98	4.60	11.40	11.30

[a] From the starting amino alcohol or 2-deoxy-2-amino-D-glucose. [b] C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, **30**, 491 (1965). [c] Trihydrate, ref 9. [d] Reference 14. [e] T. Taguchi, M. Kojima, and T. Muro, *J. Amer. Chem. Soc.*, **81**, 4322 (1959). [f] Potassium salt monohydrate, mp 171° dec: A. G. Lloyd, F. S. Wusteman, N. Tudball, and K. S. Dodgson, *Biochem. J.*, **92**, 68 (1964).

Table II

Chemical Shifts (δ Scale) for Acyclic Alkylamine and Amino Alcohol Sulfates

Registry no.	Compd	CHNDR	$CHCH_2NDR$	$CHCH_2CH_2NDR$
38911-11-4	$CH_3CH_2NDSO_3Na$	2.97	1.11	
38911-12-5	$HOCH_2CH_2ND_2$	2.87	3.67	
38911-13-6	$HOCH_2CH_2ND_3^+Cl^-$	3.12	3.80	
38974-13-9	$HOCH_2CH_2NDSO_3Na$	3.09	3.69	
14849-14-0	$^-O_3SOCH_2CH_2ND_3^+$	3.30	4.27	
38960-84-8	$NaO_3SOCH_2CH_2ND_2$	2.86	4.03	
38911-15-8	$NaO_3SOCH_2CH_2NDSO_3Na$	3.24	4.15	
38911-16-9	$CH_3CH_2CH_2NDSO_3Na$	2.89	1.52	0.89
38911-17-0	$HOCH_2CH_2CH_2ND_2$	2.70	1.68	3.66
38911-18-1	$HOCH_2CH_2CH_2ND_3^+Cl^-$	3.15	1.89	3.74
38911-19-2	$HOCH_2CH_2CH_2NDSO_3Na$	3.06	1.80	3.70
38911-20-5	$^-O_3SOCH_2CH_2CH_2ND_3^+$	3.18	2.08	4.19
38911-07-8	$NaO_3SOCH_2CH_2CH_2ND_2$	2.72	1.80	4.13
38960-85-9	$NaO_3SOCH_2CH_2CH_2NDSO_3Na$	3.09	1.93	4.15

be seen in this table, N-sulfation produces a chemical shift of the proton attached to the carbon atom bearing the amino group downfield by 0.21–0.36 ppm compared to that of the corresponding proton in nonsulfated free amines. The same shift is also seen in conjugated amines. The chemical shift of the proton attached to the carbon atom bearing *O*-sulfate moves to a lower magnetic field by 0.36–0.47 ppm by O-sulfation, and this proton, in both cyclic and acyclic amino alcohols, resonates at *ca.* 1 ppm lower field than that attached to the carbon atom bearing *N*-sulfate. This approximately corresponds to the difference between the corresponding nonsulfated compounds and is considered to be the difference in the electronegativity of N and O. See Table III.

The coupling constants of CHNDR and CHOR in *trans*-2-aminocyclohexanol and its sulfate ester are J_{aa} = 9 and J_{ae} = 4.5 cps, and one of its conformers, in which both amino and hydroxyl groups are diequatorial, is considered to be fixed. The chemical shift of the proton attached to the carbon atom bearing the amino group is at a lower field by 0.23 ppm by N-sulfation compared to that of the corresponding proton in nonsulfated free amines, and the downfield shift is 0.33 ppm in conjugated amines. A similar effect of O-sulfation on the corresponding proton is a downfield shift of 0.65 ppm, indicating that the effect of O-sulfation is greater.

In the case of *cis*-2-aminocyclohexanol, there must be a rapid inversion between two chair conformers, since the CHNDR and CHOR of *cis*-2-aminocyclohexanol are broad and there is only a relatively sharp single peak of methylene.

The effect of N-sulfation of 2-deoxy-2-amino-D-glucose is a downfield shift of the C-2 proton by 0.57 ppm for the α anomer and by 0.47 ppm for the β anomer compared to the chemical shift of the corresponding proton in nonsulfated free amine (α anomer, δ 2.63; β anomer, δ 2.51). The downfield shifts for anomeric protons are 0.23 ppm for the equatorial proton and 0.14 ppm for the axial proton. Of more significance is the fact that almost the same downfield shift is also seen in conjugated amine.

Dodgson and others[5] studied the ir spectra of *O*-sulfate esters of alcohols, amino alcohols, and hydroxylated amino acids and reported that absorptions due to S–O vibration appear at 1150–1230 and 1350–1450

TABLE III

CHEMICAL SHIFTS (δ SCALE) FOR *cis*- AND *trans*-2-AMINOCYCLOHEXANOL SULFATES AND α- AND β-2-DEOXY-2-SULFOAMINO-D-GLUCOSE

Compd $\ulcorner(CH_2)_4\urcorner$ $\llcorner CHOR_1\text{-}CHNDR_2$			Trans			Cis		Δ (cis–trans)	
	Registry no.	$CHOR_1$	$CHNDR_2$	Registry no.	$CHOR_1$	$CHNDR_2$	$CHOR_1$	$CHNDR_2$	
R_1	R_2								
H	D	38899-06-8	3.33	2.67	38899-07-9	3.82 (17[a])	2.80 (23[a])	0.49	0.13
H	$D_2{}^+Cl^-$	38899-08-0	3.56	3.00	38899-09-1	4.10 (16)	3.37 (23)	0.54	0.37
H	SO_3Na		3.34	2.90		4.03 (17)	3.26 (25)	0.69	0.36
SO_3^-	$D_2{}^+$	38898-64-5	4.28	3.23	38898-65-6	4.66[b]	3.46 (24)	0.38	0.23
SO_3Na	D	38898-66-7	3.98	2.68	38898-67-8	4.47 (18)	2.89 (22)	0.49	0.26
SO_3Na	SO_3Na		4.13	3.18		4.70[b]	3.31 (25)	0.57	0.13

	α (38904-97-1)		β (38904-98-2)	
	H-1 (J_{12})	H-2 (J_{23})	H-1 (J_{12})	H-2 (J_{23})
2-Deoxy-2-sulfoamino-D-glucose	5.42 (3.5)	3.20 (10.0)	4.70 (8.0)	2.98 (10.0)

[a] Peak width (cps). [b] Overlapping with the peak of water.

cm^{-1} and that due to C–O–S vibration at 770–810 cm^{-1} in covalent sulfates, while only the absorption due to S–O vibration appears at 1210–1250 cm^{-1} in acid sulfates. Ir spectra of heparin and 2-deoxy-2-sulfoamino-D-glucose have been reported,[6,7] but those of simple *N*-sulfate esters are very few.[6] We therefore measured the ir spectra of N-sulfated and/or O-sulfated amino alcohols used in the present work, and found that they exhibited absorptions due to S–O vibration within the prescribed limits 1170–1250 and 1420–1450 cm^{-1}.

The characteristic absorptions of the *N*-sulfate group can be divided into the following two kinds.

(1) $\nu_{as}(SO_2)$ 1420–1450 cm^{-1}. The starting amine and *O*-sulfates do not show any absorption in this region or exhibit a sharp absorption of weak intensity in the region of 1390–1410 cm^{-1}, while the *N*-sulfate shows absorption of relatively broad width and median intensity at 1420–1450 cm^{-1}.

(2) $\nu_s(SO_2)$ 1200–1220 cm^{-1}. Both *N*-sulfates and *O*-sulfates have several absorptions of strong intensity or one broad absorption, and absorption of the *N*-sulfates is in a lower wavenumber side by 10–48 cm^{-1} than that of the corresponding *O*-sulfates.

Absorption due to C–N–S vibration appears in the same region in the starting amine and there is no characteristic absorption for *N*- and/or *O*-sulfates.

Nmr and ir spectral data of sulfated esters measured in the present work should give important information for nmr and ir analyses of natural N-sulfated and/or O-sulfated polysaccharides.

Experimental Section

Nmr spectra were measured at 35° with a Varian T-60 nmr spectrometer operated at 60 MHz (for alkylamine and amino alcohol sulfates) or measured at 32° with a Varian HA-100 nmr spectrometer operated at 100 MHz (for 2-deoxy-2-sulfoamino-D-glucose) in D_2O containing sodium 4,4-dimethyl-4-silapentane-1-sulfonate as an internal standard. Ir spectra were measured in KBr pellets with a Shimadzu IR-27G spectrophotometer.

The sodium salts of ethylsulfamic acid and propylsulfamic acid were prepared according to the usual procedure.[13] Selective N-sulfation of amino alcohol was carried out by the method of Warner and Coleman,[14] and selective O-sulfation by the method of Reeves and Guthrie.[15]

Disodium 2-Sulfatoethylsulfamate.—To the solid complex prepared from SO_3 (11 ml) and dry pyridine (44 ml), distilled 2-aminoethanol (5 ml) was added dropwise, with sitrring, over a period of 4 hr. The reaction mixture was heated at 60° for 1 hr and kept at room temperature overnight. The pyridine supernatant was decanted and the solid residue was neutralized, under vigorous stirring and cooling, with 1 *N* methanolic MeONa. The precipitate formed was collected by filtration, dissolved in water, and added with 10% barium acetate solution. After $BaSO_4$ was filtered off, the filtrate was passed through a column of Dowex 50W X8 (Na^+ form, 20–50 mesh). The eluate was evaporated to dryness, the residue was crystallized from methanol–water, and recrystallization was repeated with the same solvent, yield 22.0 g (72.3%) of trisodium 2-sulfatoethylimidodisulfonate.

Trisodium 2-sulfatoethylimidodisulfonate (5 g) dissolved in water (50 ml) was adjusted to pH 1.2 with Dowex 50W X8 (H^+ form, 20–50 mesh), stirred at room temperature for 1 hr, and filtered. After the filtrate was neutralized with 2 *N* NaOH solution and added to 10% barium acetate solution, $BaSO_4$ was filtered off and the filtrate was passed through a column of Dowex 50W X8 (Na^+ form, 20–50 mesh). The eluate was evaporated to dryness, and the residue was crystallized from methanol–water, yield 2.72 g (75.2%) of disodium 2-sulfatoethylsulfamate.

Disodium 3-Sulfatopropylsulfamate.—Mild acid hydrolysis of trisodium 3-sulfatopropylimidodisulfonate (4.83 g) at pH 1.2 for 2 hr, prepared by a method virtually identical with that described for trisodium 2-sulfatoethylimidodisulfonate, gave disodium 3-sulfatopropylsulfamate, yield 1.91 g (53.0%).

(±)-*trans*- and (±)-*cis*-2-Aminocyclohexanol.—Anhydrous 2-acetaminophenol (15.1 g, 0.1 mol) suspended in 120 ml of anhydrous ethanol was hydrogenated in the presence of 5% Rh on Al_2O_3 (6.6 g) under 42 psi at 64°. Treatment of the reaction mixture gave a crystalline product which contained two components, as observed by silica gel thin layer chromatography. The rhombic crystals, mp 144–145°, were obtained by fractional crystallization from methanol and prismatic crystals, mp 123–124° by fractional crystallization of the mother liquor from acetone. The residual mixture was chromatographed over silica gel and separated into two components by elution with chloroform–acetone (1:1), yield of rhombic crystals 5.93 g, prismatic crystals 7.65 g (total yield 86.4%).

After each compound was refluxed for 2 hr with 6 *N* HCl, each reaction mixture was evaporated to dryness and the residue was washed with acetone and crystallized from ethanol–benzene. The hydrolysate of the rhombic crystals gave (±)-*cis*-2-aminocyclohexanol hydrochloride, mp 190–191°, and that of prismatic crystals gave (±)-*trans*-2-aminocyclohexanol hydrochloride, mp 175–176°.

Treatment of each aminocyclohexanol hydrochloride by the usual procedure gave (±)-*cis*-2-aminocyclohexanol, mp 70–71°, bp 111° (35 mm), and (±)-*trans*-2-aminocyclohexanol, mp 61–62°, bp 121° (30 mm).

Sodium *trans*-2-Sulfoaminocyclohexanol.—To a solution of *trans*-2-aminocyclohexanol (7.0 g) in water (90 ml), pyridine–SO_3 (10.1 g) was added in small portions over a period of 2 hr, with sufficient 10% NaOH added gradually to maintain the pH at about 11.2–11.4. At the end of the reaction time, the reaction mixture was concentrated *in vacuo* to 50 ml, and added to ethanol (160 ml). After the resulting precipitate was removed by centrifugation, acetone (630 ml) was added to the supernatant.

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The precipitate was collected and crystallized from 95% ethanol, giving 5.70 g of long, hexagonal crystals (41.5%).

trans-2-Aminocyclohexyl Sulfate.—To a suspension of *trans*-2-aminocyclohexanol (1.15 g) in dry $CHCl_3$, chlorosulfonic acid (0.67 ml) in CCl_4 (2 ml) was added dropwise below 0° during 1 hr. After stirring for 2 hr at room temperature, the reaction mixture was evaporated to dryness and freed from HCl *in vacuo* over KOH pellets. The residue was dissolved in ice water, and the solution was neutralized with solid $BaCO_3$ and then with $Ba(OH)_2$ solution. The precipitate was filtered off, and the filtrate was concentrated to a small volume and passed through a column of Dowex 50W X8 (H^+ form, 20–50 mesh) to remove the starting material. The eluate was neutralized with Dowex 1 X2 (OH^- form, 100–200 mesh) and concentrated, and the residue was crystallized from water, giving 0.53 g (27.2%) of prismatic crystals.

Disodium *trans*-2-Sulfoaminocyclohexyl Sulfate.—(±)-*trans*-2-Aminocyclohexanol (1.52 g) was sulfated by a method virtually identical with that described for disodium 2-sulfatoethylsulfamate, giving 0.82 g (19.5%) of needle crystals.

All the sulfated *cis*-2-aminocyclohexanols were prepared by the method used to prepare the corresponding trans derivatives described above.

Sodium 2-Deoxy-2-sulfoamino-D-glucose.—2-Deoxy-2-amino-D-glucose (12.9 g) was dissolved in water (180 ml) and the pH of the solution was adjusted to 9.6 by the addition of 10% NaOH. Pyridine–SO_3 (11.5 g) was added to the well-stirred solution over a period of 9.5 hr at room temperature. During this addition, the pH of the mixture was maintained between 9.6 and 10 by the addition of 10% NaOH. After stirring overnight at room temperature, the solution was concentrated to *ca.* 40 ml and added to 10% barium acetate solution. Precipitated $BaSO_4$ was filtered off through Radiolite 100 and the filtrate was adjusted to pH 4.6 by the addition of acetic acid and passed slowly through a column of Dowex 50W X8 (Na^+ form, 20–50 mesh). The eluate was immediately neutralized with NaOH and concentrated to *ca.* 20 ml. The product was precipitated by the addition of ethanol (400 ml), and the precipitate was collected by centrifugation and washed with ethanol. Solid Ag_2CO_3 was added to the solution of the product dissolved in water (50 ml). Precipitated AgCl and excess Ag_2CO_3 were centrifuged off and the supernatant was neutralized with Dowex 50W X8 (H^+ form, 20–50 mesh). The solution was concentrated to *ca.* 10 ml and the product was precipitated by the addition of ethanol (200 ml). The crude product, a white powder (6.47 g, 34.1%), was twice crystallized from methanol and water after treatment with activated charcoal, giving colorless crystals (3.70 g, 19.5%), $[\alpha]^{25}D$ + 48° (*c* 1, H_2O), mp 235° dec.

Registry No.—SO_3, 7446-11-9; 2-acetaminophenol, 614-80-2; (±)-*cis*-2-aminocyclohexanol hydrochloride, 38898-68-9; (±)-*trans*-2-aminocyclohexanol hydrochloride, 33092-83-0; (±)-*cis*-2-aminocyclohexanol, 38898-70-3; (±)-*trans*-2-aminocyclohexanol, 33092-82-9; 2-aminoethanol, 141-43-5; 3-amino-1-propanol, 156-87-6; 2-deoxy-2-amino-D-glucose, 3416-24-8.

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Radicals and Scavengers. II. Scavengers, Viscosity, and the Cage Effect in a Meisenheimer Rearrangement[1,2]

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Radical scavengers have been used to study the thermal Meisenheimer rearrangement of *N*-benzyl-*N*-methylaniline *N*-oxide (I) in alkaline 80% aqueous ethanol at 70°. Oxygen at ≥1 atm reduces the yield of *N*-benzyloxy-*N*-methylaniline (II) to a minimum of 36%, while the yield under pure N_2 is 89%. A thiol and CCl_4, at higher concentrations, also reduce the yield of II. The three scavengers lead to benzaldehyde, toluene, and chloroform, not found in their absence. In the viscous solvent cyclohexanol at 70°, the "minimum" yield of II under O_2 is 69% of that under N_2. Rearrangement in chloroform at 60° gives CIDNP. These results support operation of a 40% cage effect as an important component of the homolytic dissociation–recombination mechanism previously proposed.

Many cases of inefficiency in the production of free radicals have been convincingly interpreted in terms of the "cage effect,"[4] and this phenomenon is now well enough understood to possess predictive value. The organic systems studied have but rarely involved either (a) a stable radical,[2,5,6] or (b) dissociation of only one bond,[2,7-9] the geminate radicals thus being in contact.

The thermal "Meisenheimer" rearrangement of tertiary amine oxides,[10] exemplified by that of *N*-benzyl-*N*-methylaniline *N*-oxide (I) (eq 1), must have both these characteristics if, as proposed by Schöllkopf,[11,12] it proceeds *via* a homolytic dissociation–recombination mechanism (eq 2, 3).

We have recently demonstrated[2] that the rearrangement of I in 80% ethanol–20% water at 70° proceeds with a 37% cage effect. Our evidence was that molecular oxygen at 1 atm, a scavenger of carbon radicals, reduced the yield from 89% (observed under nitrogen) to 33%. Oxygen did not, however, prevent the formation of II altogether; such behavior is diagnostic of a cage effect.

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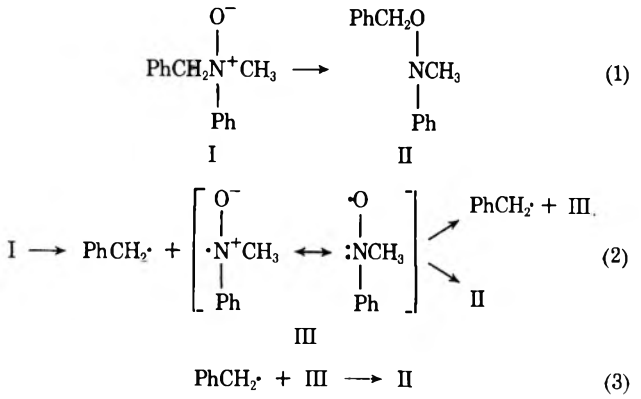


We were at that time unaware of a series of "crossover" experiments by Schöllkopf, *et al.*,[13] implying a cage effect of 75–95% in water or aqueous methanol at 40–80°, markedly incompatible with our estimate. We have now extended our investigation to a much higher pressure of oxygen, to other scavengers, to aqueous methanol at 40° (the conditions used by Schöllkopf, *et al.*), and finally to the viscous solvent cyclohexanol. We now present these results, which support our earlier estimate of the cage effect. We shall explain the disagreement between our estimate and that from the crossover experiment, relate the cage effect to the mechanism of rearrangement, and comment on some puzzling observations.

Results

Reaction Products.—The rearrangement of I, prepared and stored as its hydrochloride, I HCl, was originally conducted in aqueous ethanol in the presence of a variety of bases, most frequently sodium hydroxide and the primary amine, tris(hydroxymethyl)aminomethane (Tris). Whenever Tris was used, the product II was accompanied by a basic by-product, IV, at first thought to be an isomer, which showed nmr absorption characteristic of a methyl and a benzyl group, as well as aromatic absorption not resolved from that of II. Much to our embarrassment, IV proved to be the reduction product, *N*-benzyl-*N*-methylaniline, from which the oxide had originally been prepared. This was shown by extracting IV from the mixture with mineral acid and converting it to the picrate, which was identical by melting point and mixture melting point with a sample prepared from our starting material. Although IV had also arisen in runs using sodium hydroxide, it subsequently became clear that, in the presence of a slight excess of base, no detectable amount of IV was produced. We thus abruptly abandoned the use of Tris in favor of NaOH. Although thermal reactions of amine oxides have invariably produced the corresponding amine, the mechanism of this reduction appears not to be understood. We found that *ca.* 50% reduction product arose from I HCl in concentrated aqueous pyridine, but a careful search for pyridine *N*-oxide as the oxidation product netted only a 5% yield.

A search was made for bibenzyl and toluene as reaction products. Both compounds were detected by glpc analysis of the crude reaction products: bibenzyl in *ca.* 0.1% yield from rearrangement of 0.028 *M* I HCl in 80% aqueous ethanol at 70°; toluene was found only when I HCl was initially 0.007 *M* (*cf.* Table II). Schöllkopf has reported the identification of bibenzyl by tlc.[13] No other products were identified under these reaction conditions, although the maximum yield of II under nitrogen was only 89%.

A few observations were made using chloroform as the reaction solvent, with the thought that its low polarity might accelerate the reaction, which involves the dissipation of opposite charges. Addition of DABCO (1,4-diazabicyclo[2.2.2]octane), or triethylenediamine, to a chloroform solution of I HCl led to precipitation of some DABCO hydrochloride and shifts in the nmr spectrum of the solution attributable to formation of at least some free oxide. The solution seemed stable enough at room temperature, but rearrangement took place at slightly higher temperatures, so that, even at 60°, CIDNP[14] was observed for both methyl and benzyl protons of II. The half-time at this temperature must not have exceeded a few minutes, while that in 80% ethanol at 70° is about 2 hr. Further work has not been done using chloroform, but we conclude that the rate in chloroform is at least ten times, and possibly more than one hundred times, greater than in ethanol.

Kinetics.—The rate of rearrangement of I under nitrogen and under oxygen was measured at 70.3° with the same techniques used to determine products (*cf.* Experimental Section). Because of the small size of aliquots, the yields probably entail larger errors than the "one-point" runs conducted with 200 ml or more of solution. Table I shows typical series of yields of II at various times. Plots of log $[II_f/(II_f - II_t)]$ against time were linear, and data for both N_2 and O_2 fit the same plot. The first-order rate constant was found to be $1.0 \pm 0.1 \times 10^{-4}$ sec^{-1}, corresponding to a half-life of 110 min.

TABLE I

KINETICS OF REARRANGEMENT OF I[a] AT 70.3° UNDER N_2 AND O_2

Time, min	Yield of II, *M* under N_2	Time, min	Yield of II, *M* under O_2
0	0	0	0
20	0.00294	20	0.00064
30	0.00434	70	0.00408
60	0.00844	170	0.00552
90	0.00969	220	0.00774
185	0.01196	280	(0.00968)
435	0.01786	400	0.00896
715	0.01932	1355	0.00976
755	0.02032		

[a] Initial concentration of I HCl = 0.02804 *M*; of NaOH, 0.0282 *M*, in 80% aqueous ethanol.

Oxygen as Scavenger.—Rearrangement of I HCl in the presence of excess sodium hydroxide in 80% aqueous ethanol at 70° was conducted while bubbling into the solution nitrogen, air, or pure oxygen, as previously reported.[2] The reaction has subsequently been conducted in a Parr bottle under 5 atm of pure oxygen, using vigorous magnetic stirring. The results are collected in Table II. The high-pressure run, performed, like the others, in duplicate, gave the same yield of II as the run under 1 atm of oxygen. Thus,

(13) U. Schöllkopf, U. Ludwig, M. Patsch, and W. Franken, *Justus Liebigs Ann. Chem.*, **703**, 77 (1967).

(14) (a) H. R. Ward and R. G. Lawler, *J. Amer. Chem. Soc.*, **89**, 5518 (1967); (b) H. Fischer and J. Bargon, *Z. Naturforsch.*, **229**, 1556 (1967).

TABLE II

PRODUCT YIELDS IN REARRANGEMENT OF I AT 70.3° IN 80% ETHANOL

		Yield,[a] %			
Scavenger	$(I)_0$, M	II	Toluene	PhCHO	Bibenzyl, $PhCH_2$-CH_2Ph
None	0.007	67.3	0.66	[b]	
None	0.028	88.6	[b]	[b]	0.08
None	0.112	41.9[c]	[b]	8	
Air	0.028	41.2	[b]	Trace	
O_2 (1 atm)	0.028	36.0	[b]	17	
O_2 (5 atm)	0.028	35.3		43	

[a] After 13 hr (*ca.* 6 half-lives); averages of duplicate results. [b] None detected. [c] Also 23% IV and some tar.

oxygen at 1 atm has in fact reduced the yield of II to a minimum.

We originally reported[2] that benzaldehyde was produced in 4% yield in the oxygen experiments (and a trace amount under air). However, using a milder means of evaporating the pentane used to extract the product, we found benzaldehyde in 17% yield and at 5 atm, 37 and 49%, by integrating the formyl proton resonance relative to those of the product, II. The formation of benzaldehyde supports the notion of scavenging of benzyl radicals by oxygen, according to eq 4 and 5. It is puzzling, however, that a compound

$$PhCH_2\cdot + O_2 \longrightarrow PhCH_2OO\cdot \xrightarrow{SH} PhCH_2OOH \quad (4)$$

$$PhCH_2OOH \xrightarrow{OH^-} PhCHO + H_2O \quad (5)$$

so sensitive to autoxidation survives in the presence of peroxy radicals, and that attempts to detect its oxidation product, benzoic acid, were negative.

tert-**Dodecanethiol as Scavenger.**—The rearrangement was conducted under N_2 under the same conditions, except with the addition of various amounts of *tert*-dodecanethiol, a good scavenger of carbon radicals, but expected to be less effective than oxygen.[15] The yields of II appear in Table III, and indeed a rather high concentration of the thiol was required to reduce the yield of II to the level attained by the very small

$$PhCH_2\cdot + RSH \longrightarrow PhCH_3 + RS\cdot \quad (6)$$

concentration of dissolved oxygen in equilibrium with the gas at 1 atm. No attempt was made to ascertain whether higher thiol concentrations would further reduce the yield of II. The yields of toluene determined by glpc are also included in Table III, and roughly account for the deficit in the yield of rearrangement product. Control experiments showed substantial losses of toluene during work-up, and the correction factor which is included in the data of Table III is undoubtedly not constant, in reality.

A possible complication in these experiments would be hydrogen-bond formation between I and the thiol. Amine oxides are known to be strong acceptors;[16] thiols will form hydrogen bonds to strong acceptors such as sulfoxides, but S–H stretching frequency shifts in the infrared are only one-fourth those for the corresponding O–H analogs,[17] and formation constants are

TABLE III

YIELDS OF PRODUCTS IN REARRANGEMENT OF I WITH OTHER SCAVENGERS

	Scavenger	Yield, %		
Scavenger	concn, M	II	Toluene[a]	II + toluene
RSH	0.00	86.4		86.4
RSH	0.021	84.5	[b]	84.5
RSH	0.042	75.4	4.3	79.7
RSH	0.084	69.9	12.2	82.1
RSH	0.105	66.1	21.8	87.9
RSH	0.525	33.9	(95)[c]	(129)
CCl_4	0.040	82.3		
CCl_4	0.124	76.9		
CCl_4	1.30	59.0		

[a] Corrected on basis of 31% recovery in control work-ups. [b] Trace only. [c] Estimate must be high; recovery during work-up probably >31%.

not reported. The presence of a thiol molecule at the birth of the geminate radical pair might cause some scavenging of caged nitroxyl radicals as in reaction 7;

$$RSH + \cdot ONR_2 \longrightarrow RS\cdot + HONR_2 \quad (7)$$

reaction 6, however, is too slow to allow this possibility, the reported rate constant for α-toluenethiol and benzyl radical being $5 \times 10^4\ M^{-1}\ sec^{-1}$.[18] Were reaction 7 able to compete with diffusion, then bulk scavenging should have diminished the yield of II at much lower thiol concentrations than actually observed. Therefore, hydrogen bond formation between I and thiol is probably without consequence in this system.

Tetrahalomethanes as Scavengers.—Carbon tetrabromide, bromotrichloromethane, and carbon tetrachloride were expected to be fair to excellent scavengers for the benzyl radical, as per reaction 8. The tetra-

$$PhCH_2\cdot + CX_4 \longrightarrow PhCH_2X + CX_3\cdot \quad (8)$$

bromide in particular is known to be as good a chain transfer agent as *n*-butanethiol in styrene polymerization,[15] and bromotrichloromethane is an excellent reagent for chain bromination of alkanes and aralkanes.[19] Unfortunately, CBr_4 and $BrCCl_3$ could not be used as scavengers, since they caused the pH of reaction mixtures to decrease markedly, in accord with literature reports that they undergo chain reactions with ethanol, producing acid, haloforms, and acetaldehyde.[20] In the presence of CBr_4 or $BrCCl_3$, considerable IV appeared, even if base was in moderate excess; $BrCCl_3$ in ethanol was even found to consume dilute alkali rapidly. It is, of course, possible that CBr_4 and $BrCCl_3$ might be used in chloroform as solvent.

Only CCl_4, a relatively poor chain-transfer agent in styrene polymerization, could be used as a scavenger in the rearrangement of I, and the results at various CCl_4 concentrations are presented in Table III. Even at 1.3 M CCl_4, the yield of II decreased only to 59%; a small amount of chloroform was detected by glpc in this run, but not the others, arising presumably from reaction 9. It may be doubted that attack on CCl_4

$$CCl_3\cdot + CH_3CH_2OH \longrightarrow HCCl_3 + CH_3\dot{C}HOH \quad (9)$$

(15) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 152, 153.

(16) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960.

(17) A. Wagner, H. J. Becher, and K. G. Kottenhahn, *Ber.*, **89**, 1708 (1956).

(18) R. D. Burkhart, *J. Amer. Chem. Soc.*, **90**, 273 (1968).

(19) (a) E. S. Huyser, *ibid.*, **82**, 391 (1960); (b) G. J. Gleicher, *J. Org. Chem.*, **33**, 332 (1968).

(20) J. W. Heberling, Jr., and W. B. McCormack, *J. Amer. Chem. Soc.*, **78**, 5433 (1956).

actually took place, in view of Walling and Lepley's detection[21] of less than 1% of benzyl chloride in thermolysis of phenylacetyl peroxide in CCl_4 at 40°. In the latter study, however, the concentration of benzyl radicals was probably many times greater than in the present work, a factor which favors coupling.

Methanol as Solvent.—In order to eliminate the solvent as a variable and reconcile our results with those of the Schöllkopf group,[13] we performed two experiments in 97% methanol–3% water at 45°, one under nitrogen and one under oxygen. The yield of II under nitrogen was 68%; under oxygen, 34%. Since a rough estimate of the uncertainty of these yields is ±4%, the cage effect might range from 40 to 60%, *i.e.*, 50 ± 10%.

Cyclohexanol as Solvent.—Cage effects in homolytic dissociation reactions are well known to increase with viscosity, as the separation by diffusion of geminate radical pairs becomes more difficult.[4,5,9,22] In search of a strong operational test[23] of a cage effect, we conducted the rearrangement of I in the viscous solvent cyclohexanol, which even at 70° is *ca.* ten times more viscous than ethanol.[24] It was at first hoped that product yields could be determined by the uv spectrophotometric method previously used for measuring rates of appearance of II and its substituted analogs.[13] In this way, we obtained the rate constant $4.7 \pm 0.1 \times 10^{-4}$ sec^{-1} under either nitrogen or oxygen. This technique could not, however, be used to measure yields, because the absorbance after several half-lives was the same under oxygen as under nitrogen. Since the yield was expected to be less under oxygen, this result was ambiguous and indicated that the byproducts, which must also have contained trigonal nitrogen bonded to phenyl, had essentially the same absorbance as II. The yield of II was measured instead using the nmr technique previously employed, with the results shown in Table IV, which also gives the

TABLE IV
YIELD OF REARRANGEMENT OF I IN ETHANOL AND CYCLOHEXANOL

Solvent	% yield of II under N_2	% yield of II under O_2 (1 atm)	Cage effect, %
78% ethanol		29.5[a]	40[b]
97% cyclohexanol	84	58	69

[a] Average of duplicate runs; all runs used the same batch of of I HCl and were performed by the same worker. [b] *Cf.* text.

yield in aqueous ethanol under oxygen as determined by the same worker during the same period, with the same sample of I HCl. The yield of II under oxygen in cyclohexanol is thus evidently doubled compared to the yield in ethanol.

Discussion

The Meisenheimer rearrangement presents several intriguing mechanistic problems, which have been discussed by Johnstone[10d] and by Schöllkopf.[13] That of the operation of a cage effect and its magnitude under certain conditions has, we believe, been solved through the experiments described herein. It is best to discuss the evidence for the cage effect in the context of existing evidence for mechanism.

Dissociation mechanisms are supported by a variety of data, despite the early thought[25] that an SNi mechanism might operate.

(1) The entropy of activation for rearrangement of I in 97% methanol is +33 eu,[13] consistent with formation of two particles, but highly inconsistent with an intramolecular migration, which must involve decrease of rotational entropy. A complication is the probably concomitant loss of water hydrogen bonded to the oxygen.

(2) Optically active *N*-benzyl-α-d_1-dimethylamine oxide, in which the benzyl α carbon is asymmetric, produces the dimethyl analog of II with 61–78% racemization, *i.e.*, 22–39% retention of configuration.[12] A dissociation mechanism explains this result, but a concerted, intramolecular mechanism is expected to be completely stereospecific. In the cage part of the rearrangement, one expects coupling to compete with rotation[4] of the benzyl radical; some net retention of configuration should result.

Additional data are consistent with dissociation mechanisms in general and support or require a radical mechanism in particular.

(3) CIDNP[14] (chemically induced dynamic nuclear polarization, now more correctly called chemically induced nuclear spin sorting) has been observed in at least two examples of the Meisenheimer rearrangement, that of I[26a] and that of benzyldimethylamine oxide hydrate (neat).[26b] That is, when the rearrangement has been conducted in an nmr spectrometer at a temperature such that it is rapid, the products have shown emission with greatly enhanced intensity, rather than absorption of normal intensity. This is compelling evidence that a major part of the reaction follows a radical cleavage–recombination mechanism. That both methyl and benzyl protons of I and the dimethyl analog have shown emission is in accord with prediction for geminate radicals.[27] The kinetics observed under both O_2 and N_2 (*cf.* discussion, *vide infra*) are consistent with a single cleavage mechanism, only part of which produces trappable radicals.

(4) Methylphenyl nitroxide radical has been detected during rearrangement of I in methanol, *via* esr spectroscopy.[13] The amount of radical produced was very small, however, and it might arise from a minor competing process. We believe otherwise, but the mere observation of the radical by no means proves that all the rearrangement involves it.

(5) The yield of toluene from rearrangement of I in aqueous ethanol is vanishingly small. A carbanion mechanism should produce a large quantity of toluene by diffusion-controlled proton transfer from the protic solvent (eq 10).

$$PhCH_2^- + ROH \longrightarrow PhCH_3 + RO^- \qquad (10)$$

(21) C. Walling and A. R. Lepley, *J. Amer. Chem. Soc.*, **94**, 2007 (1972).

(22) W. Braun, L. Rajbenbach, and F. R. Eirich, *J. Phys. Chem.*, **66**, 1591 (1962).

(23) F. E. Herkes, J. Friedman, and P. D. Bartlett, *Int. J. Chem. Kinet.*, **1**, 193 (1969).

(24) "Chemical Engineers' Handbook," J. H. Perry, Ed., McGraw-Hill, New York, N. Y., 1950, pp 372, 373; the viscosities of cyclohexanol and 70% ethanol at 70° are, respectively, 6.2 and 0.59 cP (the latter interpolated between values for 40 and 100% ethanol).

(25) (a) G. M. Bennett and A. W. Chapman, *Ann. Rep.*, 122 (1930); (b) C. R. Hauser and S. W. Kantor, *J. Amer. Chem. Soc.*, **73**, 1437 (1951).

(26) (a) G. Ostermann and U. Schöllkopf, *Justus Liebigs Ann. Chem.*, **737**, 170 (1970); (b) A. R. Lepley, *J. Amer. Chem. Soc.*, **92**, 1101 (1970).

(27) R. Kaptein, *Chem. Commun.*, 732 (1971); we assume the α-proton hfc for benzyl radical to be negative, for the β (CH_3) protons of the nitroxyl radical, positive, and the latter has the larger *g* value.

(6) Polar substituents affect the rate of rearrangement of I much less than expected if dissociation produced a carbanion. Thus, substitution in the migrating benzyl group gives ρ +0.9,[13a] while substitution in *N*-phenyl gives ρ +0.9 also.[13b] In contrast, the base-catalyzed hydrogen isotope exchange of substituted toluenes has ρ +4.0.[28] The sign of ρ for the rearrangement is inconsistent with formation of benzyl cation; benzyl radical is therefore implicated.

The sign of ρ is the opposite of that usually found for radical reactions, *e.g.*, radical chain halogenations of substituted toluenes; bromination by Br_2 or NBS has ρ −1.4.[29] The usual explanation has been contribution of charge-transfer resonance structures to the transition state, as depicted for bromination and Meisenheimer rearrangement in eq 11 and 12. Zavitsas has

$$[PhCH_2\cdot\cdots\dot{H}\cdots\dot{B}r \longleftrightarrow PhCH_2^+\cdots\dot{H}\cdots Br^-] \longrightarrow PhCH_2\cdot + HBr \quad (11)$$

$$\left[PhCH_2\cdot\cdots\overset{O^-}{\overset{|}{\underset{|}{\dot{N}^+}}}\!\!-CH_3 \longleftrightarrow PhCH_2\cdot\cdots\overset{\cdot O}{\overset{|}{\underset{|}{\dot{N}}}}\!\!-CH_3 \longleftrightarrow PhCH_2^-\cdots\overset{O}{\overset{\|}{\underset{|}{\dot{N}^+}}}\!\!-CH_3\right] \longrightarrow \text{Radicals} \quad (12)$$

(Ph on N)

recently questioned this idea,[30] and shown that substituent effects in certain systems correlate remarkably closely with differences in bond energies. Either interpretation of substituent effects focuses attention on the covalent bond scission. Schöllkopf, however, has neglected this approach in attributing the ρ values to dissolution of the oxide–water hydrogen bond. In support, he notes that the dissociation constants of the conjugate acids of the amine oxides give ρ +1.3. While this factor may contribute in the proper direction, it is unlikely that dissociation of hydrogen bonds, in which the proton is less than 20% transferred to the basic atom,[31] can have a ρ value as large as that for Brønsted acidity and, even less likely, a $\Delta H^{\pm}$ value in excess of 30 kcal/mol.

The charge-transfer hypothesis is supported by published rate data[32] (Table V). Most striking is the 40-fold acceleration due to two *p*-nitro groups in diphenylmethyldimethylamine oxide. The failure of the 9-fluorenyl analogs to rearrange significantly faster than diphenylmethyl must be due to compensation by an opposing effect, the absence of steric strain in the 9-fluorenyl oxide. The 2.5-fold greater rate of the *o*-tolyl compound suggests that relief of steric strain is important. Alternatively, the data of Table V could be explained according to Zavitsas, that is, in terms of the ability of substituents to decrease bond energies by delocalizing the unpaired electron.

TABLE V
EFFECT ON MIGRATING GROUP STRUCTURE ON REARRANGEMENT RATE

	$-10^3 k$, sec^{-1}, for stationary groups—		
Migrating group	$(CH_3)_2$	$-(CH_2)_5-$	$-(CH_2)_2-O(CH_2)_2-$
Diphenylmethyl	4.4	3.5	1.8
9-Fluorenyl	5.3	5.1	3.5
Phenyl-*o*-tolylmethyl	11.8	10.0	5.2
p,p'-Dinitrodiphenylmethyl	200		

Reversibility of Radical Cleavage.—The initial cleavage, 2, is probably irreversible, because optically active I in which the chiral center is nitrogen does not racemize during rearrangement.[13] Reversibility should lead to a detectable, if small, degree of racemization.

The fact that the rate of rearrangement of I is the same under oxygen as under nitrogen further supports this conclusion. If the scission were reversible, bulk radicals should also couple to regenerate I, as well as to form II. Oxygen would eliminate this and raise the observed rearrangement rate. A classic case in which this occurs is the thermal rearrangement of *N*-(1-cyanocyclohexyl)pentamethyleneketenimine to 1,1′-dicyanobicyclohexyl, which proceeds by dissociation into pairs of 1-cyanocyclohexyl radicals.[33]

Effect of Solvent on Rate.—The Meisenheimer rearrangement appears to be accelerated by decreases in solvent polarity, although the available data are limited. The rate for I increases by over two orders of magnitude when the solvent is changed from 97% methanol to 3% water–97% tetrahydrofuran.[13] We have concluded (*vide supra*) that the reaction is some two orders of magnitude more rapid in chloroform than in aqueous ethanol. These observations deserve further investigation, in order to determine whether the rate variations are due to (a) favoring of the dissipation of charge at the transition state by less polar solvents, or (b) weakening of hydrogen bonding, *i.e.*, solvation, of the oxide, raising its energy and increasing its rate of dissociation.

The Cage Effect.—The effect of radical scavengers on the outcome of the Meisenheimer rearrangement has not previously been taken into account. We have found the scavenger oxygen, known to react very rapidly with carbon radicals,[15] to reduce the yield of II from I to a limiting value which is 40% of that in its absence. In addition, *tert*-dodecanethiol and possibly carbon tetrachloride also diminished the yield of II, although limiting yields were not established in these cases. The role of all three of these must be to react with free benzyl radicals according to eq 4, 6, and 8, preventing them from reacting with free nitroxide radicals; the products benzaldehyde, toluene, and chloroform are indicative of these reactions. Operation of a cage effect explains the existence of a limiting yield, the inability of the scavenger to react with 100% of the radicals which form. Previous studies of cage effects have shown that, even when the radical–scavenger reaction is diffusion controlled, more than 0.1 *M* scavenger concentration is required to interfere with a cage effect.[34] In our experiments the

(28) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 29.
(29) R. E. Pearson and J. C. Martin, *J. Amer. Chem. Soc.*, **85**, 3142 (1963).
(30) A. A. Zavitsas, *ibid.*, **94**, 7390 (1972).
(31) D. Gurka, R. W. Taft, L. Joris, and P. v. R. Schleyer, *ibid.*, **89**, 5957 (1967).
(32) A. H. Wragg, T. S. Stevens, and D. M. Ostle, *J. Chem. Soc.*, 4057 (1958).
(33) C-H. S. Wu, G. S. Hammond, and J. M. Wright, *J. Amer. Chem. Soc.*, **82**, 5386 (1960).
(34) H. P. Waits and G. S. Hammond, *ibid.*, **86**, 1911(1964).

concentration of oxygen in solution never exceeded 0.01 M, and was usually much less. The thiol used and CCl_4 were expected to be less reactive than oxygen toward benzyl radicals, and accordingly much higher concentrations were required to depress the yield of II. Thus, even at the concentrations of 0.5 and 1.3 M, respectively, these compounds could not have suppressed the cage effect itself. CCl_4 at 1.3 M decreased the yield only to 59%. The cage effect in 80% ethanol at 70° is thus regarded as being 40%, and that in 97% methanol at 45°, *ca.* 50%. If the latter is significantly greater than the former, it is consistent with the known tendency of cage effects to increase at lower temperatures, as viscosity increases.[4]

It might be argued that a different mechanism is responsible for the 36% yield of II not eliminated by oxygen. This is the Achilles' heel of the cage effect hypothesis, which may be defended in the following four ways.

(1) The phase of the CIDNP effect (in the case of I and its dimethyl analog, emission) agrees with theory for geminate radicals. Existing theory[35] is powerful and has succeeded in accounting for enhancement factors, phase, the multiplet effect, and other aspects of CIDNP. The most convincing experiment in the present context would be observation of CIDNP in the presence of an efficient scavenger to prevent coupling of any but geminate radicals. This might be done using CBr_4 or $BrCCl_3$ in chloroform solution.[35a]

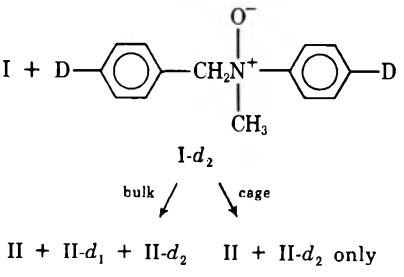
(2) If the rearrangement could be conducted in the vapor phase, in the presence of a scavenger, the yield should fall to zero, since at low pressures there are no cages. Although this experiment has provided elegant support for other cage effects, *e.g.*, that which forms methyl acetate in the thermal decomposition of acetyl peroxide,[36] it is probably not applicable here because of the low or nil volatility of amine oxides.

(3) The rate constant for the rearrangement of I is the same under oxygen as under nitrogen. Were another mechanism involved, a different rate constant should apply to the nonscavengeable part of the reaction. The rate constant under nitrogen would be the sum of that rate constant and the rate constant characteristic of the production of free radicals. Since the cage effect is roughly one-third of the total, the rate should be one-third under oxygen what it is under nitrogen, if two mechanisms were involved. For the cage-effect mechanism, the rate-limiting step, cleavage of I into two radicals, is the same whether caged or free radicals are considered. Following, as we have done, the formation of product, one in effect neglects two-thirds of the reaction, but, since the kinetics are first order, the rate constant is the same. We are not aware of the application of this criterion in any previous case, nor, more important, are we aware of any case which *does* involve two mechanisms, one nonradical, the other producing radicals with almost no cage effect, and both producing the same product.

(4) The limiting yield of rearrangement product is greater in a more viscous solvent. This criterion has been applied often, like no. 2; it depends on the anticipated decrease in rate of diffusion of radicals from their cage as the viscosity increases. We find the limiting yield in cyclohexanol to be 58%, which is 69% of the yield under nitrogen. A cage effect of 69% is nearly double that found in ethanol, an increase which is consistent with increases observed in other systems. It is noteworthy that viscous alcohols, including also glycerol and other glycols, have been used only twice previously[37,38] for investigating cage effects. Although this has provided us some anxious moments, the burden of proof is on the one who dares to suggest that a viscous solvent will not increase a cage effect. We prefer the thought that this observation and the previous ones extend the range of viscous solvents useful for investigating cage effects.

It might be argued that the alleged increase in cage effect in cyclohexanol is an illusion, actually due to decreased efficiency of oxygen as scavenger. That is, if the scavenging reaction is diffusion controlled, its rate must decrease considerably with a tenfold increase in viscosity, and a significant amount of coupling of bulk radicals to II might compete with scavenging. While an experiment conducted at 5 atm would settle the matter, we can present two additional observations which strongly refute this objection. First, the solubility of oxygen must be greater in cyclohexanol than in aqueous ethanol, both at 70°, by Henry's law, since the former is much less volatile; *i.e.*, the partial pressure of oxygen over cyclohexanol is more nearly 1 atm. Second, the decrease in rate of scavenging due to viscosity increase would be comparable to that due to decreasing the partial pressure of oxygen, as by changing from pure oxygen to air. In the ethanol experiments, this increased the yield of II from 36% to only 41%, an increase of less than one-fifth.

Discrepancy between the Present Results and Those of Schöllkopf, *et al.*.—The Schöllkopf group has argued[13] that the rearrangement in methanol or water is intramolecular, *i.e.*, has a cage effect, to the extent of 75–95%, depending on solvent and temperature, in serious conflict with our estimate using the scavenger method. Their crossover experiment, decomposition of equal mixtures of I and I-d_2, and mass spectrometric analysis of the product for II, II-d_1, and II-d_2, is capable of



(13)

affording an accurate estimate of cage effect. An analogous experiment[39] with the thermal decomposition of azo-1-phenylethane at 105° gave a result in excellent agreement with that of a scavenger experiment.[40] Evidently, however, the amine oxide solutions were not degassed; so most of the product isolated, in unstated yield, must have been cage product. This

(35) G. L. Closs, *J. Amer. Chem. Soc.*, **91**, 4552 (1969); R. Kaptein and L. J. Oosterhoff, *Chem. Phys. Lett.*, **4**, 195, 214 (1969).

(35a) NOTE ADDED IN PROOF.—A. R. Lepley has recently reported to the senior author very strong emission from II in a mull of IHCl, DABCO, and $BrCCl_3$.

(36) L. Herk, M. Feld, and M. Szwarc, *J. Amer. Chem. Soc.*, **83**, 2998 (1961).

(37) W. N. White, H. S. White, and A. Fentiman, *ibid.*, **92**, 4477 (1970).

(38) W. K. Robbins and R. H. Eastman, *ibid.*, **92**, 6076, 6077 (1970).

(39) S. Seltzer and E. J. Hamilton, *ibid.*, **88**, 3775 (1966).

(40) F. D. Greene, M. A. Berwick, and J. C. Stowell, *ibid.*, **92**, 867 (1970).

explains the fact that the product was predominantly II and II-d_2, with very little II-d_1. Our experiments with methanol underscore this interpretation.

Stereochemistry of the Rearrangement of I.—We have noted in our communication[2] that the cage effect of I and the extent of retention of configuration in migrating benzyl-α-d_1 in the dimethyl analog of I are similar, although, owing to low rotation values, the latter value is not accurately known. Nevertheless, since the bulk reaction must lead to quantitative racemization, the retention occurs entirely in the cage process, and is very high, 62–100%. A second case, also involving the cleavage of only one bond, has been studied by Porter, *et al.*,[7] the photodissociation of optically active phenylazo-2-phenylbutane. In hexadecane, only about 10% racemization of azo compound took place, while about 50% of the remaining azo compound had undergone dissociation (inferred from the dependence of the quantum yield on viscosity in a series of paraffins).

The behavior of a typical two-bond initiator, azo-1-phenylethane, contrasts strongly with the pattern set by the Meisenheimer rearrangement and Porter's azo compound. Thermal decomposition of the optically active azoethane gave 2,3-diphenylbutane which was nearly a statistical mixture of *d*, *l*, and meso forms, even for the cage process (in the presence of the scavenger 2-methyl-2-nitrosopropane).[40] In this case a nitrogen molecule intervenes between the geminate radicals, and this may increase the probability that a 1-phenylethyl radical will rotate by 180° from its original orientation. Since, however, these experiments were performed at 105°, one should await a study of the photolysis at ambient temperature before pinning the blame on the nitrogen molecule.

Why is the yield of the Meisenheimer rearrangement nearly quantitative? In other words, why isn't more bibenzyl formed, if part of the reaction involves free radicals? Those radicals which diffuse into the bulk would normally give three coupling products in ratio 1:2:1, one of which should be bibenzyl. The clue is that one radical, methylphenyl nitroxide, is observable,[13] while the other, benzyl, is not. The nitroxide cannot couple with itself, but it can scavenge benzyl radicals. A similar situation obtains in the thermal decomposition of *tert*-butyl triphenylperacetate, $Ph_3CCO_3C(CH_3)_3$, in cumene, in that triphenylmethyl radical builds up and scavenges *tert*-butoxy and cumyl radicals; dicumyl cannot be detected.[6]

The way in which the nitroxide radical attains its high concentration has already been suggested by Schöllkopf: dimerization early in the reaction destroys benzyl radicals, converting them to bibenzyl. Formation of 0.05% bibenzyl from 0.01 *M* I allows the formation of 10^{-5} *M* nitroxide, easily detected by esr. The rapid rate of scavenging of benzyl radicals by nitroxide—inferred from the existence of a cage effect involving both—keeps the concentration of benzyl below observable limits. Schöllkopf did not believe that the detectable nitroxide radicals played a major role in the reaction, while our postulated cage effect of *ca.* 40% indicates that they produce more than half the product. Johnstone[10d] considered the kinetic and esr results to conflict, in that intermolecularity implied to him a departure from first-order kinetics. If, however, bond scission is rate determining, no amount of complications after this step can affect the kinetics, provided that there is no attack of radicals on amine oxide.

Experimental Section

General.—Nmr spectra were recorded and integrated on a Varian A-60 instrument; for later work a Jeolco C-60HL was utilized. For quantitative analyses of II, benzaldehyde, and toluene, the sample was dissolved in a known volume of CCl_4 containing a known concentration of anisole (δ for methyl protons, 3.55 ppm, remote from peaks of any products), and the methyl and/or methylene or formyl singlets integrated. Synthetic mixtures of II, toluene, and anisole were likewise integrated, and corrections applied.

Glpc analyses were performed with an F & M Model 700 chromatograph, the recorder equipped with a disc integrator. Quantitative analysis of toluene and bibenzyl was achieved with reference to synthetic mixtures.

Monoperphthalic Acid.—The method of Payne[41] was used with slight modification. A solution of sodium carbonate monohydrate (62 g, 0.5 mol) in 250 ml of water in a 1-l. beaker was cooled to −3 to −5° in brine, stirred magnetically, and chilled 30% hydrogen peroxide (68 ml, 0.6 mol) was added; the temperature remained below 0°. Phthalic anhydride, well pulverized (75 g, 0.5 mol), was added and the solution was stirred vigorously for 30 min, when all the anhydride had usually dissolved. Ether (350 ml) was added, then slowly 30 ml of concentrated sulfuric acid in 150 ml of water; gas was evolved; and a slushy white precipitate of phthalic acid formed. After filtration through glass wool into a 2-l. separatory funnel, the aqueous layer was further extracted with three 250-ml portions of ether. The combined ether extracts were washed with cold 40% ammonium sulfate solution and dried over magnesium sulfate in the refrigerator. Analysis by iodimetry, treatment of 2 ml of ethereal solution with 15 ml of 20% aqueous potassium iodide, followed by titration with 0.100 *N* sodium thiosulfate solution, indicated a yield of 88%; yields ranged from 69 to 99% in other runs.

***N*-Benzyl-*N*-methylaniline *N*-Oxide Hydrochloride (I HCl).**—A modification of the method of Stevens, *et al.*,[32] was used. A chilled solution of *N*-benzyl-*N*-methylaniline (Eastman) (70 g, 0.35 mol) in anhydrous ether was treated with ethereal monoperphthalic acid solution in 10% excess, at 0°, in a resin kettle equipped with a thermometer and stirring bar, immersed in an ice–salt bath. After stirring for 16–20 hr at −2 to 0°, the ether was decanted, the pale yellow-green cake on the kettle walls was dissolved in methylene chloride, and dry hydrogen chloride was bubbled through for 0.5 hr. The solution turned deep rose and phthalic acid precipitated. This was filtered off and the solvent was stripped under vacuum. The clear brown, viscous syrup which remained was dissolved in 100 ml of warm acetone, when a copious crop of white crystals appeared, which were collected under suction and dried. The material was stable indefinitely if stored under hydrogen chloride gas. The yield was 44.0 g (50.6% of theory); mp 126–127° with slow heating, 134–135° with rapid heating (lit. mp 124–126°,[42] 131°,[32] or 135°[43]); nmr δ 4.22 (3 H, singlet, methyl) and 5.46 ppm (2 H, AB quartet, methylene), in chloroform; aromatic absorption hidden by solvent. *Anal.* Calcd for $C_{14}H_{16}NOCl$ (mol wt, 249.7): C, 67.20; H, 6.44; N, 5.60; Cl, 14.20. Found: C, 67.32; H, 6.48; N, 6.09; Cl, 14.34.

Oxygen Scrubber.—Prepurified nitrogen was passed through a scrubber, prepared as follows, on its way to the reaction vessel. Zinc amalgam was prepared by adding mossy zinc to mercury in a beaker. To this was added 3 *N* hydrochloric acid to clean the zinc and hasten its amalgamation. The amalgam, washed several times with distilled water, was transferred to a 0.5-l. gas washing bottle. An aqueous solution of 60 ml of perchloric acid and 20.5 g of chromic perchlorate hydrate in 500 ml of water was added to the bottle. The resulting blue-black solution turned bright peacock blue as nitrogen passed through it for several hours. When the amalgam becomes exhausted, the green color of chromic ion appears.

(41) M. Payne, *J. Org. Chem.*, **24**, 1354 (1959).

(42) J. Meisenheimer and J. Hoffmeinz, *Justus Liebigs Ann. Chem.*, **385**, 117 (1919).

(43) J. Meisenheimer, *ibid.*, **449**, 188 (1926).

General Procedure for Rearrangement of I.—The reaction vessel was typically a 1-l., three-necked, round-bottomed flask fitted with two 1.5-ft condensers in series, a calibrated thermometer graduated in 0.1°, and a glass tube for bubbling oxygen or nitrogen through the solution. For runs conducted under nitrogen, a four-necked flask was used, the fourth neck being attached *via* flexible tubing (latex or Tygon) to a second, two-necked flask in which a solution of base was purged of air before being poured under slight nitrogen pressure into the solution of I HCl. Both flasks were thermally equilibrated in a large constant-temperature water bath for *ca.* 1 hr or more before mixing.

For a typical run under nitrogen, I HCl (0.495 g, 1.99 mmol), in 200 ml of 80% ethanol in the four-necked flask, and NaOH, (0.150 g, *ca.* 3.7 mmol) in 200 ml of 80% ethanol in the two-necked flask, were purged with scrubbed nitrogen and equilibrated at 70.3°. The base solution was poured into the I solution through the tubing and the mixture was allowed to stand under a slow nitrogen stream for 20 hr. The reaction mixture was poured into 800 ml of ice-cold saturated salt solution and extracted with five 150-ml portions of pentane. The pentane was stripped through a 1-ft glass helices packed column by means of a warm water bath. The residue, 2.5 ml, was analyzed by nmr (*vide supra*) after addition of 1.0 ml of 1.98 *M* anisole in CCl_4. The yield of II was 67%; no IV was detected.

Runs under air or oxygen were carried out similarly, except that purging prior to mixing was usually omitted.

The two runs at 5 atm oxygen employed a 500-ml Parr pressure bottle connected by copper tubing and compression fittings to the outlet of a reducing valve on an oxygen cylinder. Stirring was done with an oval Teflon-covered stirring bar and a magnet, attached to a speedometer cable, immersed in the water bath and driven by a stirring motor. The reducing valve was set at 60 psig after the vapor space had been purged briefly with oxygen, the flask was immersed in the bath, and stirring was begun. After *ca.* 13 hr, more than 6 half-lives, the pressure was released and the solution was worked up as described above. In these and 1 atm oxygen or air runs, benzaldehyde was detected and determined by nmr (formyl resonance at 10.0 ppm), as well as by odor. The yield of benzaldehyde was high only if the stripping of pentane was done with tepid water; use of hot water or steam resulted in low yields.

When *tert*-dodecanethiol was used as scavenger, it was added *via* a disposable syringe after mixing of the amine oxide and base solutions. CCl_4 when used as scavenger was added to the base solution before mixing.

Kinetics of the Rearrangement of I HCl.—Kinetic runs were carried out with slight modifications of the above techniques. In place of the thermometer there was a long Teflon syringe needle, to withdraw aliquots, 100 ml at first, decreasing to 50 ml at the end, as the concentration of product increased. The aliquots were quenched in ice water and worked up and analyzed for II as above. Rate constants were calculated from slopes of plots of log $[II_f/(II_f - II_t)]$ *vs.* time. The length of time required for one-point experiments was chosen according to the results (*cf.* text).

Recovery of Toluene.—Synthetic mixtures containing *ca.* 0.5 mmol of toluene and some II in 80% ethanol were prepared and subjected to the standard work-up procedure. The recovery of toluene averaged 31% while that of II was quantitative. The observed yields of toluene were corrected by dividing by 0.31. No control was run for the largest amount of toluene observed, 1.13 mmol; in this case the correction factor should probably be smaller than 1/0.31.

Reaction of Tetrahalomethanes with Ethanolic Base.—A 0.10 *M* solution of bromotrichloromethane in 80% ethanol was allowed to stand overnight at room temperature. The apparent pH as measured with a meter was 1.8; a 5-ml aliquot diluted to 45 ml had pH 2.5. Standard aqueous 0.1 *N* NaOH was added; 5.0 ml brought the pH to 3.00, 6.5 ml to 4.70, and 10.0 ml to 11.80. Ten minutes later, the pH had drifted to 3.4.

A 0.10 *M* solution of carbon tetrabromide in 80% ethanol had pH 1.3 after standing overnight. Standard aqueous 0.1 *N* base, 3.0 ml, brought the pH to 11.60; 10 min later the pH was 10.0.

A 0.10 *M* solution of carbon tetrachloride in 80% ethanol, after standing for 40 min, had pH 7.3; dilution with 40 ml of ethanol brought the pH to 5.4. Only 0.5 ml of 0.1 *N* base was required to bring the pH to 12.3, where it remained for at least 10 min.

Rearrangement of I in Chloroform.—I HCl (3.0 g, 12 mmol) was dissolved in 200 ml of chloroform, and ammonia was bubbled in for 0.5 hr at 0°. The white precipitate of ammonium chloride was removed by filtration, and the chloroform was stripped on a rotary evaporator over a steam bath. CCl_4 (25 ml) was added and evaporated to remove traces of chloroform. The residue, a golden yellow liquid, bp 90° (0.1 mm), weighed 2.28 g (10.7 mmol) (maximum), 89% of theory: nmr δ 2.90 (3 H, singlet, methyl) and 4.76 ppm (2 H, singlet, methylene), in the aliphatic region, identical with the spectrum of the product from rearrangements in 80% aqueous ethanol. There was no absorption due to IV, which absorbs at δ 2.84 (3 H, methyl) and 4.35 (2 H, methylene) ppm, both singlets. *Anal.* Calcd for $C_{14}H_{15}NO$ (mol wt, 213.27): C, 78.84; H, 7.08; N, 6.56. Found: C, 78.42; H, 6.88; N, 6.74.

CIDNP from Rearrangement of I in Chloroform.—I HCl (*ca.* 125 mg, 0.5 mmol) was dissolved in 1 ml of chloroform in an nmr tube. The spectrum showed a methyl singlet at δ 4.22 and a methylene AB quartet at 5.46 ppm. After addition of DABCO (1,4-diazabicyclo[2.2.2]octane), *ca.* 100 mg (0.9 mmol), stoppering, and shaking, some precipitate remained. It was previously shown that DABCO hydrochloride is insoluble in chloroform. The nmr spectrum now showed, besides the singlet at 3.0 ppm due to DABCO, both methyl and methylene signals of I at higher field by *ca.* 0.3 ppm. Addition of more DABCO caused slight further shifts to higher field. The solvent shifted simultaneously to lower field by *ca.* 0.3 ppm, attributed to hydrogen bonding to both DABCO and the free amine oxide. (A solution of pyridine *N*-oxide in chloroform showed a similar low-field shift of the solvent resonance.)

The probe of the A-56-60 spectrometer was heated to 60° and the tube containing the chloroform solution of I and DABCO was reinserted. Scans of the spectrum within the first 2 min showed negative emission singlets at 2.9 and 4.7 ppm, characteristic chemical shifts of the methyl and methylene protons of II. Within 10 min, these became positive absorption peaks.

***N*-Benzyl-*N*-methylaniline.**—I HCl (12.1 g, 0.0485 mol) was allowed to rearrange for 19 hr at 72° in 350 ml of 80% ethanol in the presence of tris(hydroxymethyl)aminomethane (Tris) (29.0 g, 0.24 mol) under nitrogen. The work-up proceeded as above, affording 7.7 g of orange-yellow oil, the nmr spectrum of which showed singlets in the aliphatic region characteristic of both II and IV. The product was partitioned between pentane and aqueous 0.1 *N* HCl, the aqueous phase was made basic with dilute NaOH solution, and the oil which separated was extracted into pentane, which was stripped, leaving IV (3.2 g, 0.015 mol) (31%), bp 85° (0.15 mm), nmr as given above for IV. Addition of authentic IV (Eastman) enhanced existing nmr peaks. For picrates, the reaction product (from MeOH) had mp 101–102°; authentic IV (from MeOH) had mp 101–102°; the mixture had mp 101–102°; authentic material (from EtOH) had mp 101–104°; the mixture of picrates of an authentic sample (from MeOH and EtOH) had mp 101–104° (lit. mp 103°,[44] 128°[10b]; the latter melting point reported for material from EtOH, combustion analysis reported to agree with formula $C_{20}H_{18}N_4O_7$).

Anal. (of authentic material from EtOH). Calcd for $C_{20}H_{18}N_4O_7$ (mol wt, 426.37): C, 56.47; H, 4.03; N, 13.17. Found: C, 56.20; H, 4.21; N, 13.30.

We conclude that the report[10b] of mp 128° for IV picrate is in error.

Reactions of Amines with Amine Oxides. A. I HCl and Triethylamine.—I HCl (1.0 g) and triethylamine (4.1 g) in 50 ml of 90% ethanol were heated at 70° for 4 hr, and the standard work-up was applied. The products showed no evidence of IV in the nmr. Repetition of the experiment at 80° for 10 hr with the same, and then threefold, amount of triethylamine gave traces of IV.

B. Trimethylamine Oxide and *N*-Benzyl-*N*-methylaniline.—A solution of these compounds, 4.0 and 1.8 g, respectively, in 50 ml of 90% ethanol was refluxed for 19 hr. Following standard work-up, the nmr of the product showed no evidence of II.

C. I HCl and Pyridine.—A solution of these compounds (1.0 and 5 g, respectively) in 50 ml of 90% ethanol was refluxed for 4 hr under nitrogen. Standard work-up gave a product consisting of IV and II in approximate ratio 2:1. Pilot experiments were undertaken to develop a method of determining pyridine *N*-oxide: the reaction mixture was to be diluted with several hundred milliliters of water and the pyridine removed by distillation; pyridine *N*-oxide would remain in the residue and be determined

(44) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds, A Laboratory Manual," 5th ed, Wiley, New York, N. Y., 1964, p 336.

by uv absorption. Pyridine has λ_{max} 256 nm (log ϵ 3.5); pyridine N-oxide has λ_{max} 255 nm (log ϵ 4.1). Distillation of a dilute solution of pyridine caused eventual disappearance of the 256-nm maximum, but end absorption persisted off scale at low wavelength; evidently an impurity had been concentrated. Distillation had no effect on the absorbance of dilute pyridine N-oxide solution [N-oxide from Aldrich was recrystallized from CCl_4; colorless plates, mp 68–69° (lit.[45] mp 65–66°), were used]. Distillation of a solution of pyridine and pyridine N-oxide gave a uv spectrum lacking the fine structure characteristic of pyridine, but with λ_{max} 255 nm, and going off scale as characteristic of the impurity in pyridine. The reaction mixture, after pentane extraction of II and IV, gave after distillation a residue with the uv maximum typical of pyridine N-oxide and the impurity; absorbance of 2.1 l. of solution was 0.60; concentration of oxide was therefore 4.3×10^{-5} M, total 9.1×10^{-5} mol; theoretical yield of oxide assuming 65% yield of IV was 2.7×10^{-3} mol; actual yield was 3.3% of theory.

(45) H. S. Mosher, L. Turner, and A. Carlsmith, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 828.

Registry No. —I HCl, 16547-17-4; II, 6880-03-1; IV, 614-30-2; IV picrate, 38734-75-7; monoperthalic acid, 2311-91-3; O_2, 7782-44-7; *tert*-dodecanethiol, 25103-58-6; CCl_4, 56-25-3.

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Mechanism of the Base-Induced Decomposition of N-Nitroso-N-methylurea

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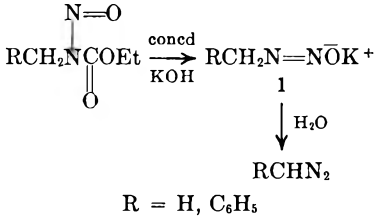
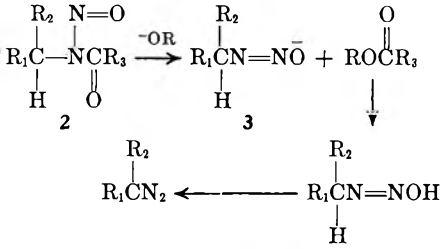
The mechanism corresponding to the base-induced decomposition of N-nitroso-N-methylurea is discussed. Evidence is presented for the decomposition which is consistent with initial abstraction of a urea proton, but not with a mechanism involving initial nucleophilic addition to the nitroso or carbonyl groups.

The base-induced decomposition of N-nitrosoamides, -carbamates, and -ureas to diazoalkanes has been the subject of many synthetic and mechanistic investigations. The mechanistic considerations, in particular, have stimulated considerable debate. In 1894, von Pechmann established that the hydroxide-induced decomposition of nitrosocarbamates afforded diazoalkanes.[1] Hantzsch and Lehmann[2] isolated the methyl and benzyl diazotates (1) and demonstrated that treatment of 1 with water afforded the corresponding diazoalkanes.



An investigation by Gutsche and Johnson[3] of the methoxide-induced decomposition of several N-nitroso-N-benzylcarbamates expanded this scheme (Scheme I) and the subsequent isolation of methyl ethyl carbonate[4] from the base-induced conversion of N-nitroso-N-cyclohexylurethane (2a) provided convincing evidence for a mechanism initiated by methoxide attack on the carbonyl carbon. This scheme has also been established as operative for the decomposition of N-nitrosoamides.[5-7] Similarly, by indicating the formation of alkyl carbamate, Applequist and McGreer[8] implied that the alkoxide-induced decomposition of N-nitroso-N-cyclobutylurea (2b) to diazocyclobutane was initiated by attack on the carbonyl moiety.

SCHEME I

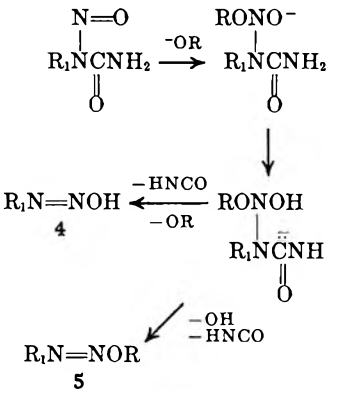


a, R_1 = H; R_2 = C_6H_{11}; R_3 = OEt
b, R_1R_2 = $(CH_2)_3$; R_3 = NH_2

In 1966, however, Jones, Muck, and Tandy[9] described experiments which appeared to exclude the Applequist and McGreer scheme as a possible mechanism for the conversion of N-nitroso-N-(2,2-diphenylcyclopropyl)urea to 2,2-diphenyldiazocyclopropane. They provided an alternate mechanism involving alkoxide attack on the nitroso moiety of the urea (Scheme II). A third mechanism which involved proton abstraction as the first step (Scheme III) was also excluded on the basis of several observations. Jones, *et al.*,[9] were careful to limit their discussion to the decomposition of N-nitroso-N-(2,2-diphenylcyclo-

(1) H. von Pechmann, *Chem. Ber.*, **27**, 1888 (1894).
(2) A. Hantzch and M. Lehmann, *Chem. Ber.*, **35**, 897 (1902).
(3) C. D. Gutsche and H. E. Johnson, *J. Amer. Chem. Soc.*, **77**, 109 (1955).
(4) F. W. Bollinger, F. N. Hayes, and S. Siegel, *J. Amer. Chem. Soc.*, **72**, 5592 (1950).
(5) R. Huisgen and J. Reinertshofer, *Justus Liebigs Ann. Chem.*, **575**, 174 (1952).
(6) R. Huisgen, *Justus Liebigs Ann. Chem.*, **573**, 173 (1951).
(7) C. D. Gutsche and I. Y. C. Tao, *J. Org. Chem.*, **28**, 883 (1963).
(8) D. E. Applequist and D. E. McGreer, *J. Amer. Chem. Soc.*, **82**, 1965 (1960).
(9) W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., *J. Amer. Chem. Soc.*, **88**, 68 (1966).

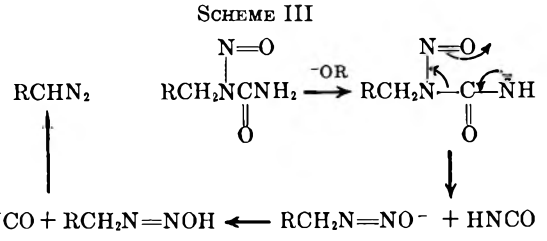
SCHEME II



propyl)urea. A subsequent review has, unfortunately, indicated the validity of the mechanistic conclusions for "several nitrosoureas."[10] We therefore wish to discuss our findings for the base-induced decomposition of *N*-nitroso-*N*-methylurea.

During the course of a study on the generation and utilization of diazomethane, it became apparent that the mechanism outlined in Scheme II was inconsistent with the alkoxide-induced decomposition of *N*-nitroso-*N*-methylurea, a transformation which might better be rationalized by the mechanism outlined in Scheme III. The experiments which led to this conclusion

SCHEME III



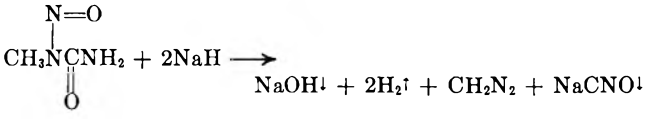
have been described briefly in a previous report.[11] A more detailed description of these experiments, with additional evidence in favor of the proton abstraction mechanism, is now presented.

Results and Discussion

Published evidence excluding the carbonyl addition mechanism (Scheme I) for the base-induced decomposition of *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea is substantial. Jones, *et al.*,[9] found less than 1% ethyl carbamate resulting from the lithium ethoxide induced decomposition of *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea. They also determined that ethyl carbamate, had it been formed, would have been stable to the reaction conditions, a finding which has been corroborated in this laboratory. Also, decomposition *via* the mechanism outlined in Scheme I would require the presence of at least a catalytic amount of ethanol. Alcohol-free lithium ethoxide was found to effect the decomposition of *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea in anhydrous ether in 20 min at 0°. A similar result has been obtained in this laboratory for *N*-nitroso-*N*-methylurea. These two lines of evidence are sufficient to exclude the carbonyl addition mechanism for the decomposition of *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea or *N*-nitroso-*N*-methylurea.

In addition, the finding that lithium 2,2-diphenylcyclopropyl diazotate was stable to lithium ethoxide–ethanol and to isocyanic acid strongly suggested that the mechanism outlined in Scheme III could not be operative for the decomposition of *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea, since it contained the diazotate as an obligatory intermediate. In this regard the chemistry of methyl diazotate appears to differ from that of lithium 2,2-diphenylcyclopropyl diazotate. Specifically, treatment of $CH_3N{=}NO^-K^+$ with excess isocyanic acid in tetrahydrofuran at 0°, under rigorously anhydrous conditions, afforded potassium cyanate and nitrogen liberation, corresponding to the formation of diazomethane. When decomposition was effected in the presence of isocyanic acid and a less acidic carboxylic acid, the methyl carboxylate was formed. Similar results were obtained when a single equivalent of isocyanic acid was employed or when excess diazotate was present. Thus, there exists at least one diazotate whose reactivity with isocyanic acid is consistent with the mechanism outlined in Scheme III.

Clearly, this finding suggests that the proton-abstraction mechanism should not be dismissed *a priori* as incorrect for all *N*-nitroso-*N*-alkylureas. Simple considerations of acid–base equilibria make a rapid, quantitative proton transfer (urea, $pK_a \cong 16$; ethanol, $pK_a \cong 17$) an attractive first step in the decomposition. Moreover, several experiments suggest that the proton-abstraction mechanism (Scheme III) is actually operative in the decomposition of *N*-nitroso-*N*-methylurea. For example, treatment of *N*-nitroso-*N*-methylurea with sodium hydride in dry 1,2-dimethoxyethane under anhydrous conditions resulted in the decomposition of the urea to diazomethane[12] in quantitative yield, according to the following equation.



The strongly basic nature of sodium hydride (pK_a = 40) undoubtedly precludes nucleophilic addition to the nitroso group in the presence of the relatively acidic urea protons (pK_a = 16).[13] A similar result was obtained from the addition of 1 equiv of anhydrous *n*-butyllithium to a solution of *N*-nitroso-*N*-methylurea in dry 1,2-dimethoxyethane. Immediate decomposition of the urea to diazomethane was observed; this material could be used in the conversion of 1 equiv of a carboxylic acid to its methyl ester (87% yield). If the decomposition was run in the presence of a second equivalent of *n*-butyllithium, lithium methyl diazotate was formed.

The decomposition of *N*-nitroso-*N*-methylurea with hindered bases also supports this mechanism. Treatment of the urea with excess triethylamine in 1,2-dimethoxyethane effected decomposition to diazo-

(10) G. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 1191 (1970).

(11) S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, 5147 (1972).

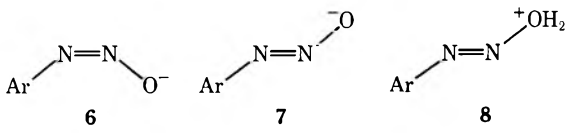
(12) *N*-Nitroso-*N*-methylurea is stable to a suspension of sodium hydroxide in dry 1,2-dimethoxyethane, under the reaction conditions.

(13) W. P. Jencks and J. Regenstein in "CRC Handbook of Biochemistry," 2nd ed, H. A. Sober, Ed., Chemical Rubber Company, Cleveland, Ohio, 1970, pp J-187–J-226.

nium products. Since triethylamine is a very hindered base, which exhibits poor nucleophilic properties as a result of this steric hindrance, the proton-abstraction mechanism (Scheme III) would seem more consistent with the observed results. Treatment of *N*-nitroso-*N*-methylurea with 1 equiv of potassium *tert*-butoxide also resulted in the rapid formation of diazomethane. Treatment with a twofold excess of potassium *tert*-butoxide resulted in the formation of potassium methyl diazotate, which rapidly decomposed to diazomethane upon addition of water.[14]

Additional supporting evidence may be obtained from the decomposition of *N*-nitroso-*N*-methylurea with anions of widely varying base strength and nucleophilic character. The mechanism outlined in Scheme III can only be operative in the presence of a strong base. In this context, it is significant that the half-life of *N*-nitroso-*N*-methylurea in the presence of phenoxide and thiophenoxide anions was ~75 and 210 sec, respectively, in the sense that phenoxide is a stronger base than thiophenoxide (although a far weaker nucleophile). Under the same conditions, the decomposition of *N*-nitroso-*N*-methylurea by hydroxide ion was too fast to measure. Further verification of base control in the decomposition was provided by the smaller amount of *N*-nitroso-*N*-methylurea decomposed by a given amount of thiophenoxide, relative to the phenoxide anion (Figure 1).

The results of decomposition obtained for *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea and *N*-nitroso-*N*-methylurea might be considered compatible if the apparent stability of 2,2-diphenylcyclopropyldiazotate to moderately strong acids could be explained. A reasonable approach to this problem might be the initial assumption that the reaction pathway from the individual diazotates to their respective final products was achieved *via* transition states of rather different energies. For example, early work in this field[15] established the difference in reactivities of syn and anti aryl diazotates. While the syn diazotates (6) rapidly afforded diazonium ions, their anti isomers (7) yielded these products slowly, the rate-determining step in the latter case apparently involving isomerization to the syn diazotate or formation of the conjugate acid (8).[16] Although alkyl diazotates have not been



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noted to isomerize, ostensibly owing to the instability of each of the geometrical isomers,[17] 2,2-diphenylcyclopropyldiazotate might be thought to exist largely as the less reactive anti isomer owing to steric constraints and to possess a higher energy barrier to decomposition than other alkyl diazotates on the basis of steric or electronic effects associated with the 2,2-diphenylcyclopropyl moiety. Alternatively, 2,2-diphenylcyclopropyl diazotate might be thought to form the observed ring-opened product *via* some species other than a diazoalkane, *e.g.*, a carbene.[18]

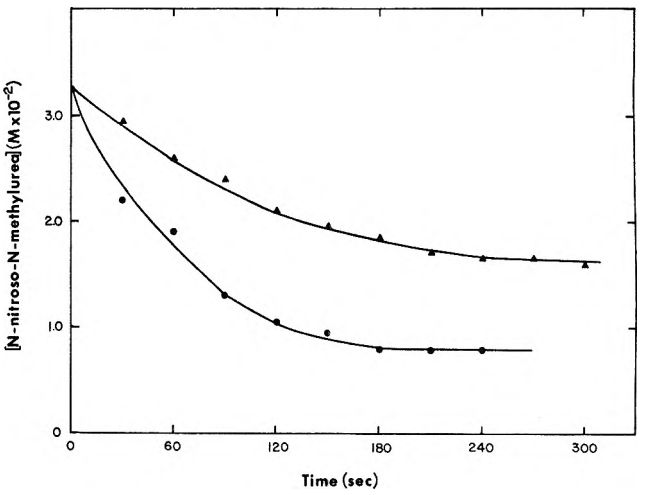

Figure 1.—Decomposition curves for *N*-nitroso-*N*-methylurea in the presence of thiophenoxide (▲) and phenoxide (●) anions, respectively.

Experimental Section

Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Infrared spectra were determined on a Perkin-Elmer 457A spectrophotometer, through the courtesy of Professor Dietmar Seyferth.

Treatment of Potassium Methyl Diazotate with Isocyanic Acid in Tetrahydrofuran.—Isocyanic acid was generated by thermolysis of cyanuric acid at 380–400° and introduced into tetrahydrofuran which had been precooled to 0°. The normality of the solution was determined by titration of an aliquot with a standardized sodium hydroxide solution. Potassium methyl diazotate (0.10 g, ~1.0 mmol) was suspended in 10 ml of THF at 0°. Isocyanic acid (~0.6 mmol) in 50 ml of THF was added and the mixture was stirred at 0° under anhydrous conditions for 3 hr, during which time gas evolution was observed. The reaction mixture was then concentrated and an infrared spectrum of the residue revealed the presence of cyanate ion (2275 cm^{-1}).

This reaction was repeated utilizing an isocyanic acid solution which contained excess *p*-nitrobenzoic acid. At the conclusion of the reaction the solution was concentrated and treated with ether. The ethereal layer was extracted with water and sodium bicarbonate solution and dried. Concentration afforded methyl *p*-nitrobenzoate in 90% yield, based on limiting diazomethane.

Decomposition of *N*-Nitroso-*N*-methylurea with Sodium Hydride in 1,2-Dimethoxyethane.—To a suspension of sodium hydride (1.00 g, 41.7 mmol) in 20 ml of 1,2-dimethoxyethane at 0° was added *N*-nitroso-*N*-methylurea (2.15 g, 20.8 mmol) in 15 ml of 1,2-dimethoxyethane. The suspension was maintained under anhydrous conditions. Gas evolution began immediately and the mixture was stirred at 0° for 3 hr. The solution slowly turned yellow owing to the generation of diazomethane. The diazomethane solution was decanted and utilized in the methylation of an excess of *p*-nitrobenzoic acid (3.43 g of ester isolated, corresponding to 91% diazomethane formation.) No *N*-nitroso-*N*-methylurea remained at the conclusion of the reaction, as judged by ultraviolet spectroscopy.

Decomposition of *N*-Nitroso-*N*-methylurea with *n*-Butyllithium in 1,2-Dimethoxyethane. One Equivalent of *n*-Butyllithium.—To a solution of *N*-nitroso-*N*-methylurea (220 mg, ~2.2 mmol) in 10 ml of 1,2-dimethoxyethane was added *n*-butyllithium (1 ml, 2.2 *M* in pentane, 2.2 mmol). Lithium cyanate (98 mg, 91%, identified by infrared spectroscopy) precipitated from solution, which assumed the yellow color indicative of diazomethane formation. The diazomethane solution was utilized in the esterifi-

(14) For Scheme II to be operative here, it would be necessary to postulate that *deprotonation* of the diazohydroxide occurred faster than its decomposition while *protonation* of the diazotate was slow.

(15) H. Zolling, "Diazo and Azo Chemistry, Aliphatic and Aromatic Compounds," Interscience, New York, N. Y., 1961.

(16) B. A. Porai-Koshits, *Zh. Org. Khim.*, **2**, 1125 (1966).

(17) E. H. White, T. J. Ryan, and K. W. Field, *J. Amer. Chem. Soc.*, **94**, 1360 (1972).

(18) For a thorough discussion of possible intermediates see (a) W. M. Jones and M. H. Grasley, *Tetrahedron Lett.*, 927 (1962); (b) ref 9; (c) W. M. Jones and J. M. Walbrick, *J. Org. Chem.*, **34**, 2217 (1969).

cation of *p*-nitrobenzoic acid (346 mg of methyl *p*-nitrobenzoate isolated, 87% yield, based on limiting CH_2N_2).

Two Equivalents of *n*-Butyllithium.—To a sodium of *N*-nitroso-*N*-methylurea (220 mg, ~2.2 mmol) in 10 ml of 1,2-dimethoxyethane under N_2 was added *n*-butyllithium (2 ml, 2.2 *M* in pentane, 4.4 mmol). A precipitate (202 mg) formed and no diazomethane generation was observed. Quenching of the isolated precipitate with H_2O afforded rapid gas liberation and diazomethane, suggesting that the precipitate was a mixture of lithium cyanate and the methyl diazotate. This was supported by the infrared spectrum of the solid, which had bands at 2275 (cyanate) and 2180 cm^{-1} (diazotate).

Decomposition of *N*-Nitroso-*N*-methylurea with Triethylamine in 1,2-Dimethoxyethane.—To a solution of *N*-nitroso-*N*-methylurea (0.50 g, ~5 mmol) in 15 ml of 1,2-dimethoxyethane at 0° was added triethylamine (2.7 ml, 25 mmol). Gas evolution began immediately and the decomposition of the urea was followed spectrophotometrically. The reaction was complete in 45 min. The final solution contained cyanate ion, as judged by infrared spectroscopy. The diazomethane generated by this procedure could be trapped by the addition of *p*-nitrobenzoic acid to the initial reaction mixture.

Decomposition of *N*-Nitroso-*N*-methylurea with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.—To a solution of potassium *tert*-butoxide (2.17 g, 19.4 mmol) in 50 ml of *tert*-butyl alcohol at 20° was added *N*-nitroso-*N*-methylurea (1.0 g, 9.7 mmol). The suspension was maintained under nitrogen and stirred for 20 min. Essentially no diazomethane was observed to have been formed. The suspension of potassium cyanate was filtered, yield 0.73 g (96%), identification by infrared spectroscopy. The filtrate was concentrated under diminished pressure to afford potassium methyl diazotate as a yellow solid, yield 0.76 g (~80%, identification by infrared spectroscopy), which rapidly decomposed (gas evolution) upon addition of water. Decomposition of the urea with 1 equiv of potassium *tert*-butoxide resulted in the rapid formation of diazomethane. The diazomethane could be utilized in the conversion of *p*-nitrobenzoic acid to its methyl ester. The yield of diazomethane (based on methyl *p*-nitrobenzoate formed in the presence of excess *p*-nitrobenzoic acid) was about 90%. Work-up of the initial reaction mixture indicated the presence of potassium cyanate (93%) and methyl diazotate (18%).

Rate of Decomposition of *N*-Nitroso-*N*-methylurea by Sodium Phenoxide and Sodium Thiophenoxide.—*N*-Nitroso-*N*-methylurea (67 mg, 0.65 mmol) was dissolved in 20 ml of 1,2-dimethoxyethane. The solution was cooled to 0° and sodium phenoxide (75 mg, 0.65 mmol) was added quickly. At 30-sec intervals, 20 μl of the solution was added to 2 ml of EtOH and acidified with 2 drops of 1 *N* hydrochloric acid solution, which quenched the reaction. The ultraviolet absorbance spectrum (A_{230}) was recorded for each aliquot and then 4 *N* sodium hydroxide solution was added to decompose the unreacted urea. The solution was reacidified and A_{230} was again recorded. The difference in each set of two spectra was employed as a measure of unreacted *N*-nitroso-*N*-methylurea. A control experiment demonstrated that all *N*-nitroso-*N*-methylurea absorbance was eliminated by the acid–base treatment and did not affect the other reactants.

Data for the phenoxide- and thiophenoxide-induced decompositions of *N*-nitroso-*N*-methylurea indicated half-lives of decomposition of ~75 and 210 sec, respectively.

Registry No.—*N*-Nitroso-*N*-methylurea, 684-93-5.

Acknowledgments.—We thank Professors C. G. Swain and F. D. Greene for helpful discussions during the course of this work.

Synthesis of 2-Aminomethylpyrroles and Related Lactams

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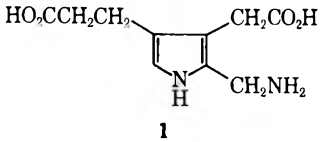
The potassium enolate of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate was C-alkylated and C-acylated with methyl iodide, ethyl iodide, *n*-propyl iodide, ethyl bromoacetate, ethyl chloroformate, and benzyl chloroformate and the corresponding ethyl 2-oxobutyrate, 2-oxocaproate, 2-oxoglutarate, and the oxalacetates were obtained. The same procedure afforded the 2-benzyloxy and 2-anisyloxy oxalacetates. Reductive cyclization of the α-keto monoesters afforded the corresponding ethyl 5-methoxy-6-azaindole-2-carboxylates and in several cases also the 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-ones. The 6-azaindoles were transformed with hydrobromic acid into the corresponding 6-azaindanones, which were reduced to the corresponding 2-carboxy-3-alkylpyrrole lactams. The latter were transformed into the corresponding 4-alkyl-3-carboxymethyl-2-aminomethylpyrroles. The catalytic hydrogenation of the oxalacetates, followed by cyclization of the resulting 5-aminopyridines, afforded 2,3-dicarbethoxy-6-azaindoles and 2,3-dicarbethoxy-6-azaindanone. The latter were transformed by catalytic hydrogenation into diethyl 5-oxo-3a,4,5,6-tetrahydro-1*H*-pyrrolo[2,3-c]pyridine-2,3-dicarboxylate which could not be saponified to a 2-aminomethylpyrrole.

The synthesis of 2-aminomethyl-3-carboxymethylpyrroles was a task of particular interest in pyrrole chemistry ever since it was conclusively established[1] that the natural metabolite porphobilinogen was a 2-aminomethyl-3-carboxymethyl-4-carboxyethylpyrrole **1**. This unique compound has no other metabolic



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analogs and, since it is the precursor of all the natural porphyrins, chlorins, and corrin derivatives,[2] it was tempting to develop a synthetic method which should afford not only porphobilinogen but also analogous 2-aminomethylpyrroles to study their chemical and biological behavior. 2-Aminomethylpyrroles proved also to be very suitable intermediates for dipyrrylmethane synthesis,[3] being in many senses more advantageous than the classical 2-bromomethyl or 2-acetoxymethylpyrrole derivatives.

In our previous work[4] we approached the problem of the synthesis of porphobilinogen **1** by considering it to be a derivative of a 5-oxo-4,5,6,7-tetrahydro-6-azaindole (pyrrole lactam) structure. The synthesis of the 6-azaindole ring was then achieved[4] by a sequence modeled on the Reissert-type synthesis of indoles, which was based on the synthesis of the ethyl *o*-nitro-4-pyr-

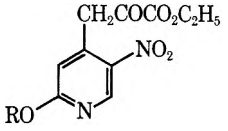
(1) G. H. Cookson and C. Rimington, *Biochem. J.*, **57**, 476 (1954).

(2) J. Lascelles, "Tetrapyrrole Biosynthesis and its Regulation," W. A. Benjamin, New York, N. Y., 1964, p 47.

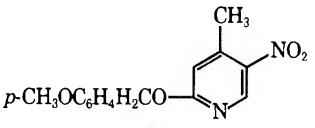
(3) B. Frydman, S. Reil, A. Valasinas, R. B. Frydman, and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 2738 (1971).

(4) B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 3530 (1965); B. Frydman, S. Reil, M. E. Despuy, and H. Rapoport, *ibid.*, **91**, 2338 (1969).

idinepyruvates **2** and **3**, and its catalytic hydrogenation and subsequent cyclization to give the corresponding ethyl 6-azaindole-2-carboxylates. The easily available potassium enolates of **2** and **3** offered the possibility of obtaining different 4-alkyl-2-aminomethyl-3-carboxymethylpyrroles by a C-alkylation of the pyruvate carbon atom followed by subsequent synthetic sequence analogous to that used in our previous porphobilinogen synthesis.[4] The C-alkylation on the same carbon atom could also open the possibility of obtaining 2-aminomethylpyrroles with β-unsaturated residues. An additional ethyl pyridinepyruvate was obtained by preparing 2-anisyloxy-5-nitro-4-methylpyridine **4** and condensing it with ethyl oxalate in the presence of potassium ethoxide. The resulting ethyl 2-anisyloxy-5-nitro-4-pyridinepyruvate **5** had the potential synthetic



2, R = CH_3
3, R = $CH_2C_6H_5$
5, R = $CH_2C_6H_4$-*p*-OCH_3



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advantage of the lability of the anisyloxy group to treatment with mild acids.

By treating the potassium enolate of **2** with alkyl iodides or ethyl bromoacetate the corresponding α-keto esters **6**, **7**, **8**, and **9** were obtained. The attempted alkylation of the potassium enolate with ethyl β-iodopropionate was unsuccessful and led to the recovery of the ethyl pyridinepyruvate **2** and to formation of ethyl acrylate by a β-elimination reaction. The C-acylation of **2** with ethyl chloroformate and benzyl chloroformate afforded the corresponding oxalacetates: diethyl 3-(2′-methoxy-5′-nitro-4′-pyridyl)oxalacetate (**10**) and the benzyl ethyl oxalacetate **11**.

In a similar manner, treatment with ethyl chloroformate of the potassium enolates of **3** and **5** allowed the synthesis of the oxalacetates **12** and **13** (Scheme I and Table I).

TABLE I

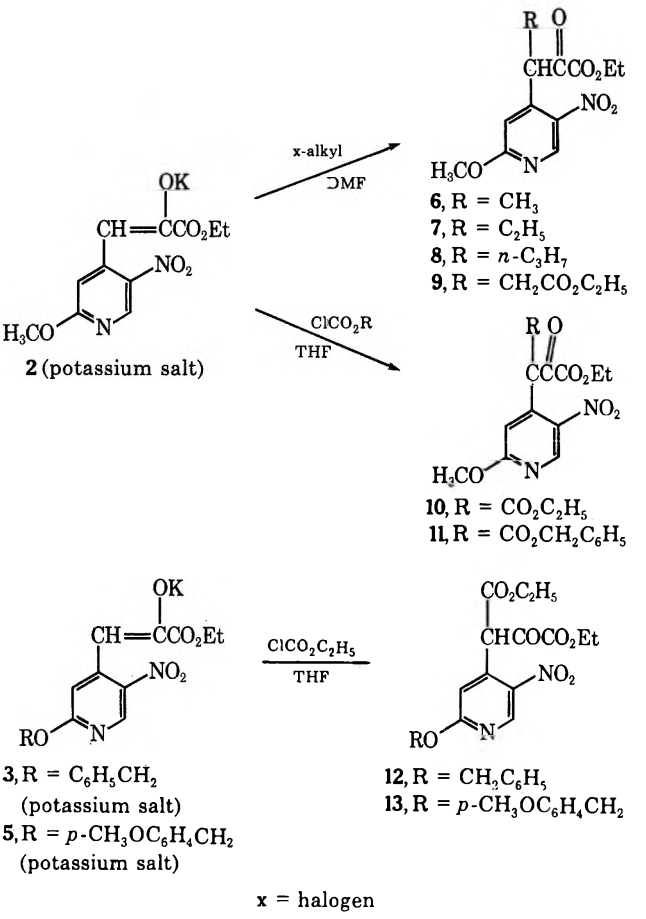
ETHYL 3-(5′-NITRO-4′-PYRIDYL)-2-KETO ESTERS[a]

Compd	Mp, °C	Yield, %
6	83–84	40
7	35–36	32[b]
8	48–50	14[b]
9	...[c]	24[b]
10	64–65	65
11	84–86	50[d]
12	83–84	60[d]
13	64–65	40[d]

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds: Ed. [b] Prepared with the same procedure used for the synthesis of **6**. [c] Bp 188–190° (0.005 mm). [d] Prepared with the same procedure used for the synthesis of **10**.

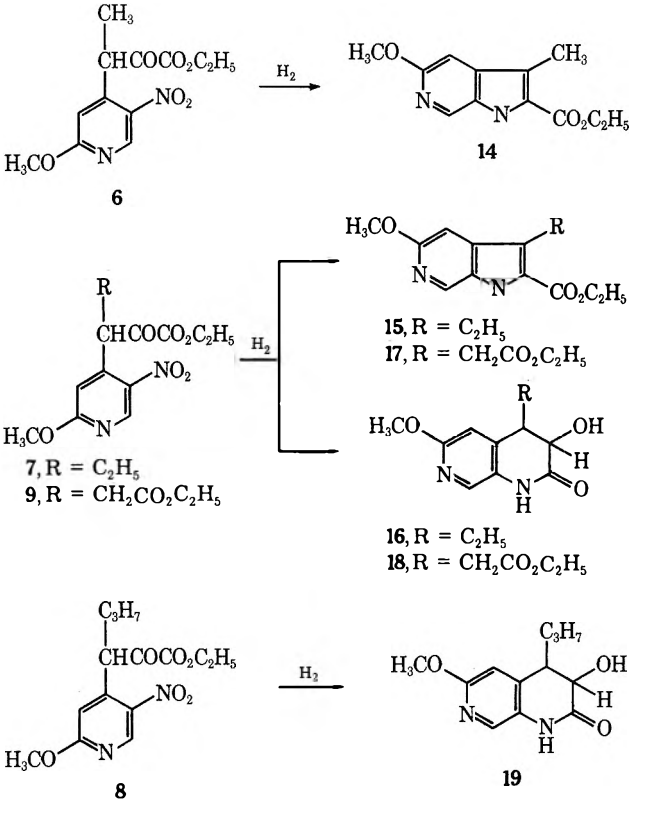
The catalytic hydrogenation of **6** over palladium afforded exclusively the ethyl 3-methyl-5-methoxy-6-azaindole-2-carboxylate **14**, formed by the spontaneous cyclization of the intermediate 5-aminopyridine. When the same reductive cyclization was applied to the α-ketovalerate **7** two compounds were obtained: the ethyl 3-ethyl-5-methoxy-6-azaindole-2-carboxylate

SCHEME I



15 (23%) and the 1,2,3,4-tetrahydro-3-oxy-4-ethyl-6-methoxy-1,7-naphthyridin-2-one **16** (47%) (Scheme II). Both substances could be easily separated due to

SCHEME II

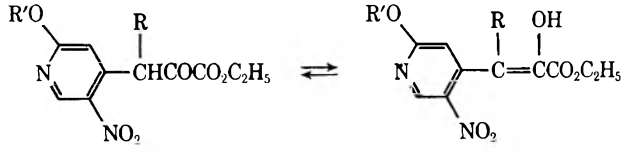


their different basicities, since the naphthyridinone **16** gave a water-soluble hydrochloride while the 6-azaindole **15** did not. The catalytic hydrogenation of the α-ketoglutarate **9** afforded the 3-ethoxycarbonylmethyl-6-azaindole **17** (73%), together with some 3-oxynaphthyridinone **18** (11%), and they were also separated by making use of their different basicities. The catalytic hydrogenation of the α-ketocaproate **8**, resulted in the exclusive formation of the 3-oxy-4-propyltetrahydronaphthyridinone **19**.

The formation of both types of ring systems, 6-azaindoles and 1,7-naphthyridinones, can be rationalized on the basis of the keto–enol equilibrium of the α-keto esters. As can be seen in Table II the 4′-pyridyl-2-keto esters exist in a keto–enol equilibrium. The shift of the hydroxylic proton in the latter (δ 7.2) suggest that it exists in an intramolecular hydrogen bond, probably bridged with the oxygen of the vicinal ester carbonyl group. When the simultaneous hydrogenation of the enol form and the nitro group took place, the formation of the six-membered ring was the only choice and a 3-oxynaphthyridin-2-one was obtained. In the case of **6**, where the steric effect of the methyl group and the ethoxycarbonyl group repressed entirely the enol formation, only a 6-azaindole was obtained, since the formation of a five-membered ring could be expected to prevail as long as the α-keto group is available. This was also the predominant compound during the reductive cyclization of **9**, while **8** afforded only a naphthyridinone and **7** a mixture of both types of compounds, as could be expected from the equilibrium between the keto and enol forms (Table II).

TABLE II

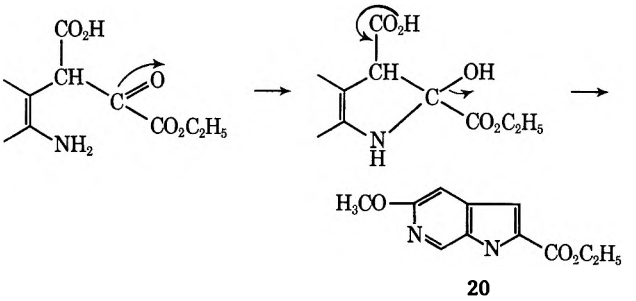
KETO–ENOL EQUILIBRIUM OF ETHYL 3-(5′-NITRO-4′-PYRIDYL)-2-KETO ESTERS[a]



Compd	H_3	C=C(OH)	R
6	5.2, q, 1 (J = 7.0)		1.6, d, 3 (J = 7.0)
7	5.5, t, 0.5 (J = 8.0)	7.32, s, 0.5	1.4, t, 4.5; 4.3, m, 3
8		7.2, s, 1	0.9, t, 3 (J = 6.0) 1.67, q, 2 (J = 6.0) 3.9, t, 2 (J = 6.0)
9	5.5, t, 1 (J = 8.0)		3.05, d, 2 (J = 8.0)
10		7.25, s, 1[b]	
11		7.2, s, 1	
12		7.7, s, 1	
13		7.65, s, 1	

[a] Nmr spectra: (δ values, multiplicity, integral value (J in Hz). [b] Ir spectra 3500 (OH), 1790, 1750 (CO esters), 1670 cm^{-1} (CO keto).

The catalytic hydrogenation of the oxalacetates **10**–**13** took a different course. The benzyl ethyl oxalacetate **11**, when reduced with hydrogen either over palladium or over platinum under mild conditions, was unexpectedly transformed into the ethyl 5-methoxy-6-azaindole-2-carboxylate **20**. The loss of the benzyloxycarbonyl group could originate in a previous hydrogenolysis of the benzyl group followed by a decarboxylation during the cyclization process.



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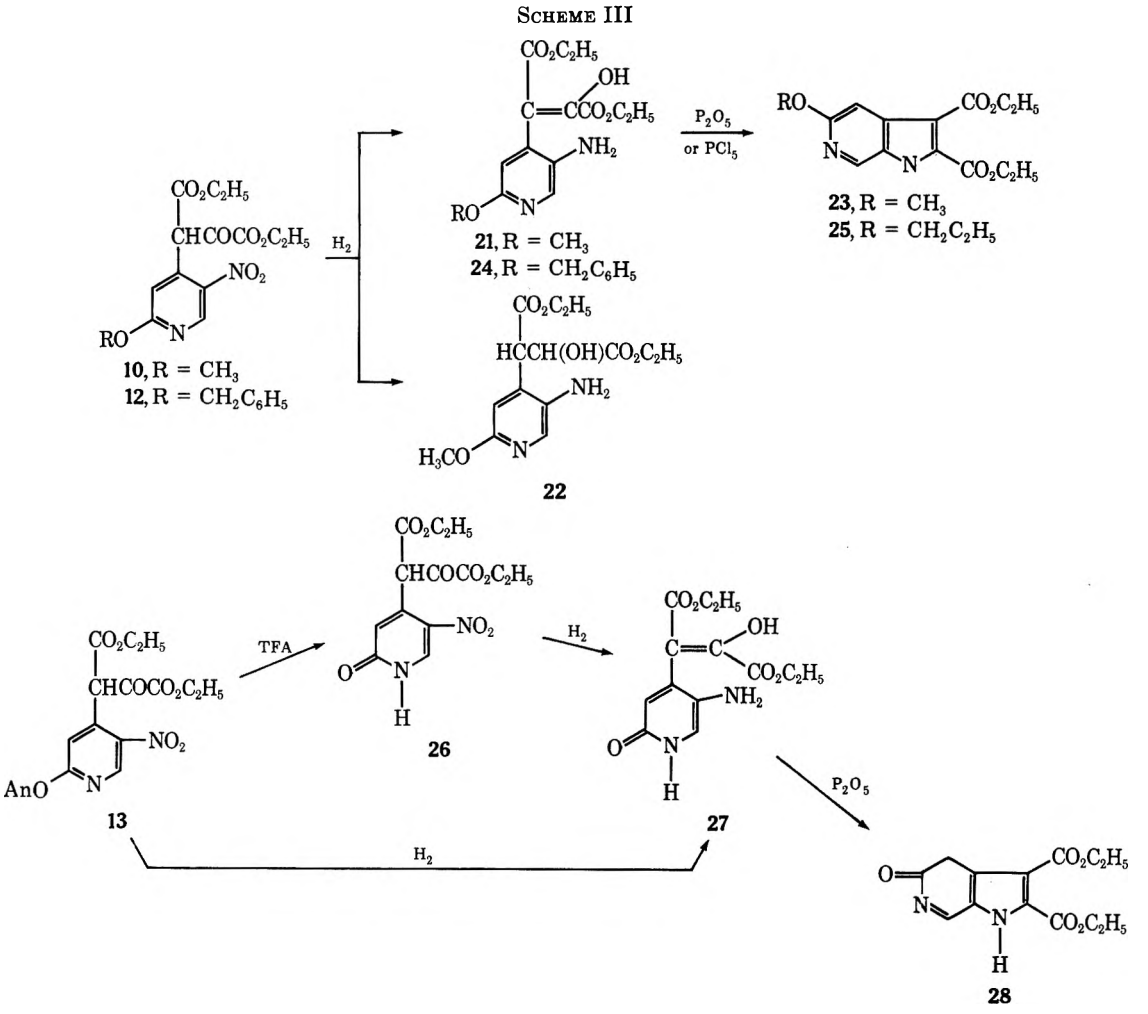
The catalytic hydrogenation of the diethyl oxalacetate **10**, however, afforded the 5-aminopyridine derivative **21** together with a small amount of its reduced derivative, the diethyl malate **22** (Scheme III). The 5-aminopyridine **21** existed entirely in its enolic form (see Experimental Section) and the nonformation of a 3-oxynaphthyridinone derivative must be attributed to the steric effect across the double bond, with the ethoxycarbonyl and aminopyridyl groups lying trans to each other. Its cyclization could not be achieved by thermal means (boiling butanol or decaline) or by treatment with *p*-toluenesulfonyl chloride in pyridine. An efficient cyclization method was achieved by treatment with phosphorus pentoxide in xylene, which resulted in the exclusive formation of the diethyl 6-azaindole-2,3-dicarboxylate **23**. In an analogous manner, the catalytic hydrogenation of the 2′-benzyloxy diethyl oxalacetate **12** afforded the 5-aminopyridine derivative **24**, which was cyclized by treatment with phosphorus pentachloride in dry chloroform to the 5-benzyloxy-6-azaindole derivative **25**.

The catalytic hydrogenation of the 2′-anisyloxy-4′-pyridyloxalacetate **13** took place with a simultaneous hydrogenolysis of the anisyloxy group which could also be cleaved with trifluoroacetic acid first, and the resulting 2′-hydroxy-5′-nitro-4′-pyridyl oxalacetate **26** could then be hydrogenated to the 5-aminopyridine derivative **27**. The ir and nmr data indicated that both **26** and **27** had the α-pyridone structure. The ester **27** could also be obtained directly from **12** by catalytic hydrogenation, as mentioned above, but the overall yields were lower than in the two-step procedure. The diethyl 5-aminopyridone oxalacetate **27**, was then cyclized by means of the phosphorus pentoxide–xylene procedure and the 6-azaindanone **28** was obtained. The structure of **28** was assigned on the basis of its spectral data. The cyclic amide carbonyl adsorbed at 1675 and 1640 cm^{-1}, the nmr spectra indicated the presence of a methylene group and an aromatic proton in the ring, and the fragmentation in the mass spectrum showed the loss of a ring carbonyl group. The 6-azaindoles **14**, **15**, and **17** were then transformed into the corresponding 2-aminomethylpyrroles. The synthesis of **17** by a multistep procedure and its transformation into 3,4-dicarboxymethyl-2-aminomethylpyrrole has already been described.[4] The present simplified synthesis of **17** makes the aforementioned pyrrole easily accessible. The two azaindoles **14** and **15** were treated with hydrobromic acid, the ether group was cleaved and the 6-azaindanones **29** and **30** were obtained (Scheme IV).

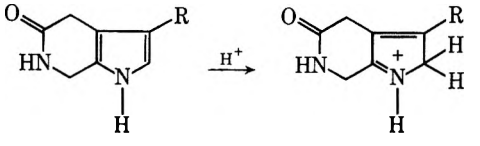
The ir and nmr spectra confirmed the assigned structures, isomeric with the formerly described 6-azainda-

SCHEME III



An = anisyl

none **28**. By catalytic hydrogenation of **29** and **30**, the 2-carboxypyrrole lactams **31** and **32** were obtained. They were decarboxylated by heating at 100° in water. The obtained lactams **33** and **34** were very stable to oxidation by air and to heat (they were easily sublimed), unlike the open-chain alkylpyrroles. In trifluoroacetic acid they existed entirely in the conjugated α-pyrrolenine form (see Experimental Section).



They were saponified at room temperature to the corresponding 2-aminomethylpyrroles **35** and **36** (Scheme IV). These pyrroles were very unstable and started to polymerize at 37° forming porphyrins, as was discussed in detail elsewhere.[5]

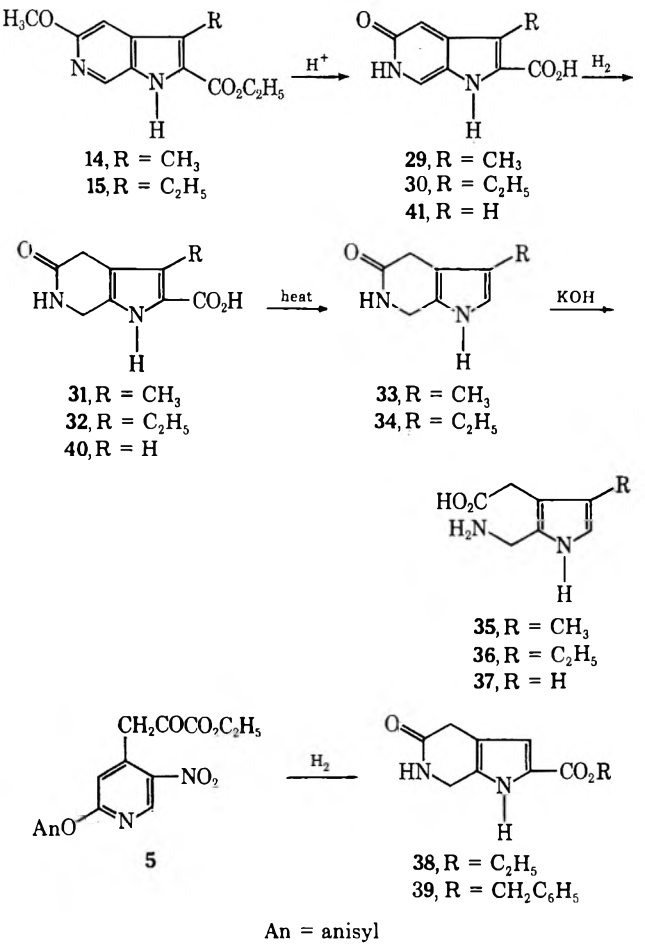
The available intermediates also allowed a simple synthesis of the interesting 2-aminomethyl-3-carboxymethylpyrrole **37**. The catalytic hydrogenation of the anisyloxy pyridinepyruvate **5** afforded directly the 2-ethoxycarbonylpyrrole lactam **38** in good yield. (Scheme IV). The intermediate 6-azaindanone derivative was not isolated and must be reduced "*in situ*" during the hydrogenation. The lactam **38** was transesterified to the benzyl ester **39** and the latter was transformed by hydrogenolysis into the 2-carboxypyrrole **40**. The transformation of **40** into **37** has already been described elsewhere.[4]

The sequence of reactions depicted in Scheme IV was now applied to the 2,3-dicarbethoxy-6-azaindoles in the hope of obtaining the lactam **42**. When the azaindole **23** was treated with hydrobromic acid, the carboxy group at C-3 was unexpectedly cleaved and the 2-carboxy-6-azaindanone **41** was obtained. Hydrogenolysis of the diethyl 5-benzyloxy-6-azaindole-2,3-carboxylate **25** afforded the 3a,4,5,6-tetrahydro-6-azaindole **43**, instead of the expected pyrrole lactam **42** (Scheme V).

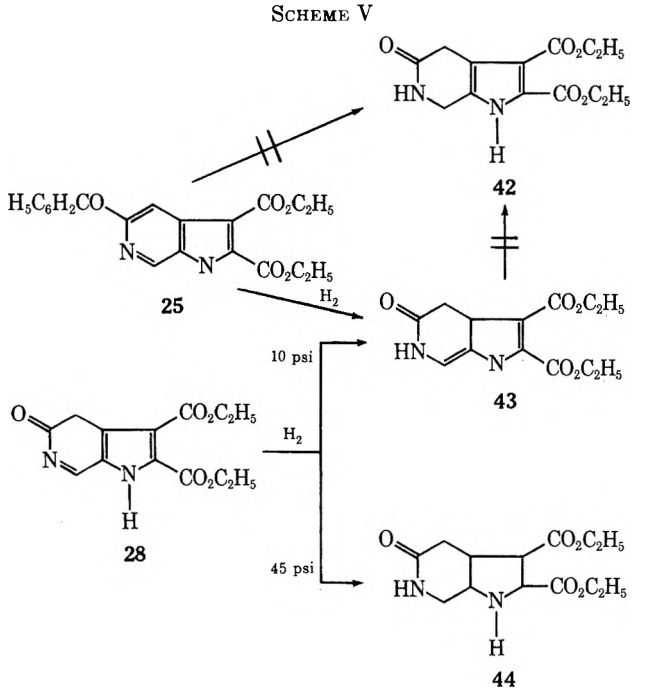
This was also an unexpected result since the ethyl 5-benzyloxy-6-azaindole-2-carboxylate was transformed directly by hydrogenolysis into the 2-ethoxycarbonylpyrrole lactam **38**.[4] Catalytic hydrogenation of **28** under the usual conditions (45 psi) afforded a fully reduced compound whose mass spectrum (M^+ 284) and nmr spectrum were consistent with structure **44**. Catalytic hydrogenation of **28** at low pressure stopped at the tetrahydro stage and the lactam **43** was obtained. Treatment of **43** with base or acids did not isomerize it to the desired pyrrole lactam **42**. Saponification attempts of **43** failed to give definite products, probably due to secondary transformations in the open-ring enamine structure.

(5) R. B. Frydman, S. Reil, and B. Frydman, *Biochemistry*, **10**, 1154 (1971).

SCHEME IV



SCHEME V



The synthesis of pyrrole lactam **42** was thus frustrated. The existence of the 4,5-dihydro structure in **28**, instead of the 5,6-dihydro structure present in **29**, **30**, and **41** must be due to the presence of an electronegative substituent at C-3. It lead to the formation of the pyrrole lactam **43**, which could not be transformed any more in a 2-aminomethylpyrrole. The usefulness of 6-azaindoles as starting materials for 2-aminomethylpyrrole synthesis seems thus limited to the preparation of pyrroles with β-alkyl residues.

Experimental Section[6]

2-Anisyloxy-4-methyl-5-nitropyridine (4).—2-Chloro-4-methyl-5-nitropyridine[4] (25 g, 0.14 mol) was added to a solution of 3.5 g (0.15 g-atom) of sodium in 925 ml of anisyl alcohol. The mixture was kept at 37° for 18 hr, and the reaction was completed by heating at 100° for 2 hr. The excess of anisyl alcohol was distilled off *in vacuo* [130° (0.25 mm)], and the crystalline residue washed with water (2 × 200 ml) and recrystallized from ethanol: 62 g (80%); mp 110–111°; uv_{max} 282 nm (ϵ 9800).

Anal. Calcd for $C_{14}H_{14}O_4N_2$: C, 61.3; H, 5.1; N, 10.2. Found: C, 61.1; H, 5.2; N, 10.1.

Ethyl 2-Anisyloxy-5-nitro-4-pyridinepyruvate (5).—To a solution of 300 ml of ether and 25 ml of absolute ethanol was added 4.3 g (0.11 g-atom) of potassium, and the mixture was stirred under anhydrous conditions until all the potassium dissolved. Diethyl oxalate (16 ml, 0.12 mol) was then added, followed after 5 min by 30.2 g (0.11 mol) of 2-anisyloxy-5-nitro-4-methylpyridine **4**, and the red mixture was stirred for 36 hr. The precipitated potassium enolate was removed by filtration, washed with ether, dried, suspended in 500 ml of water, and decomposed by adjusting the solution to pH 5 with acetic acid. After cooling at 5° during 30 min, the formed precipitate was filtered, dried, and recrystallized from ethanol when 37.9 g (92%) of pyruvate were obtained: mp 115–116°; uv_{max} 224 nm (ϵ 24,300), 282 (9700); nmr ($CDCl_3$) δ 1.5 (t, CH_3), 3.8 (s, OCH_3), 4.4 (q, CH_2), 4.5 (s, CH_2CO), 5.4 (s, 2, $C_6H_5CH_2O$), 6.9 (d, 2, $H_{2'}$ and $H_{6'}$), 7.4 (d, 2, $H_{3'}$ and $H_{5'}$), 7.2 [s, 1, CH=C(OH)], 7.6 (s, 1, H_3), 9.1 (s, 1, H_6).

Anal. Calcd for $C_{18}H_{18}O_7N_2$: C, 57.7; H, 4.8; N, 7.5. Found: C, 57.8; H, 4.8; N, 7.4.

Ethyl 2-Oxo-3-(2′-methoxy-5′-nitro-4′-pyridyl)butyrate (6).—The potassium enolate of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate **2** (15.3 g, 0.05 mol) was dissolved in 1000 ml of *N*,*N*′-dimethylformamide, 7 ml of methyl iodide was added, and the mixture was heated at 100° for 90 min with occasional stirring. Two additional portions (7 ml each) of methyl iodide were added every 30 min during the heating period. The solvent was then evaporated to dryness *in vacuo*, the residue dissolved in water (250 ml), and the aqueous layer extracted with chloroform (3 × 150 ml). The pooled extracts were washed with a small volume of water, dried (Na_2SO_4), and evaporated to dryness. The oily residue was dissolved in a small volume of a chloroform–benzene mixture (1:1), adsorbed on a silica gel column (5 cm × 30 cm), and the product was eluted by using the same solvent. The obtained ester was distilled at 129° (0.002 mm): 5.7 g, (40%); mp 83–84°; uv_{max} 282 nm (ϵ 12,500); nmr ($CDCl_3$) δ 1.35 (t, CH_3), 1.6 (d, 3, J = 7 Hz, $CHCH_3$), 4.05 (s, OCH_3), 4.37 (q, CH_2), 5.2 (q, 1, J = 7 Hz, $CHCH_3$), 6.73 (s, 1, H_3), 9.00 (s, 1, H_6); R_f 0.35 (tlc, chloroform–benzene, 1:1).

Anal. Calcd for $C_{12}H_{14}O_6N_2$: C, 51.5; H, 4.9; N, 9.9. Found: C, 51.2; H, 5.0; N, 9.8.

Diethyl 3-(2′-Methoxy-5′-nitro-4′-pyridyl)oxalactate (10).—The potassium salt of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate **2** (15 g) was suspended 2000 ml of dry tetrahydrofuran, 20 ml of ethyl chloroformate was added, and the mixture was heated under reflux for 30 min. The heating was then discontinued, a second portion of 30 ml of ethyl chloroformate was added, and the heating was resumed for an additional hour. The solvent was evaporated to dryness *in vacuo*, the residue dissolved in 250 ml of chloroform, the chloroform washed with water (2 × 50 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 ml of a mixture of benzene and chloroform (1:1 v/v), adsorbed on a silica gel column (30 × 5 cm) prewashed with the same solvent, and the desired product eluted with 2000

(6) All melting points were taken on the Kofler block; uv absorptions were measured in ethanol; ir spectra were obtained on potassium bromide wafers, and nmr spectra were taken as noted. Microanalyses were performed by the Alfred Bernhardt Mikroanalytisches Laboratorium (Mulheim). Mass spectra were performed by the Morgan and Schaffer Corp. (Montreal). When tlc on cellulose was run, the upper layer of a butanol–acetic acid–water mixture (4:1:5) was used as solvent. The α-keto esters were spotted by spraying the tlc plates with piperidine, which gave red to orange spots with the former. The silica gel used for column chromatography was Kieselgel G (Fluka AG).

ml of the same solvent. Evaporation to dryness of the eluate, followed by crystallization of the residue from benzene–petroleum ether, afforded the diethyl oxalacetate **10**: 11 g (65%); mp 64–64°; R_f 0.35 (tlc, benzene–chloroform, 1:1 v/v); uv_{max} 245 nm (ε 33,600), 304 (sh); nmr ($CDCl_3$) δ 1.34. 1.36 (t, 6, CH_3), 4.1 (s, 3, OCH_3), 4.35 (m, 4, CH_2), 6.92 (s, 1, H_3), 7.25 (s, 1, COC=COH), 9.0 (s, 1, H_6).

Anal. Calcd for $C_{14}H_{16}O_5N_2$: C, 49.4; H, 4.7; N, 8.2. Found: C, 49.3; H, 4.8; N, 8.4.

Ethyl 3-Methyl-5-methoxy-6-azaindole-2-carboxylate (14).—The ethyl 2-oxobutyrate **6** (7.2 g of chromatographically pure but nondistilled product were used) was dissolved in 100 ml of ethanol and reduced at 25 psi with hydrogen over 2 g of 10% palladium on charcoal during 45 min. The catalyst was removed and washed with ethanol, the combined filtrates and washings were concentrated *in vacuo* to 5 ml, and the product was precipitated by addition of water. The product was filtered and recrystallized from ethanol–water: 3.5 g (59%); mp 135–136° [sublimed at 130° (0.010)]; uv_{max} 285 nm (ε 10,000), 293 (11,600), 346 (6100); nmr (TFA) δ 1.6 (t, 3, CH_3), 2.78 (s, 3, CH_3), 4.3 (s, 3, OCH_3), 4.78 (q, 2, CH_2), 7.6 (s, 1, H_4), 8.6 (b, 1, H_7).

Anal. Calcd for $C_{12}H_{14}O_3N_2$: C, 61.5; H, 6.0; N, 11.9. Found: C, 61.3; H, 6.0; N, 11.9.

Ethyl 3-Ethyl-5-methoxy-6-azaindole-2-carboxylate (15) and 1,2,3,4-Tetrahydro-3-oxy-4-ethyl-6-methoxy-1,7-naphthyridin-2-one (16).—Ethyl 2-oxo-3-(2′-methoxy-5′-nitro-4′-pyridyl)valerate **7** (7.4 g) was reduced with hydrogen with the same procedure used for the ethyl 2-oxobutyrate **16**. The crude product obtained on evaporation of the solvent (4.4 g) was dissolved in 150 ml of water; the solution was adjusted to pH 2 with concentrated hydrochloric acid and kept at 5° for 15 hr. The precipitate was filtered, dried, and crystallized from ethanol–water affording 1.4 g (23%) of 6-azaindole **15**: mp 110–112° [sublimed at 100° (0.1 mm)]; uv_{max} 285 nm (11,300), 294 (13,000), 358 (3500); nmr ($CDCl_3$) δ 1.3 (t, 3, $CO_2CH_2CH_3$), 1.4 (t, J = 7 Hz, 3, CH_2CH_3), 3.1 (q, J = 7 Hz, 2, CH_2CH_3), 4.0 (s, 3, OCH_3), 4.5 (q, 2, $CO_2CH_2CH_3$), 6.97 (s, 1, H_4), 8.5 (s, 1, H_7).

Anal. Calcd for $C_{12}H_{16}O_3N_2$: C, 62.9; H, 6.4; N, 11.3. Found: C, 62.9; H, 6.4; N, 11.2.

The acidic mother liquors were adjusted to pH 10 with solid sodium carbonate and extracted with chloroform (4 × 30 ml). The chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*, the residue was crystallized from ethanol, and 2.6 g (47%) of the naphthyridone was obtained: mp 173° (sublimed); uv_{max} 246 nm (17,800), 298 (6200); nmr ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3, CH_3), 3.05 (s, 1, OH), 3.17 (b, 1, C-4 H), 3.65–4.15 (m, 3, CH_2CH_3 and CHOH), 3.9 (s, 3, OCH_3), 6.6 (s, 1, H_5), 7.7 (b, 1, H_8).

Anal. Calcd for $C_{11}H_{14}O_3N_2$: C, 59.4; H, 6.3; N, 12.6. Found: C, 59.3; H, 6.5; N, 12.7.

1,2,3,4-Tetrahydro-3-oxy-4-*n*-propyl-6-methoxy-1,7-naphthyridin-2-one (19).—The ethyl 2-oxoeaproate **8** (1.5 g) was reduced with hydrogen over palladium as described above, and the obtained product was crystallized from ethanol affording 400 mg (34%) of the naphthyridinone **19**: mp 136°; nmr (TFA) δ 1.0 (t, 3, CH_3), 1.8 (q, J = 8 Hz, 2, $CH_2CH_2CH_3$), 3.62 (s, 1, COH), 3.7 (b, 1, C-4 H), 3.8 (m, 2, $RCH_2CH_2CH_3$), 4.15 (s, 3, OCH_3), 4.27 (m, 1, C-3 H).

Anal. Calcd for $C_{12}H_{16}O_3N_2$: C, 61.0; H, 6.8; N, 11.9. Found: C, 61.1; H, 6.7; N, 11.8.

Ethyl 5-Methoxy-3-ethoxycarbonylmethyl-6-azaindole-2-carboxylate (17) and 1,2,3,4-Tetrahydro-3-oxy-4-ethoxycarbonylmethyl-6-methoxy-1,7-naphthyridin-2-one (18).—The diethyl 2-oxoglutarate **9** (7 g of ester purified by chromatography) was reduced with hydrogen over palladium following the usual procedure. The product was dissolved at 50° in 100 ml of water adjusted to pH 3.5 with hydrochloric acid, the solution was kept for 12 hr at 5° and filtered, and the filtrates were kept for further work-up. The obtained product was recrystallized from ethanol–water affording 2.2 g (73%) of the 6-azaindole **17**: mp 125–126°; uv_{max} 283 nm (ε 13,000), 292 (16,000), 348 (4100); nmr (TFA) δ 1.4 (t, 3, $CH_2CO_2CH_3$), 1.6 (t, 3, $CO_2CH_2CH_3$), 4.3 (s, 3, OCH_3), 4.4 (s, 2, CH_2), 4.5 (q, 2, $CH_2CO_2CH_2CH_3$), 4.8 (q, 2, $CO_2CH_2CH_3$), 7.7 (s, 1, H_4), 8.95 (s, 1, H_8).

Anal. Calcd for $C_{15}H_{18}O_5N_2$: C, 58.8; H, 5.9; N, 9.1. Found: C, 58.7; H, 6.0; N, 9.0.

The substance was identical (mp, ir, tlc) with a sample prepared by the action of diazoethane on the 2-carboxy-5-methoxy-6-azaindole-3-acetic acid.[4]

The aqueous acidic filtrates obtained after filtering the 6-azaindole were adjusted to pH 10 with sodium carbonate and extracted with chloroform (4 × 25 ml). The chloroform extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol affording 0.5 g (11%) of 1,7-naphthyridinone: mp 136–138°; uv_{max} 248 nm (ε 15,000); nmr (TFA) δ 1.4 (t, 3, CH_2CH_3), 3.7 (s, 1, COH), 3.8 (b, 1, C-4 H), 4.35 (s, 3, OCH_3), 4.27 (b, 1, C-3 H), 4.6 (b, 2, CH_2CO_2), 7.6 (s, 1, H_5), 8.2 (s, 1, H_8).

Anal. Calcd for $C_{13}H_{16}O_5N_2$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.6; H, 5.8; N, 10.1.

Diethyl 3-(2′-Methoxy-5′-amino-4′-pyridyl)oxalacetate (21) and Diethyl 3-(2′-Methoxy-5′-amino-4′-pyridyl)malate (22).—Diethyl oxalacetate **10** (2 g) dissolved in 100 ml of ethanol was reduced with hydrogen over 0.5 g of 10% palladium on charcoal at 25 psi during 45 min. The catalyst was removed and the solvent was evaporated to dryness; the residue was dissolved in a small volume of a benzene–methanol (9:1 v/v) solution and adsorbed on a silica gel column (30 cm × 3 cm) prewashed with the same solvent. Elution was carried out with the same solvent. The first 100 ml of eluate were collected and discarded. Fifty fractions of 2 ml each were then collected. Fractions 15–30 were pooled and evaporated to dryness *in vacuo* affording 820 mg (45%) of the diethyl oxalacetate **21**: mp 93–95° (from benzene–cyclohexane); R_f 0.60 (tlc, benzene–methanol, 9:1 v/v); uv_{max} 236 nm (ε 17,000), 299 (4300); ir 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.25, 1.35 (t, 6, CH_3); 3.35 (b, 2, NH_2), 3.9 (s, 3, OCH_3), 4.3 (9, 4, CH_2CH_3), 4.8 (b, 1, C=COH), 6.6 (s, 1, H_3), 8.3 (b, 1, H_6); mass spectrum *m/e* (rel intensity) 310 (M^+, 35) 237 (M − $CO_2C_2H_5$, 90), 209 (M − $COCO_2H_5$, 30), 191 (237 − C_2H_5OH, 80), 163 (209 − HOC_2H_5, base peak), 135 (163 − CO, 22).

Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.2; H, 5.8; N, 9.0. Found: C, 54.4; H, 5.8; N, 9.2.

Fractions 41–47 were pooled and evaporated to dryness *in vacuo* affording 51 mg (6%) of the diethyl malate **22**: mp 79–81° (benzene–petroleum ether); R_f 0.48 (tlc, benzene–methanol, 9:1 v/v); uv_{max} 232 nm (ε 27,600), 285 (4000); ir 3350 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.25, 1.28 (t, 6, CH_3), 3.0 (m, NH_2), 3.9 (s, 3, OCH_3); 4.0–4.5 (m, 6, CH_2CH_3, CHOH), 6.5 (s, 1, H_3), 7.5 (b, 1, $PyCHCO_2$), 8.3 (s, 1, H_6); mass spectrum *m/e* (rel intensity) 312 (M^+, 12), 266 (M − HOC_2H_5, base peak), 193 (266 − $CO_2C_2H_5$, 50), 165 (266 − $CO_2C_2H_5CO$, 90).

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.8; H, 6.4; N, 8.9. Found: C, 53.7; H, 6.4; N, 9.1.

When the benzyl ethyl oxalacetate **11** was reduced using the same procedure it afforded ethyl 5-methoxy-6-azaindole-2-carboxylate **20**: 440 mg (80%); mp 103–106°; identical with a sample prepared as described[4] (by tlc, ir, and mmp).

Diethyl 5-Methoxy-6-azaindole-2,3-dicarboxylate (23).—The diethyl oxalacetate **21** (300 mg) was dissolved in 200 ml of dry xylene, 400 mg of phosphorus pentoxide were added, and the mixture was heated with continuous stirring at 130° for 3 hr. The solvent was then evaporated to dryness at reduced pressure, the residue was dissolved in 30 ml of water adjusted to pH 10 with sodium carbonate, and the solution was extracted with chloroform (3 × 10 ml). The chloroform extracts were pooled, dried (Na_2SO_4), and evaporated to dryness. The residue was filtered through a silica gel column (20 cm × 2 cm) using a 3% methanol in benzene solution as eluent. The eluates were evaporated to dryness affording 122 mg (42%): mp 55–57° (ethanol–water); R_f 0.80 (tlc, benzene–3% methanol); uv_{max} 242 nm (ε 12,800), 263 (11,100), 316 (5600); nmr ($CDCl_3$) δ 1.3 (m, 6, CH_3); 3.9 (s, 3, OCH_3), 4.3 (m, 4, CH_2), 6.8 (b, 1, H_4), 8.9 (b, 1, H_7); mass spectrum *m/e* (rel intensity) 292 (M^+, 95), 247 (M − OC_2H_5, 30), 219 (M − $CO_2C_2H_5$, 90), 174 (219 − OC_2H_5, base peak), 146 (174 − CO, 90).

Anal. Calcd for $C_{14}H_{16}O_5N_2$: C, 57.5; H, 5.4; N, 9.6. Found: C, 57.3; H, 5.5; N, 9.7.

Diethyl 3-(2′-Benzyloxy-5′-amino-4′-pyridyl)oxalacetate (24).—Diethyl oxalacetate **12** (700 mg) was dissolved in 100 ml of ethanol and reduced with hydrogen over 70 mg of platinum oxide at 15 psi during 45 min. The catalyst was filtered and the solvent was evaporated to dryness; the residue was dissolved in a small volume of benzene containing 7% methanol and adsorbed on a silica gel column (30 cm × 3 cm) prewashed with the same solvent. The substance was eluted with the same solvent affording after evaporation 344 mg (53%): mp 82–84° (benzene–cyclohexane); uv_{max} 240 nm (ε 21,600), 296 (5100); nmr ($CDCl_3$) δ 1.3 (m, 6, CH_3), 3.3 (m, 2, NH_2), 4.3 (m, 4, CH_2CH_3), 4.8 (b, 1, OH), 5.3 (s, 2, $CH_2C_6H_5$), 5.65 (s, 1, H_3), 7.4 (b, 5, C_6H_5), 8.4 (b, 1, H_6).

Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.2; H, 5.7; N, 7.2. Found: C, 62.3; H, 5.9; N, 7.4.

Diethyl 5-Benzyloxy-6-azaindole-2,3-dicarboxylate (25).—The diethyl oxalacetate **24** (300 mg) was dissolved in 50 ml of dry chloroform, and 300 mg of finely powdered phosphorus chloride was added in small portions with continuous stirring at 5°. The solution was kept at room temperature for 24 hr and then washed with a 1 *N* sodium hydroxide solution. The excess of alkali was washed out with water and the chloroform layer dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from ethanol–water: 200 mg (70%); mp 54–55°; uv_{max} 235 nm (ϵ 14,700), 263 (10,800), 318 (5500).

Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.2; H, 5.4; N, 7.6. Found: C, 65.0; H, 5.6; N, 7.4.

Diethyl 3-(2′-Hydroxy-5′-nitro-4′-pyridyl)oxalacetate (26).—The anisyl derivative **13** (1 g) was dissolved in 10 ml of trifluoroacetic acid, and the mixture was kept for 24 hr at room temperature. The solution was then poured in a large excess of ice–water and the formed precipitate filtered and crystallized from ethanol: 584 mg (80%); R_f 0.70 (tlc, benzene–10% methanol); uv_{max} 237 nm (ϵ 16,300); ir 1780, 1750 (CO esters), 1675, 1640 cm^{-1} (bands I and II, CO amide); nmr (TFA) δ 1.4, 1.5 (t, 6, CH_3), 4.5 (m, 4, CH_2), 7.1 (s, 1, H_3), 7.8 (s, 1, COC=COH), 8.9 (s, 1, H_6).

Anal. Calcd for $C_{13}H_{14}O_8N_2$: C, 47.8; H, 4.3; N, 8.6. Found: C, 47.8; H, 4.3; N, 8.7.

Diethyl 3-(2′-Hydroxy-5′-amino-4′-pyridyl)oxalacetate (27).—Diethyl oxalacetate **26** (1 g) was dissolved in 100 ml of ethanol and reduced with hydrogen over 500 mg of 10% palladium on charcoal at 15 psi during 45 min. The catalyst was filtered, the solvent evaporated to dryness *in vacuo*, and the residue filtered through a column of silica gel (20 cm × 2 cm) using a 10% methanol in benzene solution as eluent: 568 mg (58%); mp 217–218° (methanol–ether); R_f 0.43 (tlc, benzene–10% methanol); uv_{max} 245 nm (ϵ 14,800), 330 (4200); ir 3200 (broad, OH), 1630, 1600 cm^{-1} (CO amide, bands I and II); nmr (TFA) 1.2 (m, 6, CH_3), 3.8 (m, 2, NH_2), 4.6 (m, 4, CH_2), 7.4 (s, 1, H_3), 8.3 (b, 1, H_6); mass spectrum *m/e* (rel intensity) 296 (M^+, 66), 223 (M − $CO_2C_2H_5$, 90), 195 (223 − CO, 80), 177 (M − $CO_2C_2H_5HOC_2H_5$, 95), 150 (M − $2CO_2C_2H_5$, base peak).

Anal. Calcd for $C_{13}H_{16}O_6N_2$: C, 52.7; H, 5.4; N, 9.5. Found: C, 52.6; H, 5.4; N, 10.0.

The amino derivative **27** was also obtained by direct hydrogenation at 45 psi (2 hr) of the anisyl derivative **13** in 21% yield.

Diethyl 5-Oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2,3-dicarboxylate (28).—Diethyl oxalacetate **27** (500 mg) was suspended in 50 ml of dry xylene, 500 mg of finely divided phosphorus pentoxide were added, and the mixture was heated under reflux with continuous stirring during 2.5 hr. The mixture was cooled, the solvent decanted, and the residue dissolved in water adjusted to pH 7 with sodium hydroxide. The aqueous solution was evaporated to dryness, and the residue was extracted with boiling absolute ethanol (3 × 100 ml). The ethanolic solution was evaporated to dryness *in vacuo*, and the residue was dissolved in 10 ml of chloroform containing 10% methanol and adsorbed on a silica gel column (20 cm × 2 cm) previously washed with the same solvent. The 6-azaindanone **28** developed on the column as a fluorescent yellow band and was eluted using the same solvent affording 282 mg (60%): mp 144–146° (benzene–cyclohexane); R_f 0.54 (tlc, chloroform–10% methanol); uv_{max} 227 nm (ϵ 25,300), 257 (15,300), 366 (6900); ir, 1780, 1740 (CO ester), 1675, 1640 cm^{-1} (CO lactam, bands I and II); nmr (Cl_3CD) δ 1.35, 1.39 (t, 6 CH_3), 4.35, 4.40 (q, 4, CH_2), 6.7 (s, 2, CH_2CO), 8.3 (s, 1, H_7); mass spectrum *m/e* (rel intensity) 278 (M^+, 25), 233 (M − OC_2H_5, 15), 206 (M − $CO_2C_2H_4$, 80), 160 (206 − HOC_2H_5, base peak), 132 (160 − CO, 85), 104 (132 − CO, 26).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.1; H, 5.0; N, 10.1. Found: C, 56.2; H, 5.0; N, 10.1.

5-Oxo-3-methyl-5,6-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (29).—6-Azaindole **14** (3 g) was dissolved in 90 ml of 48% hydrobromic acid, and the mixture was heated under reflux for 4 hr. The dark solution was evaporated to dryness; the residue was dissolved in a small volume of a concentrated ammonium hydroxide solution, adsorbed on a neutral alumina column (25 × 2 cm) prewashed with a normal ammonium hydroxide solution, and eluted with the same solvent collecting fractions of 10 ml. The eluates were acidified to pH 4; the precipitated acid of the pure fractions was collected by filtration, dried, and washed with boiling methanol (5 × 10 ml): 1.2 g (50%); mp dec above 300°; uv_{max} 242 nm (ϵ 22,000), 298 (8600), 302 (7500).

Anal. Calcd for $C_9H_8N_2O_3$: C, 56.2; H, 4.2; N, 14.6. Found: C, 56.1; H, 4.3; N, 14.7.

5-Oxo-3-ethyl-5,6-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (30) was obtained following the same procedure used for the 3-methyl derivative **29**. From 2.2 g of the 6-azaindole **15**, 990 mg (55%) of **30** were obtained: mp dec above 300°; uv_{max} 235 nm (ϵ 22,000), 298 (9500), 302 (8700).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.2; H, 4.8; N, 13.6. Found: C, 58.3; H, 4.5; N, 13.5.

5-Oxo-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (31).—6-Azaindanone **29** (1 g) was dissolved in 30 ml of a sodium carbonate solution at pH 8–9 and reduced with hydrogen at 50 psi over 0.5 g of 10% palladium on charcoal for 2 hr. The catalyst was removed and the solution was adjusted to pH 4 with acetic acid, cooled at 5°, and filtered: 720 mg (72%); mp dec above 315°; uv_{max} 272 nm (ϵ 11,700).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.1; N, 14.4. Found: C, 55.6; H, 5.2; N, 14.5.

5-Oxo-3-ethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (32) was prepared following the procedure described for the 3-methyl analog **31**. From 1 g of the 6-azaindanone **30** was obtained 520 mg (52%) of **32**: mp 270° dec; uv_{max} 274 nm (ϵ 16,000).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.6; H, 5.7; N, 13.4.

5-Oxo-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine (33).—The acid **31** (1.8 g) was suspended in 250 ml of water and heated under reflux for 1 hr. The solution was evaporated to dryness and the residue sublimed at 200° (0.010 mm) to afford 700 mg (50%) of lactam **33**: mp dec above 260°; R_f 0.65 (tlc, ethyl acetate–methanol, 2:1 v/v); ir 1655, 1625 cm^{-1} (CO lactam); nmr (TFA) δ 2.5 (s, 3, CH_3), 3.9 (b, 2, CH_2CO), 5.1 (b, 4, CH_2NH, $=N^+HCH_2$); Ehrlich's reaction was positive in the cold.

Anal. Calcd for $C_8H_{10}N_2O$: C, 64.0; H, 6.7; N, 18.7. Found: C, 64.1; H, 6.7; N, 18.6.

5-Oxo-3-ethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine (34) was prepared following the same procedure used for the synthesis of the 3-methyl homolog **33**, except for the heating period which was extended to 90 min. The lactam **34** was obtained in 70% yield: mp dec above 250° [sublimed at 180° (0.010 mm)]; nmr (TFA) δ 0.8 (t, J = 7 Hz, 3, CH_3), 2.3 (q, J = 7 Hz, 2, CH_2CH_3), 3.7 (b, 2, CH_2CO), 4.6 (b, 4, CH_2NH, $=NH^+CH_2$); Ehrlich's reaction positive in the cold.

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.9; H, 7.3; N, 17.1. Found: C, 65.9; H, 7.3; N, 17.0.

2-Aminomethyl-4-methyl-3-pyrroleacetic Acid (35).—The sublimed lactam **33** (600 mg) was suspended in 8 ml of 4 *N* sodium hydroxide, 8 ml of ethanol was added, and the mixture was heated under reflux for 1 hr. The solution was adjusted to pH 5 with acetic acid, and a 15% aqueous mercuric acetate solution was added until no more precipitate formed. The solid was centrifuged, the precipitate suspended in water, and hydrogen sulfide passed through the suspension until all the mercuric salt was decomposed. The mercuric sulfide was centrifuged and washed with water, and the pooled supernatant and wash were evaporated to dryness at 30° *in vacuo*. The crystalline residue was recrystallized by dissolving it in water and adding methanol: 230 mg (30%); mp 150° dec; R_f 0.82 (tlc, on cellulose); nmr (D_2O) δ 2.0 (s, 3, CH_3), 3.25 (b, 2, CH_2CO_2); 3.6 (b, 2, CH_2NH_2), 6.3 (s, 1, H_5).

Anal. Calcd for $C_8H_{12}O_2N_2.H_2O$: C, 51.6; H, 7.5; N, 15.0. Found: C, 51.6; H, 7.4; N, 15.1.

2-Aminomethyl-4-ethyl-3-pyrroleacetic acid (36) was obtained in 52% yield following the same procedure described for the 4-methyl homolog **35**. The pyrrole was recrystallized by dissolving it in water and adding acetone: mp 142–144° dec; R_f 0.78 (tlc, on cellulose); nmr (D_2O) 1.1 (t, J = 7 Hz, 3, CH_3), 2.4 (q, J = 7 Hz, 2, CH_2CH_3), 3.3 (b, 2, CH_2CO), 3.6 (b, 2, CH_2NH_2), 6.5 (s, 1, H_5).

Anal. Calcd for $C_9H_{14}O_2N_2\cdot H_2O$: C, 54.0; H, 8.0; N, 14.0. Found: C, 54.3; H, 8.2; N, 14.0.

Ethyl 5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylate (38).—Ethyl pyridinepyruvate **5** (2 g) was dissolved in 100 ml of ethanol, and the solution was shaken with hydrogen at 50 psi for 90 min over 600 mg of 10% palladium on charcoal. The catalyst was filtered, the solution evaporated to dryness, and the residue crystallized from ethanol: 770 mg (70%); mp 272–

274° (lit.[4] mp 272–274°); identical by ir, nmr, and tlc with a sample prepared by reduction of ethyl 5-benzyloxy-6-azaindole-2-carboxylate.[4]

Benzyl 5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylate (39).—The 5-carbethoxylactam **38** (2 g) was dissolved in 20 ml of benzyl alcohol and 50 mg of sodium was added. The mixture was heated at 100° for 2 hr; 5 ml of the solvent was then distilled *in vacuo* at the same temperature. An equal volume of benzyl alcohol was added to the mixture and the heating was continued for an additional 4 hr. The benzyl alcohol was then evaporated to dryness *in vacuo* and the residue crystallized from a large volume of ethanol: 2.2 g (80%); mp 286–287°; ir 1690 (CO ester), 1667 (CO lactam), 695 cm^{-1} (C_6H_5).

Anal. Calcd for $C_{15}H_{14}O_3N_2$: C, 66.7; H, 5.2; N, 10.4. Found: C, 66.6; H, 5.2; N, 10.3.

5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (40).—The benzyl ester lactam **39** (1 g) was dissolved in 50 ml of glacial acetic acid and hydrogenated at 50 psi for 2 hr over 300 mg of 10% palladium on charcoal. The catalyst was filtered, the solution evaporated to dryness *in vacuo* at 50°, and the residue crystallized by dissolving in a 1 *N* sodium hydroxide solution and precipitating with concentrated acetic acid: 530 mg (80%); mp dec above 300°; R_f 0.58 (tlc, on cellulose); uv_{max} 270 nm (ε 15,000).

Anal. Calcd for $C_8H_8O_3N_2$: C, 58.88; H, 4.44; N, 15.55.

The product was identical by tlc, ir, and uv with a sample prepared by reduction of 5-oxo-5,6-dihydro-1*H*-pyrrolo[2,3-*c*]-pyridine-2-carboxylic acid.[4]

Diethyl 5-Oxo-3a,4,5,6-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2,3-dicarboxylate (43).—The 6-azaindanone **28** (300 mg) was dissolved in 20 ml of ethanol and was reduced with hydrogen over 100 mg of 10% palladium on charcoal at 10 psi for 90 min. The catalyst was filtered, the solvent was evaporated to dryness *in vacuo*, and the residue was crystallized from ethanol: 130 mg (43%); mp 216–218°; ir 1635, 1610 cm^{-1} (CO lactam); nmr (TFA) δ 1.35 (t, 6, CH_3), 3.6 (m, 2, CH_2CO), 6.4 (q, 4, CH_2CH_3), 5.25 (m, 1, $CHCH_2CO$), 7.1 (s, 1, H_7); mass spectrum *m/e* rel intensity) 280 (M^+, 90), 235 (M − OC_2H_5, 20), 207 (M − $COOC_2H_5$, base peak), 163 (207 − OC_2H_4, 30), 135 (163 − CO, 90), 107 (135 − CO, 80).

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.6; H, 5.7; N, 10.2.

The same product was obtained by reducing diethyl 5-benzyloxy-6-azaindole-2,3-dicarboxylate **25** at 50 psi for 2 hr under the described conditions.

Registry No.—**2** potassium salt, 38312-68-4; **4**, 38312-69-5; **5**, 38312-70-8; **6**, 38312-71-9; **7**, 38312-72-0; **8**, 38312-73-1; **9**, 38312-74-2; **10**, 38312-75-3; **11**, 38312-76-4; **12**, 38312-77-5; **13**, 38312-78-6; **14**, 38312-79-7; **15**, 38312-80-0; **16**, 38312-81-1; **17**, 38312-82-2; **18**, 38309-19-2; **19**, 38309-20-5; **21**, 38309-21-6; **22**, 38309-22-7; **23**, 38309-23-8; **24**, 38309-24-9; **25**, 38309-25-0; **26**, 38309-26-1; **27**, 38309-27-2; **28**, 38309-28-3; **29**, 38309-29-4; **30**, 38309-30-7; **31**, 33034-45-6; **32**, 38309-32-9; **33**, 32794-21-1; **34**, 38309-34-1; **35**, 32794-17-5; **36**, 38309-36-3; **38**, 22772-51-6; **39**, 38309-38-5; **40**, 32794-19-7; **43**, 38309-40-9; 2-chloro-4-methyl-5-nitropyridine, 23056-33-9.

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Synthesis of Oligosaccharides Containing 2-Acetamido-2-deoxyxylose by Chemical and Enzymic Methods[1a]

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O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-D-xylopyranose (1) was prepared from the β(1→4)-linked *N*-acetylglucosamine dimer (2) by formation of the diethyl dithioacetal (3), glycol cleavage with periodate, reduction with ^3H-$NaBH_4$, and dithioacetal hydrolysis. 1 was isolated by charcoal-Celite column chromatography. A by-product, *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-L-arabinopyranose, was isolated as well. 1 was also isolated from the lysozyme-catalyzed reaction of the *N*-acetylglucosamine tetramer with 5-^3H-2-acetamido-2-deoxy-α-D-xylopyranose (10), demonstrating the structure of 1 and supporting a β(1→4) linkage for the higher oligomers containing *N*-acetylxylosamine and two or three *N*-acetylglucosamine residues, which were also produced in the enzymic reaction.

In the past six years, more and more evidence has accumulated for the fascinating, but by no means new,[2] theory that the structure of an enzyme active site is "designed" to fit a conformation of the substrate close to the reaction transition state better than it fits the substrate's ground-state conformation.[3] The synthesis of organic molecules designed to test this theory is a challenging task for the chemist.

In the particular case of lysozyme, Phillips has proposed, on the basis of crystallographic studies of the hen egg white enzyme, that the catalytic region of the active site ("subsite D") can bind an *N*-acetylglucosamine residue in the "half chair" conformation, but cannot bind such a hexopyranose unit in its ground-state "chair" conformation because of steric hindrance to the hydroxymethyl group at C-5 in the latter conformation.[4] The preparation of substrate analogs containing *N*-acetylxylosamine (2-acetamido-2-deoxy-D-xylose), *i.e.*, in which a single C-5 hydroxymethyl group has been removed from an *N*-acetylglucosamine oligomer, would obviously be valuable in the further testing of Phillips' hypothesis. We have briefly reported elsewhere studies of such compounds which support this hypothesis.[5] In this paper we report the

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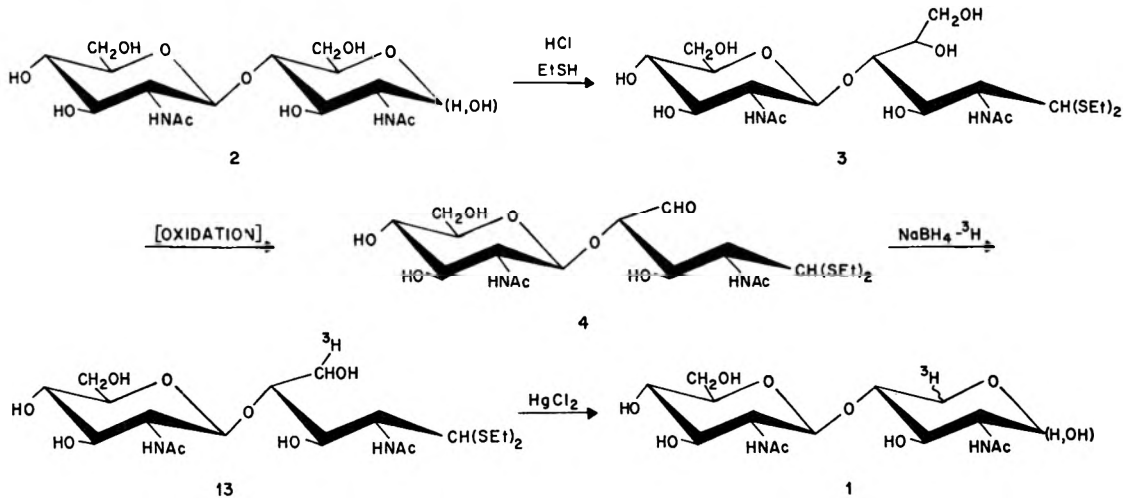
SCHEME I



details of the synthesis of *N*-acetylglucosamine-β-(1→4)-*N*-acetylxylosamine (**1**, *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-D-xylopyranose), and some related compounds, by both chemical and enzymic techniques.

The standard technique for the synthesis of oligosaccharides is, of course, to form new glycosidic bonds between the monosaccharide moieties in question, usually by the Koenigs–Knorr condensation.[6] Since xylosamine itself apparently does not occur naturally, and is not readily available synthetically,[7] and since a facile route to a xylosamine derivative protected everywhere but O-4 is not obvious, such an approach appeared unattractive to us. We chose instead to attempt the synthesis of **1** from the readily available *N*-acetylglucosamine dimer (**2**) by the route outlined in Scheme I. Although degradative routes to oligosaccharides have been fairly widely used in the past to produce oligosaccharides with glycosidic linkages of known configuration,[8] to our knowledge this is the first example of such a degradation which does not involve loss of the reducing terminal carbon.

A third alternative for preparing the desired oligosaccharides is to use an enzyme to form one or more new glycosidic linkages between saccharides. Lysozyme is known to catalyze transglycosylation reactions of chitin oligomers[9] and bacterial cell wall oligosaccharides,[10] and to demonstrate considerable specificity toward acceptors,[11] but this specificity is not absolute. For instance, Sharon and Pollock showed that the products of the incubation of the bacterial cell wall tetrasaccharide and D-xylose with lysozyme included compounds with β(1→2), β(1→3), and β(1→4) linkages to xylose.[12] Use of the enzymic route with an acceptor other than *N*-acetylglucosamine or an oligomer thereof thus requires a proof of the structure of the new linkage. The synthesis of **1** by both the degradative chemical route and the enzymic route, and the demonstration of the identity of the two products, provides a rigorous proof of the structure of **1**, as well as information which is useful for the preparation of further compounds in the series.

All the compounds that we report were synthesized with radiochemical labels. While the original reason for introducing tritium into these compounds was to make possible certain biochemical experiments, the labels turned out to be extremely useful for following the reactions and supporting the structures proposed for the products.

Results and Discussion

The diethyl dithioacetal **3** was produced from **2**[13] by the usual method with concentrated hydrochloric acid and ethanethiol.[14] No evidence for deacetylation was observed, and cleavage of the glycosidic bond occurred to a very small extent.

The crucial and most difficult step in the synthesis is the specific glycol cleavage of **3** to **4**, since **3** contains both acyclic and trans-diequatorial vicinal glycols, as well as the readily oxidizable sulfur atoms.[15] Following Wolfrom's synthesis of 2-amino-2-deoxyxylose,[7] we examined the reaction of **3** with lead tetraacetate. Immediate reduction, hydrolysis, trimethylsilylation, and vpc analysis of the reaction mixture indicated that apparently exclusive cleavage of the trans-diequatorial glycol had occurred. Examination of the reaction with periodate by the same method indicated that the glycol cleavage was exclusively at the open chain, but other evidence suggested that extensive oxidation of sulfur was taking place as well. Since no direct method (tlc, spectra) could be found for following the reaction, indirect methods were used to determine the optimum conditions for the oxidation. The disappearance of periodate was followed spectrophotometrically by the method of Dixon and Lipkin.[16] With a 50% excess of periodate at 0°, 1 mol of periodate per mole of **3** was consumed in about 2 min, and consumption of the remaining reagent occurred with a half-life of about 7

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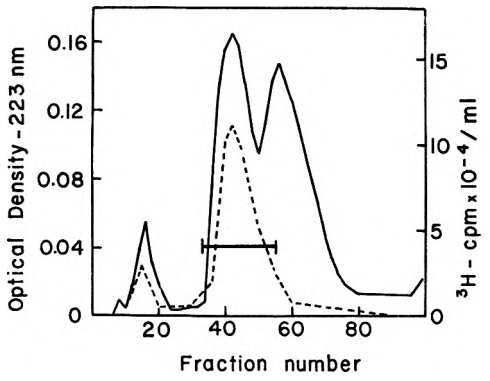


Figure 1.—First chromatography of crude 1 on charcoal–Celite column (1 × 43 cm, eluted with 0–20% ethanol gradient over 2 l.): solid line, optical density; broken line, radioactivity. Fractions marked by bar pooled for further resolution.

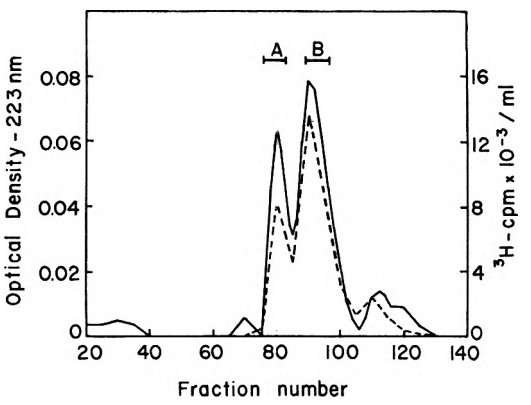


Figure 2.—Chromatographic resolution of 1 and 5 (1 × 58 cm charcoal–Celite column, eluted with 1–10% ethanol gradient over 2 l.): solid line, optical density; broken line, radioactivity. Fractions marked A pooled to isolate **5**, fractions B pooled to isolate 1.

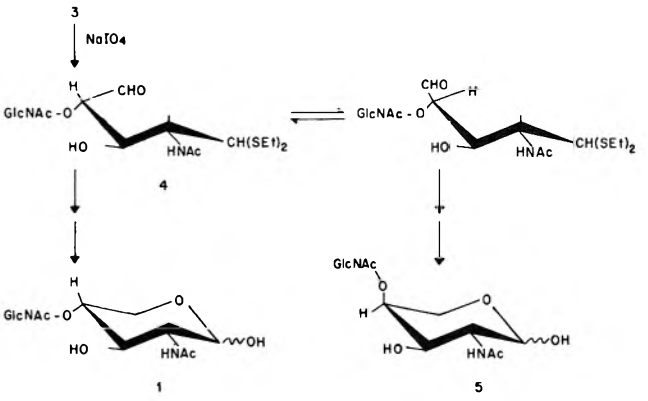
min. The incorporation of tritium into the sugar upon reduction with ^3H-borohydride was also examined. Comparison with a control reduction (*N*-acetyl-D-glucosamine) indicated that, under the final conditions chosen (30% mole excess of periodate, 5 min at 0°), oxidation of the glycol had proceeded to about 60% completion.

The glycol cleavage product **4** was reduced with tritiated sodium borohydride, and the dithioacetal was hydrolyzed with mercuric chloride and lead carbonate without intermediate work-up. The nmr spectrum of the crude product indicated that one quarter of the ethyl groups were not removed even after prolonged treatment; presumably oxidation at sulfur rendered the dithioacetal refractive to hydrolysis. The extent of glycol cleavage and sulfur oxidation seem to be in accord with the notion that the open-chain glycol is only a factor of two–fivefold more reactive toward periodate than is the dithioacetal sulfur, as indicated by the studies of periodate disappearance.

The product was isolated and purified by column chromatography on charcoal–Celite columns[13,17] in two stages. These columns proved to be extremely powerful separation tools when used with sufficiently gradual gradients of aqueous ethanol. The first column (Figure 1) served to separate the tritiated disaccharides from fragmented and deacetylated impurities, the bulk of the recovered **2**, and unhydrolyzed dithioacetals (not eluted with 20% ethanol). The second column (Figure 2) resolved two tritiated disaccharides, **1** and *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-L-arabinopyranose (**5**). Epimerization of the D-xylo residue to the L-arabino configuration presumably occurred at the aldehyde stage (Scheme II).

1 was obtained in 17% yield from **3**, or 14% overall from the *N*-acetylglucosamine dimer **2**. The product was shown to be a radiochemically pure compound on several chromatographic systems. Upon hydrolysis, D-glucosamine and D-xylosamine were obtained in equimolar quantities; only the latter was radiochemically labeled, demonstrating that the sequence of reactions had occurred as outlined in Scheme I. Hydrolysis of **5** yielded D-glucosamine and a tritium-labeled amino sugar which was assumed to be L-arabinosamine on the basis of chromatographic properties[18] and the method of preparation.

SCHEME II



A sequence of reactions identical with those used to synthesize **1** was carried out on the *N*-acetylglucosamine trimer (**6**) in an attempt to produce the next homolog of **1**, the trisaccharide *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-D-xylopyranose (**7**). The dithioacetal **8** was produced in 73% yield from **6**, and its oxidation, reduction, and dithioacetal hydrolysis were followed with results similar to those reported for the disaccharide insofar as could be determined by tritium incorporation, nmr, etc. However, all attempts to resolve the expected tritiated D-xylosamine- and L-arabinosamine-containing trisaccharides failed, even though the behavior of the product in binding experiments with lysozyme showed clearly that it was a mixture of at least two labeled compounds.

In order to further support the assigned structure of **1**, and to produce the homologous trisaccharide **7** and tetrasaccharide **9**, enzymic preparation of these *N*-acetylxylosamine-containing saccharides was also carried out. Tritium-labeled 2-acetamido-2-deoxy-α-D-xylopyranose (**10**) was prepared by the sequence of Scheme III. The ethylthiofuranoside of *N*-acetylxylosamine (**11**) was produced by the method of Wolfrom and Winkley,[7] with the introduction of tritium at C-5 from labeled borohydride, and hydrolyzed to **10** by a variation of Wolfrom and Anno's procedure.[19]

(17) S. A. Barker, A. B. Foster, M. Stacey, and J. M. Webber, *J. Chem. Soc.*, 2218 (1958).

(18) R. Kuhn and G. Baschang, *Justus Liebigs Ann. Chem.*, **628**, 193 (1959).

(19) M. L. Wolfrom and K. Anno, *J. Amer. Chem. Soc.*, **75**, 1038 (1953).

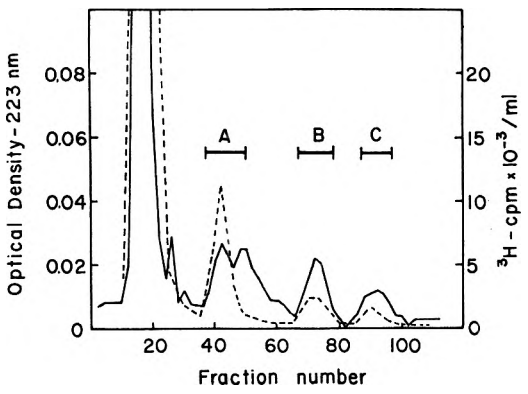
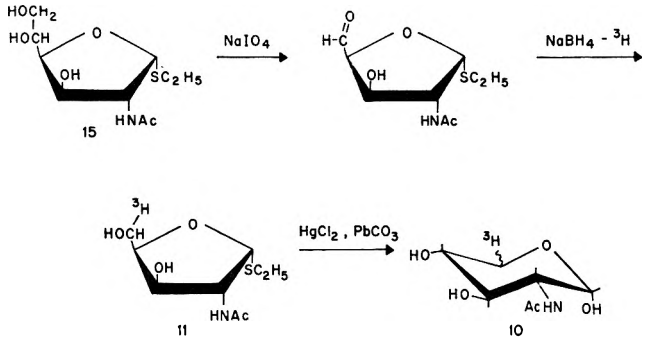


Figure 3.—Chromatographic separation of lysozyme-catalyzed reaction of *N*-acetylglucosamine tetramer (**12**) with labeled *N*-acetylxylosamine (**10**) (1 × 30 cm charcoal–Celite column, eluted with 0–40% ethanol gradient over 2 l.): solid line, optical density; broken line, radioactivity. Fractions A, B, and C pooled to isolate **1**, **7**, and **9**, respectively.

SCHEME III



Incubation of **10** and the *N*-acetylglucosamine tetramer **12** with lysozyme produced a mixture of *N*-acetylglucosamine oligomers and compounds containing tritium-labeled *N*-acetylxylosamine, which could be at least partly resolved on a charcoal–Celite column (Figure 3).

On the basis of the known transglycosylation reactions of lysozyme,[20] all the tritium-labeled oligomers must contain *N*-acetylxylosamine at their reducing termini. Although the linkage to *N*-acetylxylosamine is very probably β, there is no *a priori* reason to believe that these linkages are exclusively to O-4.[12] The identity of the *N*-acetylxylosamine-containing disaccharide produced synthetically and enzymically was demonstrated by perfect cochromatography on systems including a charcoal–Celite column. The fact that binding constants with lysozyme determined by the dialysis equilibrium technique were identical for the two products and independent of saccharide and protein concentrations[5] further demonstrates both the identity and purity of the samples. On the basis of the two alternative methods of preparation and the analysis of synthetic product, the structure of the compound obtained can only be the desired *N*-acetylglucosamine-β(1→4)-*N*-acetylxylosamine (**1**). Given that the disaccharide formed by lysozyme-catalyzed transglycosylation is exclusively the β(1→4) linked compound, it is reasonable to assume that the higher oligosaccharides **7** and **9** so produced have analogous structures.[21] They are also expected to be radiochemically pure, although neither **7** nor **9** could be freed of the respective nonradioactive *N*-acetylglucosamine oligomer of similar size.

The syntheses described here provide important compounds for testing hypotheses concerning the mechanism of lysozyme action, and starting materials and references for the preparation of more complex compounds for the further study of enzyme mechanisms. It is also likely that the synthetic scheme used here can be extended to the modification of other oligosaccharides. The introduction of a radiochemical label in the course of the synthesis turned out to be invaluable for following reactions, for verifying the course of the synthesis, and for analysis of the product. We feel that this technique will turn out to be generally useful for a wide variety of synthetic manipulations.

Experimental Section

General.—Tritiated sodium borohydride was obtained from New England Nuclear Corp. Rexyn 300, a mixed bed ion exchange resin which could be used to remove free reducing sugars[23] as well as ions in product work-ups, was obtained from Fisher Scientific Co. Unlabeled 2-amino-2-deoxy-D-xylose was prepared by the method of Wolfrom and Winkley.[7]

Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter in 10-cm microcells of 1-ml capacity.

Charcoal–Celite columns were prepared by the method of Rupley[13] from equal weights of Darco G-60 and Celite 535, and used only once before discarding. Linear gradients of increasing ethanol concentration were used for elution. Acetamido sugars were detected in the effluent by their end absorption in the uv (223 nm was generally used).

Several analytical chromatographic systems were used: system I, "Baker-flex" silica gel IB plates developed with *n*-butyl alcohol–ethanol–water (5:3:3 v/v) and visualized with a spray of 0.5 g of $KMnO_4$ and 40 g of NaOH in 100 ml of water; system II, Analtech "Avicell" cellulose glass plates developed with *n*-butyl alcohol–acetic acid–water (4:2:3 v/v) and visualized with silver nitrate–base[24] or the chlorine–starch iodide method of Powning and Irzkiewiecz;[25] system III, Analtech cellulose 300 MN glass plates developed with *n*-butyl alcohol–ethanol–water (4:1:2 v/v) and visualized as for II; system IV, Cellulose 300 MN developed with pyridine–ethyl acetate–acetic acid–water (5:5:1:3 v/v) and visualized with 0.2% ninhydrin in ethanol; and system V, descending paper chromatography on Whatman No. 1 paper with the eluent as in IV in a chamber saturated with pyridine–ethyl acetate–water (11:40:60 v/v), developed with ninhydrin. Radiochromatograms were analyzed by scraping or slicing sections into scintillation vials, adding 1 ml of water, and allowing the vials to stand overnight. "Aquasol" liquid scintillation fluid (New England Nuclear) was then added and the vials were counted in a Packard 3375 counter.

Amino Sugar Analysis.—Samples of 1–2 mg of saccharide were hydrolyzed by heating on a steam bath for 2 hr in 2 ml of 6 *N* HCl in a sealed tube. The solvent was removed *in vacuo* and the residue was dried by repeated evaporations with absolute ethanol. For qualitative analysis, chromatography in systems IV and V was used.

For quantitative analysis, the sample dissolved in 0.5 ml of 0.3 *N* HCl was chromatographed on a 1 × 20 cm column of Dowex 50-x8 resin (Cl^- form, 200–400 mesh) equilibrated and eluted with 0.3 *N* HCl, and 1-ml fractions were collected.[26]

(20) D. M. Chipman, J. J. Pollock, and N. Sharon, *J. Biol. Chem.*, **243**, 487 (1968); D. M. Chipman and N. Sharon, *Science*, **165**, 454 (1969).

(21) The disaccharide itself is undoubtedly produced by fragmentation of larger *N*-acetylglucosamine-containing saccharides, rather than direct transfer of an *N*-acetylglucosaminyl residue to *N*-acetylxylosamine.[22] The specificity of *N*-acetylxylosamine as an acceptor as compared to D-xylose[12] is not surprising after the fact, in view of the apparent presence of a strong binding site for the acetamido group in the lysozyme acceptor subsite *E*.[4]

(22) D. M. Chipman, *Biochemistry*, **10**, 1714 (1971).

(23) S. Roseman, R. H. Abeles, and A. Dorfman, *Arch. Biochem. Biophys.*, **36**, 232 (1952).

(24) J. Trevelyan, *Nature (London)*, **166**, 444 (1950).

(25) R. F. Powning and H. Irzkiewiecz, *J. Chromatogr.*, **17**, 621 (1965).

(26) S. Gardell, *Acta Chem. Scand.*, **7**, 207 (1953).

Under these conditions, glucosamine was eluted in an effluent volume of about 76 ml and xylosamine in 100 ml. The fractions were analyzed by the Elson–Morgan color test for amino sugars[27] as extended by Crumpton.[28] Standard xylosamine produced 1.21 times the absorption at 530 nm produced by an equal weight of glucosamine.

O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-D-glucopyranose (2) and higher chitin oligosaccharides were prepared by the method of Rupley,[13] except that a longer charcoal–Celite column (4.5 × 60 cm) eluted with a very slow gradient (water to 20% ethanol over 4 l.) was used to obtain complete separation. From 13 g of chitin, 1.3 g of the dimer 1, $[\alpha]^{27}D$ +15.8° (lit.[13] $[\alpha]^{30}D$ +16°), 1.1 g of trimer 6, $[\alpha]^{27}D$ +3.25° (lit.[13] $[\alpha]^{30}D$ +2.5°), and 0.67 g of tetramer 12, $[\alpha]^{27}D$ −1.4° (lit.[13] $[\alpha]^{30}D$ −2.9°) (all rotations *c* 2, water, final), were obtained.

O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-D-glucose Diethyl Dithioacetal (3).—2 (850 mg) was dissolved in 13 ml of concentrated hydrochloric acid at 0°, ethanethiol (22 ml) was added, and the mixture was stirred with a 5000-rpm mechanical stirrer for 12 hr at 0–3°. This time sufficed for all 2 to disappear (tlc, system I). The ethanethiol was decanted and the aqueous layer, which contained all of the desired product, was diluted to 125 ml and neutralized with basic lead carbonate with cooling. The suspension was filtered and the filtrate was passed through a 1.5 × 7.0 cm column of Rexyn 300 mixed bed resin.[23] The effluent (250 ml) was lyophilized, dissolved in ethanol, and filtered, and the filtrate was evaporated to yield 930 mg (82%) of white powder, which on tlc (system I) showed a major spot of R_f 0.64 and a trace of *N*-acetylglucosamine dithioacetal. Crystallization from water afforded pure **3**: mp 152–159°; $[\alpha]^{23}D$ −13.4° (c 0.82, ethanol); nmr (D_2O) δ 1.75 (t, 6, *J* = 8 Hz, CH_3CH_2S), 2.6 (s, 6, acetamido CH_3), and 3.2 (q, 4, *J* = 8 Hz, CH_3CH_2S); ir (KBr) 1670 and 1630 (amide I), 1572 and 1532 cm^{-1} (amide II).

Anal. Calcd for $C_{20}H_{38}N_2O_{10}S_2 \cdot H_2O$: C, 43.78; H, 7.35; N, 5.11; S, 11.69. Found: C, 43.56; H, 7.59; N, 4.85; S, 11.59.

O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-D-xylopyranose (1).—**3** (500 mg, 0.905 mmol) was dissolved in 30 ml of water. The solution was cooled to 0° and to it was added a solution of 251 mg (1.18 mmol) of sodium periodate (1:1.3 molar ratio) in 30 ml of water cooled to 0°. The mixture was shaken vigorously, and then stirred at 0° for 5 min, after which 100 mg (0.58 mmol) of barium hydroxide in water was added. The reaction mixture was filtered and immediately lyophilized. The resulting white residue (presumably **4**) was dissolved in 100 ml of ethanol, and the solution was filtered through Celite and concentrated under vacuum to 40 ml.

A 60-ml portion of a 0.1 *M* solution of ^3H-$NaBH_4$ (1.7 mCi/mmol) in isopropyl alcohol was added immediately to the above solution, and the mixture was stirred for 3 hr at room temperature. The solvent was removed by evaporation, and the residue was dissolved in 100 ml of water and neutralized to pH 6 with 1 *N* HCl. The solution was stirred with 5 g of Rexyn 300 and filtered, and the resin was washed with water. Lyophilization of the combined filtrate and washings yielded 500 mg of white powder, presumably **13**.

The powder was dissolved in 30 ml of water, and 3 g of lead carbonate and 1.05 g of mercuric chloride were added. The reaction was stirred for 9 hr at room temperature and filtered. Then 3 ml of pyridine and 400 mg of lead carbonate were added to the filtrate, which was allowed to stand in an ice bath for 30 min. The resulting suspension was filtered several times and lyophilized to yield 525 mg of crude 1. The nmr (D_2O) showed acetamido:ethylthio methyl groups in a 4.3:1 ratio.

Vpc Analysis of Oxidation Course.—After oxidation of 50 mg of **3** with periodate as described above, or oxidation of a similar quantity with 1 equiv of lead tetraacetate in 2 ml of pyridine, the samples were treated with Rexyn 300, dried, and reduced with a 10–20-fold excess of cold $NaBH_4$ in ethanol. After repeated addition of methanol and evaporation, the residue was hydrolyzed in 3 ml of 6 *N* HCl at 95° for 1 hr and dried *in vacuo*. The residue was then trimethylsilylated by the method of Sweeley, *et al.*,[29] using "Tri-Sil" reagent (Pierce Chemical Co.), and the pyridine was removed. The samples were taken up in hexane and analyzed by vpc on a 5 ft × 0.125 in. column of 5% QF-1 on 60/80 Chromosorb W, using flame ionization detection. The sample from lead tetraacetate oxidation showed peaks due to the TMS derivatives of glucosamine and glycerol, as identified by retention times and coinjection of authentic mixtures, but little or no material identifiable as xylosamine derivatives. The periodate oxidation product showed peaks due to the α and β derivatives of glucosamine, and xylosamine in about 1/3 the theoretical amount, as well as two unidentified peaks (arabinosamine?).

Chromatographic Purification of 1.—Crude **1** (250 mg) was applied to a 1 × 43 cm charcoal–Celite column and eluted with a gradient of water to 20% ethanol over 2 l. Fractions of 15 ml were collected at a flow rate of 0.3 ml/min. After analysis (Figure 1) fractions 33–55 were pooled and lyophilized to yield 91 mg of a white powder. A portion of this material (65 mg) was rechromatographed on a 1 × 58 cm charcoal–Celite column eluted with a gradient from water to 10% ethanol over 2 l. Fractions of 15 ml were collected at a flow rate of 0.75 ml/min. After analysis (Figure 2) fractions 89–102 (B) were pooled and lyophilized to yield 24.0 mg of **1** (calcd overall yield 17% from **3**). Rechromatography on a similar column and rejection of the front of the peak yielded material of specific activity 1.38 × 10^6 dpm/mg (0.29 mCi/mmol), $[\alpha]^{27}D$ −24.0° (*c* 2, water, final). Acid hydrolysis and analysis on chromatographic systems IV or V showed spots equivalent to authentic glucosamine and xylosamine (R_f glucosamine 1.3 in system V), only the latter of which contained radioactive label.

Anal. Calcd for $C_{15}H_{26}O_{10}N_2 \cdot 3H_2O$: C, 40.18; H, 7.18; N, 6.25. Found: C, 39.69; H, 6.65; N, 6.24.

O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-deoxy-L-arabinopyranose (5).—Fractions 76–83 from the second chromatography of crude **1** (A, Figure 2) were pooled and lyophilized to yield 15.3 mg (calcd 10% from **3**) of **5**. Rechromatography on a similar column and rejection of the tail of the peak yielded material of specific activity 1.27 × 10^6 dpm/mg (0.27 mCi/mmol), $[\alpha]^{27}D$ −13.5° (*c* 0.63, water, final). Amino sugar analysis with system V revealed a spot equivalent to authentic glucosamine and a spot of R_f glucosamine 1.18, slower than xylosamine (lit.[18] R_f glucosamine 1.1 for D-arabinosamine). Only the latter spot was radioactively labeled.

Anal. Calcd for $C_{15}H_{26}O_{10}N_2 \cdot 3H_2O$: C, 40.18; H, 7.18; N, 6.25. Found: C, 39.70; H, 6.59; N, 6.09.

O-2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-O-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-D-glucose Diethyl Dithioacetal (8).—The trimer **6** (1.0 g) was treated with ethanethiol and hydrochloric acid under conditions identical with those used for synthesis of the dimer dithioacetal (**3**) and worked up similarly to yield 850 mg (72%) of a white product. On tlc (system I) the product had R_f 0.54, and contained traces of monomer and dimer dithioacetals as contaminants: nmr (D_2O) δ 1.75 (t, 6, *J* = 8 Hz, CH_3CH_2S), 2.55 (s, 9, acetamido CH_3), 3.25 (q, 4, *J* = 8 Hz, CH_3CH_2S).

Anal. Calcd for $C_{28}H_{51}N_3O_{15}S_2 \cdot 3H_2O$: C, 43.68; H, 7.20; N, 5.46; S, 8.33. Found: C, 43.36; H, 6.96; N, 5.44; S, 7.59.

Ethyl-5-^3H-2-acetamido-2-deoxy-1-thio-α-D-xylofuranoside (11).—Ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside (**15**), mp 124–125°, $[\alpha]^{27}D$ +133° (lit.[7] mp 122–123°, $[\alpha]^{20}D$ +139 ± 3°), was prepared by the method of Wolfrom and Winkley.[7] The *O*-deacetylated compound **14** was prepared from 1.95 g (5.0 mmol) of **15** and oxidized with sodium periodate, as described.[7] After the addition of barium chloride and removal of precipitated barium iodate, the solution was immediately lyophilized. The resulting residue was dissolved in 50 ml of absolute methanol, and 10 ml of a 0.05 *M* solution of ^3H-sodium borohydride in isopropyl alcohol (14 mCi/mmol) was added. After 30 min of stirring at room temperature, a further 226 mg (5.0 mmol) of sodium borohydride in 10 ml of methanol was added, and the mixture was stirred for 30 min more. The solvent was removed under reduced pressure, and the residue was taken up in water, neutralized to pH 7, and passed down a 15 × 2.5 cm column of Rexyn 300. The effluent (200 ml) was evaporated under high vacuum, and the solid was recrystallized from ethanol to yield two crops of solid **11**, 94 mg, mp 155–156°, and 10 mg, mp 152–154° (total yield 19%) (lit. mp 153–155°,[7] 157–158°[19] for unlabeled compound).

5-^3H-2-Acetamido-2-deoxy-α-D-xylose (10).—**11** (200 mg) was dissolved in 4 ml of water and a suspension of 1.4 g of lead carbonate and 500 mg of mercuric chloride in 12 ml of water was added. The mixture was stirred at room temperature for 4 hr and filtered. After addition of 2 ml of pyridine the solution was allowed to stand at 4° overnight. The precipitated pyridine

(27) L. Elson and W. Morgan, *Biochem. J.*, **27**, 1824 (1933).
(28) M. J. Crumpton, *Biochem. J.*, **72**, 479 (1959).
(29) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

complex of mercury was filtered off, and the filtrate was lyophilized. The solid was repeatedly dissolved in methanol, the solvent was evaporated, and the white powder resulting was finally recrystallized from methanol–acetone–ether to afford 107 mg (66%) of white needles, mp 180–182° dec, $[\alpha]^{27}D$ +8.4° (c 0.74, water, final) [lit.[19] mp 184–187° dec, $[\alpha]^{29}D$ +8° (c 1, water, final) for unlabeled compound]. This material was identical in several tlc systems with an authentic sample of *N*-acetyl-α-D-xylosamine provided by the late Professor Wolfrom. It was recrystallized to a constant specific activity of 3.10×10^6 dpm/mg (0.29 mCi/mmol).

Enzymic Synthesis of Oligosaccharides Containing Xylosamine.—In a typical experiment, 17 mg (0.020 mmol) of the β(1→4)-linked tetramer of 2-acetamido-2-deoxy-D-glucose (**12**) and 17 mg (0.085 mmol) of 5-^3H-2-acetamido-2-deoxy-α-D-xylopyranose (**10**, 3.10×10^6 dpm/mg) were incubated with 2 mg of lysozyme (Worthington LYSF, three times recrystallized salt free) in 2 ml of 0.1 *M* sodium acetate–acetic acid buffer, pH 5.2, at 39.5° for 25 hr, and the mixture was applied to a 1 × 30 cm charcoal–Celite column. The column was eluted with a gradient from water to 40% ethanol over 2 l. Fractions of 10 ml were collected at a rate of 1.5 ml/min and analyzed (Figure 3). Fractions 37–50 (A) were pooled and lyophilized to yield 4.5 mg of material which was rechromatographed on a 1 × 30 cm column with a 2-l. 0–20% ethanol gradient. The major peak was collected and lyophilized to yield pure *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-D-xylopyranose (**1**). This material was shown to be identical with that produced synthetically, by tlc (systems I, II, III) and cochromatography on a 1 × 30 cm charcoal–Celite column with a 2-l. 0–15% ethanol gradient.

Fractions 67–78 from the initial chromatography (B, Figure 3) contained *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxy-D-xylopyranose (**7**), together with the β(1→4)-linked trimer of 2-acetamido-2-deoxy-D-glucose (**6**), and fractions 87–97 (C) contained *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-*O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-5-^3H-2-acetamido-2-deoxyxylopyranose (**9**), together with the β(1→4) tetramer of 2-acetamido-2-deoxy-D-glucose (**12**). Each of these peaks was pooled and rechromatographed twice, with the front of the peak being collected each time. Analysis of known weights of the final products for ^3H content revealed that the trisaccharide mixture contained 22 mol % of the xylosamine-containing compound **7** and that the tetrasaccharide mixture contained 16 mole % of the xylosamine-containing compound **9**.

Registry No.—**1**, 38864-17-4; **2**, 35061-50-8; **3**, 38864-18-5; **4**, 38864-19-6; **5**, 38864-20-9; **6**, 38864-21-0; **8**, 38864-22-1; **10**, 38864-23-2; **11**, 38864-24-3; **13**, 38864-25-4; **14**, 38859-04-0; **15**, 7115-40-4.

C-Glycosyl Nucleosides. II.[1] A Facile Synthesis of Derivatives of 2,5-Anhydro-D-allose

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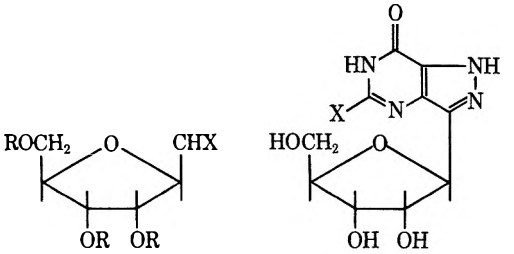
A very facile synthetic route to 3,4,6-substituted derivatives of 2,5-anhydro-D-allose is described. Reductive hydrolysis of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**3**) with Raney nickel and sodium hypophosphite in aqueous pyridine–acetic acid is accompanied by extensive elimination of benzoate to give furfural derivatives. In the presence of *N*,*N*′-diphenylethylenediamine (**6**), however, the initial aldehyde is trapped as a crystalline 1,3-diphenylimidazolidine derivative (**7**) which is obtained in 74% yield. In a similar way 5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl cyanide is converted into the corresponding imidazolidine derivative (**12**). Alkaline hydrolysis of (**7**) gives 1,3-diphenyl-2-(β-D-ribofuranosyl)imidazolidine (**8**) which can be converted into the tri-*O*-benzyl ether **9a** or the tri-*O*-acetate **9b**. Regeneration of the free 3,4,6-trisubstituted 2,5-anhydro-D-alloses from the imidazolidine derivatives can be achieved by mild acidic treatment.

In recent years a considerable number of *C*-glycosyl nucleosides have been isolated from natural sources.[2] The frequently interesting biological properties of these substances have made them interesting targets for chemical synthesis, but as yet this has proved to be a more formidable task than the preparation of conventional *N*-glycosyl nucleosides. Thus, while the preparation of 5-(β-D-ribofuranosyl)uracil (pseudouridine) has been achieved through carbon–carbon bond formation between a 5-lithiopyrimidine and a suitable derivative of ribose,[1,3] and this method has also been extended to other 5-glycosyluracils,[4] this route has not yet been readily adapted for use with other heterocycles.

A more versatile route would appear to involve the preparation of an appropriately C_1-functionalized derivative of 2,5-anhydro-D-allose or 2,5-anhydro-D-allitol (**1**), a compound already containing the desired elusive carbon–carbon bond, from which C_1 can be elaborated into a variety of heterocycles. One such derivative is the diazo compound **1a** which has been



1a, R = CH_2Ph; X = N_2
b, R = CH_2Ph; X = O
c, R = Bz; X = O

2a, X = H
b, X = OH

ingeniously converted into formycin B (**2a**)[5] and oxoformycin (**2b**)[6] *via* initial cycloaddition to dimethyl acetylenedicarboxylate.

In a related way the furanosyl keto ester (**1**, R = Ac; CHX = $COCO_2Me$) has been transformed into the

(1) For part I, see U. Lerch, M. G. Burdon, and J. G. Moffatt, *J. Org. Chem.*, **36**, 1507 (1971).

(2) For reviews, see (a) K. Gerzon, D. C. de Long, and J. C. Cline, *Pure Appl. Chem.*, **28**, 489 (1971); (b) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.

(3) D. M. Brown, M. G. Burdon, and R. P. Slatcher, *J. Chem. Soc.*, 1051 (1968).

(4) W. A. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 3315 (1966); **33**, 140 (1968).

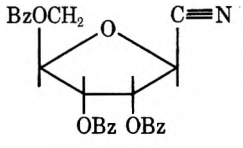
(5) E. M. Acton, K. J. Ryan, D. W. Henry, and L. Goodman, *Chem. Commun.*, 986 (1971).

(6) (a) M. Bobek, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, 4611 (1970); (b) J. Farkaš and F. Šorm, *Coll. Czech. Chem. Commun.*, **37**, 2798 (1972).

nucleoside antibiotic showdomycin,[7] and both the carboxylic acid (1, R = Bz; CHX = COOH)[8] and the thioformimidate [1, R = Bz; CHX = C(=NH)-SCH_2Ph][9] have been incorporated into derivatives of 8-β-D-ribofuranosyladenine. Finally, the recently described synthesis of a β-D-ribofuranosylethyne (R = CH_2Ph; CHX = C≡CH) paves the way to certain 4-ribosyltriazoles.[10]

A recent brief communication by Ogawa, *et al.*,[11] has described a multistep process by which glucose may be converted into 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**1b**) which was subsequently transformed into intermediates leading to the diazo compound **1a**. The free aldehyde group of **1b** is also, however, an attractive functional group for elaboration of *C*-glycosyl heterocycles, and in this paper we describe a facile route for the preparation of variously substituted derivatives of 2,5-anhydro-D-allose.[12]

The key intermediate in our synthesis is 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**3**), a crystalline compound which is readily prepared in 70–80% yields from 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide and mercuric cyanide according to the procedure of Bobek and Farkaš.[8] This substance has been both hydrolyzed to the corresponding allonic acid[8] and reduced to 1-amino-2,5-anhydro-1-deoxyallitol[13] during previous work, but the most direct route to the desired compound would appear to be reductive hydrolysis of the cyano function to the aldehyde **1c**. Such procedures have been reviewed[14] and a convenient modification would appear to be that developed by Backeberg and Staskun.[15] Indeed, the reaction of **3** with an excess of Raney nickel and sodium hypophosphite in a mixture of pyridine, acetic acid and water at 45° for 1 hr led to quite rapid conversion into a material giving a positive test for aldehydes using acidic dinitrophenylhydrazine as a spray on thin layer plates. The colored spot was,



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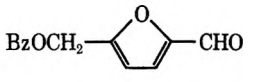

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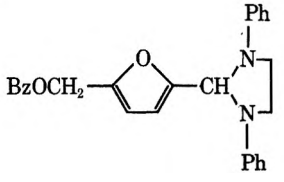
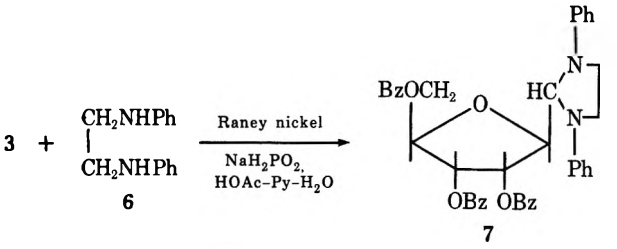


5

however, orange rather than yellow and suggested the presence of an unsaturated aldehyde. Indeed, this substance was isolated as a crystalline derivative (**5**) and shown to be the furan **4** resulting from elimination of benzoate from the desired aldehyde **1c**. It could be readily shown by tlc that this elimination took place during the reductive hydrolysis rather than during preparation of the derivative **5**. Thus regeneration of the aldehyde **4** from **5** (see later) gave a substance identical with the direct product of the reductive hydrolysis and clearly different from **1c**.

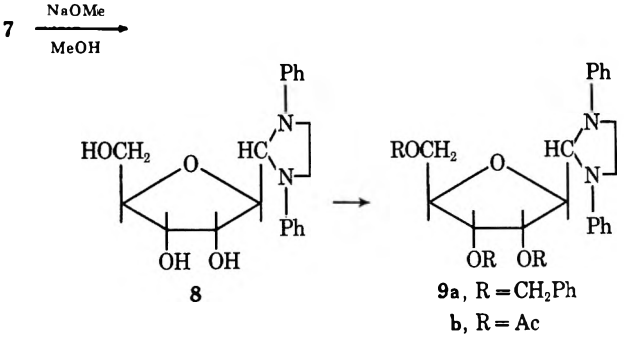
This very facile elimination reaction was finally avoided by conducting the reductive hydrolysis reaction in the presence of *N*,*N*′-diphenylethylenediamine (**6**). The latter reagent has been developed



6 **7**

by Wanzlick and Löchel[16] for the selective conversion of aldehydes[17] into 1,3-diphenylimidazolidine derivatives and has previously been used to trap aldehydes formed by hydrogenation of nitriles[18] or desulfurization of thio esters.[19] In the presence of **6** the reaction of **3** with sodium hypophosphite and Raney nickel in aqueous pyridine–acetic acid was rapid at room temperature and gave crystalline 1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazolidine (**7**) in 74% yield.

While, as will be seen later, the imidazolidine ring is very readily hydrolyzed under acidic conditions, it is very stable toward base. Thus treatment of **7** with



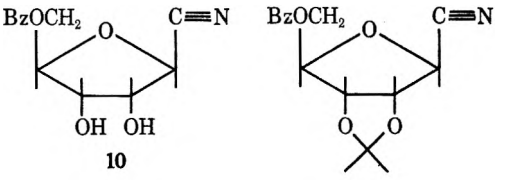
8 **9a**, R = CH_2Ph; **b**, R = Ac

methanolic sodium methoxide led to smooth cleavage of the benzoyl groups, giving crystalline 1,3-diphenyl-2-(β-D-ribofuranosyl)imidazolidine (**8**) in a yield of 73%. Subsequent benzylation of **8** using benzyl chloride and sodium hydride in dimethyl sulfoxide gave the crystalline tri-*O*-benzyl ether **9a** in 80% yield. Alternatively, simple acetylation of the triol **8** gave the tri-*O*-acetyl

(7) L. Kalvoda, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, 2297 (1970).
(8) M. Bobek and J. Farkaš, *Collect. Czech. Chem. Commun.*, **34**, 247 (1968).
(9) J. Igolen and T. H. Dink, *Chem. Commun.*, 1267 (1971).
(10) J. G. Buchanan, A. R. Edgar, and M. J. Power, *J. Chem. Soc. D*, 346 (1972).
(11) T. Ogawa, Y. Kikuchi, M. Matsui, H. Ohrui, H. Kuzuhara, and S. Emoto, *Agr. Biol. Chem.*, **35**, 1825 (1971).
(12) For a general review on 2,5-anhydro sugars, see J. Defaye, *Advan. Carbohyd. Chem. Biochem.*, **25**, 181 (1970). Routes similar to that of ref 11 have subsequently been developed by Emoto, *et al.*, for the preparation of the dimethyl acetals of other 2,5-anhydrohexose derivatives: personal communication from Drs. H. Ohrui and S. Emoto.
(13) M. Bobek and J. Farkaš, *Collect. Czech. Chem. Commun.*, **34**, 1684 (1969).
(14) (a) E. Mosettig, *Org. React.*, **3**, 218 (1954). (b) Houben-Weyl, "Methoden der organischen Chemie," 4th ed, Vol. VII, part I, Thieme Verlag, Stuttgart, 1954, p 299.
(15) O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, 3961 (1962).
(16) H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).
(17) This reagent has also been widely exploited in this laboratory by Dr. G. H. Jones, *et al.*, for the isolation of nucleoside 5′-aldehydes. See, *e.g.*, N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971). We are particularly grateful to Dr. Jones for his advice in this matter.
(18) H. Plieninger and B. Kiefer, *Chem. Ber.*, **90**, 617 (1957).
(19) (a) H. J. Bestmann and H. Schulz, *Chem. Ber.*, **92**, 530 (1959); (b) W. J. Gottstein, G. E. Bocian, L. B. Crast, K. Dadabo, J. M. Essery, J. C. Godfrey, and L. C. Cheney, *J. Org. Chem.*, **31**, 1922 (1966).

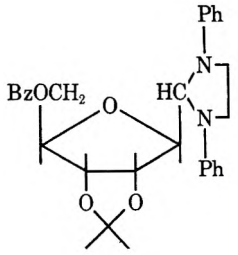
derivative **9b** in 96% yield. Clearly, other types of protecting groups could also be introduced under basic conditions if so desired.

The above methods make derivatives of 2,5-anhydro-D-allose containing protecting groups that can be subsequently removed under alkaline or reductive conditions readily available. Protection of the vicinal diol by a noneliminatable, acid-labile substituent such as an isopropylidene group was also desirable. To this end the nitrile **3** was treated with methanolic ammonia at 0° which selectively removed the secondary benzoyl groups, giving 5-*O*-benzoyl-β-D-ribofuranosyl cyanide (**10**) in 83% yield. This reaction has previously been described by Montgomery and Hewson,[20] but under the present conditions the yield of crystalline product was more than doubled without the necessity of chromatography. Subsequent treatment of **10** with acetone

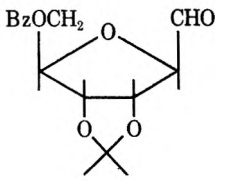


10

11



12



13

and 2,2-dimethoxypropane in the presence of perchloric acid gave a 95% yield of the crystalline isopropylidene derivative **11** which was previously described as a syrup.[20] Reductive hydrolysis of **11** in the presence of *N*,*N*′-diphenylethylenediamine gave, as above, the crystalline imidazolidine derivative **12** in 78% yield.

Regeneration of the free aldehyde function from 1,3-diphenylimidazolidine derivatives has usually been achieved by treatment with a heterogeneous mixture of ether and 3–6 *N* hydrochloric acid.[18,19a] The aldehydes can, however, be liberated under much milder conditions by treatment with 2.5–3 molar equiv of *p*-toluenesulfonic acid monohydrate in a mixture of acetone and methylene chloride at 0–20°.[21] Such treatment of **7**, **9a**, and **12** leads to the rapid precipitation of the *p*-toluenesulfonate salt of *N*,*N*′-diphenylethylenediamine which can be removed by filtration and aqueous extraction. The residual products so obtained in high yields are the 3,4,6-substituted 2,5-anhydro-D-allose derivatives (**1c**, **1b**, and **13**, respectively) which are sufficiently pure for direct use in subsequent reactions to be described in forthcoming papers.[22] It is interesting to note that, even though tlc examination of the crude reaction mixtures shows complete disappearance of the imidazolidine derivatives, small amounts (perhaps 5%) of unreacted material are usually found in the worked up products. This could be due to the precipitation of traces of the *p*-toluenesulfonate salt of the starting material which does not become solubilized until work-up. For the preparation of analytical samples these minor impurities can be removed by rapid chromatography on a column of silicic acid. By this means chromatographically and analytically pure samples of **1c**, **1b**, and **13** were obtained. Our previous experience in the chemistry of nucleoside 5′-aldehydes has made us acutely aware of the perils of elimination and epimerization reactions which attend chromatography of molecules of this sort.[23] The derivatives of 2,5-anhydro-D-allose are also potentially subject to these reactions, and, accordingly, we do not recommend chromatography as a preparative procedure. We do not have any evidence, however, for such side reactions prior to, or during, acidic removal of the imidazolidine groups. Certainly the chromatographic purity of the crude aldehydes (**1b**, **1c**, and **13**) precludes elimination reactions which are always much more prevalent than epimerization.[23] The lack of side reactions accompanying the liberation of nucleoside 5′-aldehydes from their imidazolidine derivatives under comparable conditions has been previously demonstrated.[17]

The free aldehydes are rather unstable compounds in solution and it is recommended that they be generated only immediately prior to use. For example, the tribenzoyl aldehyde **1c** can be shown by tlc to undergo extensive decomposition upon storage in chloroform at room temperature for 2 hr. It can, however, be stored as a syrup at −20° for many days. The benzyl and isopropylidene derivatives (**1b** and **13**) were, expectedly, more stable.

As an alternative procedure for the hydrolysis of the imidazolidine derivatives, we have sometimes used treatment with Dowex-50 (H^+) resin in aqueous tetrahydrofuran. This procedure is convenient since all traces of basic hydrolysis products are bound by the resin and can be removed by simple filtration. This procedure, however, requires treatment at 50–60° for several hours to complete the hydrolysis, but the reaction can be taken to completion giving chromatographically homogeneous aldehydes. By this method, the tribenzyl ether **1b** can be obtained in very high yield as described in the accompanying paper.[24]

The derivatives of 2,5-anhydro-D-allose described in this paper provide very useful starting materials for the synthesis of a wide range of *C*-glycosyl nucleosides. Such syntheses will be described in forthcoming papers in this series.[22,24]

Experimental Section

General Methods.—The general analytical methods were similar to those described previously.[1]

Nmr Data.—These are given in Tables I and II.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl Cyanide (3).—This compound was prepared in 78% yield according to Bobek and Farkaš[8] with mp 77.5–79° (lit.[8] mp 78.5–80°); $[\alpha]^{23}D$ 24.2° (*c* 0.98, $CHCl_3$); λ_{max}^{MeOH} 230 nm (ε 35,000), 274 (2800), 288 (2400).

(20) J. A. Montgomery and K. Hewson, *J. Heterocycl. Chem.*, **7**, 443 (1970).

(21) *p*-Toluenesulfonic acid has previously been used by Gottstein, *et al.*,[19b] for the liberation of penicillinaldehydes from their imidazolidine derivatives.

(22) Unpublished studies by H. P. Albrecht, D. B. Repke, and J. G. Moffatt.

(23) See, *e.g.*, G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, 1969, CARB 16.

(24) G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, **38**, 1841 (1973).

TABLE I

CHEMICAL SHIFTS (PARTS PER MILLION) AT 100 MHz[a]

Compd	Solvent[b]	C_1H	C_2H	C_3H	C_4H	C_5H	C_6H	Other
3	C		4.96 (d)	5.98 (dd)	5.82 (dd)	4.65 (m)	4.65 (m)	7.2–8.2 (m, 15, Ar)
5	C	6.14 (s)		6.26 (s)	6.26 (s)		5.15 (s)	3.75 (m, 4, NCH_2), 6.7–8.0 (m, 15, Ar)
7	C	5.86 (br s)	4.79 (d)	5.70 (dd)	5.50 (m)	4.45 (m)	4.45 (m)	3.7 (m, 4, NCH_2), 6.8 (m, 4, Ar), 7.3 (m, 15, Ar), 7.9 (m, 6, Ar)
8	P (D_2O)	5.97 (br s)	4.87 (br d)	4.52 (dd)	4.4 (m)	4.4 (m)	3.91 (s)	3.56 and 3.84 (m, 2, NCH_2), 7.0 (m, 10, Ar)
9a	C	5.52 (d)	4.52 (dd)	3.78 (dd)[c]	4.14 (dd)	3.2–3.6 (m)	3.2–3.6 (m)	3.5 (m, 4, NCH_2), 4.28, 4.38, and 4.42 (s, 2, OCH_2Ar), 6.69 (m, 4, Ar), 7.25 (m, 21, Ar)
9b	C	5.65 (d)	4.46 (dd)	5.24 (dd)	4.92 (dd)	4.08 (m)	4.08 (m)	3.7 (m, 4, NCH_2), 1.86, 1.96, and 2.00 (s, 3, OAc), 6.6–7.3 (m, 10, Ar)
10	P		5.14 (d)	4.94 (m)	4.24 (m)	4.24 (m)	4.24 (m)	7.35 (m, 3, Ar), 8.18 (dd, 2, Ar)
11	C		4.73 (d)	5.09 (dd)	4.85 (d)	4.48 (s)	4.50 (s)	1.33 and 1.50 (s, 3, CMe_2), 7.3–8.2 (m, 5, Ar)
12	B	5.62 (d)	4.51 (dd)	4.69 (dd)	4.2 (m)	4.06 (m)	4.2 (m)	1.06 and 1.27 (s, 3, CMe_2), 3.08 and 3.38 (m, 2, NCH_2), 6.6–8.1 (m, 15, Ar)

[a] The compounds are all numbered as though they were derivatives of 2,5-anhydro-D-allose. [b] The solvents used are designated as follows: B, benzene-d_6; C, $CDCl_3$; D, DMSO-d_6; P, pyridine-d_5. [c] The usual position of C_3 H upfield of C_4H is confirmed by decoupling studies.

TABLE II

COUPLING CONSTANTS (HERTZ)

Compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
3		4	5	5	*a*
5			0		
7	1	6	6	*a*	*a*
8	1	6	6	*a*	0
9a	1	5	5	5	*a*
9b	1	5.5	5.5	5.5	*a*
10		4	*a*	*a*	*a*
11		2	6	0	0
12	1.5	6	6	*a*	*a*

[a] Not resolved.

1,3-Diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazolidine (7).—Solid **3** (25 g, 53 mmol) was added to a vigorously stirred suspension of Raney nickel[25] (75 g) in a solution of monosodium hypophosphite (50 g), and *N*,*N*′-diphenylethylenediamine (21.2 g, 100 mmol) in a mixture of pyridine (375 ml), acetic acid (185 ml), and water (185 ml). The mixture was stirred at room temperature for 1.25 hr and then filtered. The precipitate was washed thoroughly with chloroform (3 × 200 ml), and the combined filtrates were diluted to a volume of 2.5 l. with chloroform and then washed three times with 200-ml portions of water. The chloroform solution was dried ($MgSO_4$) and evaporated, leaving a syrup that crystallized upon addition of methanol giving 26 g (74%) of **7** with mp 154–155°. An analytical sample from chloroform–hexane had mp 155–155.5°; λ_{max} 232 nm (ε 47,900), 252 (34,600), 282 (5900); $[\alpha]^{23}D$ 11.2° (*c* 0.1, $CHCl_3$).

Anal. Calcd for $C_{41}H_{36}N_2O_7$ (668.72): C, 73.63; H, 5.43; N, 4.19. Found: C, 73.74; H, 5.40; N, 4.05.

2-(1,3-Diphenylimidazolidin-2-yl)-5-benzoyloxymethylfuran (5).—A mixture of **3** (9.25 g, 19.6 mmol), Raney nickel (18.5 g), sodium hypophosphite (18.5 g), pyridine (140 ml), acetic acid (70 ml), and water (70 ml) was stirred at 45° for 2 hr. The mixture was then filtered and the filtrate evaporated *in vacuo*. The residue was partitioned between ethyl acetate and water, and the filtered organic phase was evaporated to dryness. The residue was dissolved in methanol (100 ml) containing **6** (5.3 g) and glacial acetic acid (2 ml) was added. After 16 hr at 23° the solution was evaporated, and the residue was chromatographed on a column of silicic acid using hexane–ether (5:2). Evaporation of the main peak followed by crystallization from methanol gave 1.4 g (18%) of **5** with mp 111.5–113°; λ_{max}^{MeOH} 231 nm (sh, ε 31,400), 251 (38,000), 281 (4800), 290 (sh, 4500); λ_{max} (KBr) 1725, 1600 cm^{-1}.

Anal. Calcd for $C_{27}H_{24}N_2O_3$ (424.48): C, 76.39; H, 5.70; N, 6.60. Found: C, 76.15; H, 5.68; N, 6.45.

1,3-Diphenyl-2-(β-D-ribofuranosyl)imidazolidine (8).—A solution of **7** (19.8 g, 29.6 mmol) in chloroform (200 ml) was added to methanolic sodium methoxide (200 ml of 0.075 *M*), and the mixture was stirred at room temperature for 2.5 hr. The solution was then neutralized by addition of Dowex 50 (H^+) resin, filtered, and evaporated to dryness leaving a residue that was freed from methyl benzoate by rapid chromatography on a column of silicic acid (1 kg) using chloroform–ethyl acetate (1:1) and then ethyl acetate. The product was then crystallized from aqueous methanol giving 7.5 g (73%) of **8** with mp 169–170°; λ_{max}^{MeOH} 250 nm (ε 36,700), 295 (5400); $[\alpha]^{23}D$ 5.3° (*c* 0.2, MeOH).

Anal. Calcd for $C_{20}H_{24}N_2O_4$ (356.4): C, 67.39; H, 6.79; N, 7.86. Found: C, 67.35; H, 7.01; N, 7.79.

1,3-Diphenyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazolidine (9a).—Carefully dried **8** (7.5 g, 21 mmol) was added to a stirred suspension of sodium hydride (9.6 g, 400 mmol) in DMSO (300 ml) and kept under argon at room temperature for 30 min. Benzyl chloride (70 ml, 600 mmol) was then added dropwise, and the mixture was heated at 60° for 2 hr. After storage overnight at room temperature the mixture was diluted with chloroform (1 l.) and washed once with 200 ml of 2 *N* acetic acid and then with saturated aqueous sodium bicarbonate and water. The organic phase was dried and evaporated, leaving a syrup that was chromatographed on a column of silicic acid using hexane–ether (4:1) and giving 10.5 g (80%) of **9a** with mp 92–94° from ether–hexane; λ_{max}^{MeOH} 254 nm (ε 33,000), 294 (4300); $[\alpha]^{23}D$ 2.6° (*c* 0.6, $CHCl_3$).

(25) No. 28 Raney nickel under water obtained from W. R. Grace and Co.

Anal. Calcd for $C_{41}H_{42}N_2O_4$ (626.76): C, 78.56; H, 6.75; N, 4.47. Found: C, 78.94; H, 6.83; N, 4.62.

1,3-Diphenyl-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolidine (9b).—A solution of **8** (760 mg, 2 mmol) in pyridine (6 ml) and acetic anhydride (3 ml) was kept for 16 hr at room temperature. Methanol (15 ml) was added, and after 1 hr the solution was evaporated to dryness. The residue was dissolved in chloroform, washed with water, dried, and evaporated giving 950 mg (96%) of crystalline **9b** with mp 109–110° unchanged upon recrystallization from ether–hexane; $[\alpha]^{23}D$ −22° (*c* 0.1, $CHCl_3$).

Anal. Calcd for $C_{26}H_{30}N_2O_7$ (482.52): C, 64.71; H, 6.27; N, 5.81. Found: C, 64.99; H, 6.38; N, 5.87.

5-*O*-Benzoyl-β-D-ribofuranosyl Cyanide (10).—A solution of **3** (61 g) in chloroform (600 ml) was added with stirring to ice-cooled, saturated methanolic ammonia (900 ml) and kept at 0° for 4.5 hr. The solvent was then evaporated *in vacuo*, and the residue was dissolved in ethyl acetate, washed with a small volume of saturated aqueous sodium bicarbonate and then water, dried, and evaporated. The residual syrup was crystallized from benzene–hexane giving 28 g (83%) of **10** with mp 117–117.5° (lit.[20] mp 118°).

5-*O*-Benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl Cyanide (11).—Solid **10** (42 g) was added to a solution of 72% perchloric acid (6 ml) in 2,2-dimethoxypropane (50 ml) and acetone (300 ml), and the resulting mixture was stirred at room temperature for 2 hr. The solution was neutralized with ammonium hydroxide and evaporated to dryness, leaving a residue that was dissolved in chloroform and washed twice with water. The organic phase was dried and evaporated and the residue crystallized from ether–hexane giving 46 g (95%) of **11** with mp 57–60° (lit.[20] as a syrup). An analytical sample had mp 60–61°.

1,3-Diphenyl-2-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazolidine (12).—Nitrile **11** (5.0 g, 17.2 mmol) was added to a suspension of Raney nickel (20 g), **6** (5.0 g), and sodium hypophosphite (10 g) in 40 ml of a mixture of pyridine, acetic acid, and water (2:1:1) and vigorously stirred at room temperature for 1 hr. The mixture was filtered, and the solid material was washed well with chloroform. The filtrate was diluted to a volume of 1 l. with chloroform and washed with water. The organic phase was dried and evaporated leaving a syrup that crystallized upon addition of methanol giving 6.6 g (78%) of **12** with mp 144–145° unchanged upon recrystallization from chloroform–hexane; λ_{max}^{MeOH} 253 nm (ε 34,700), 283 (4300), 292 (4400); $[\alpha]^{23}D$ −36.2° (*c* 0.1, $CHCl_3$); ν_{max} (KBr) 1715, 1600 cm^{-1}.

Anal. Calcd for $C_{30}H_{32}N_2O_5$ (500.57): C, 71.98; H, 6.44; N, 5.60. Found: C, 72.10; H, 6.38; N, 5.47.

2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allose (1c).—A solution of *p*-toluenesulfonic acid monohydrate (355 mg, 1.87 mmol) in acetone (10 ml) was added with stirring to an ice-cooled solution of **3** (500 mg, 0.75 mmol) in methylene chloride (25 ml). After 5 min at 0° the mixture was allowed to come to room temperature over 40 min. Since tlc (ether–hexane, 2:1) showed some residual **3**, an additional 50 mg of *p*-toluenesulfonic acid in acetone (5 ml) was added. After 15 min, tlc showed completion of the reaction, and the mixture was filtered. The precipitate was washed with methylene chloride, and the combined filtrates were evaporated *in vacuo* without heating. The residue was dissolved in methylene chloride, washed three times with cold water, dried ($MgSO_4$), and evaporated. The resulting syrup was shown by tlc to contain a small amount of unreacted **3**, which was removed by rapid chromatography on a column containing 15 g of silicic acid using ether–hexane (2:1). In this way **1c** (240 mg, 68%)[26] was obtained as a chromatographically homogeneous syrup: $[\alpha]^{23}D$ 44.7° (*c* 0.33, $CHCl_3$); nmr ($CDCl_3$) δ 9.77 ppm (d, $J_{1,2}$ = 1.5 Hz, CHO).[27]

Anal. Calcd for $C_{27}H_{22}O_8$ (474.45): C, 68.34; H, 4.67. Found: C, 68.22; H, 4.64.

Upon reaction with *tert*-butyl carbazate in ethanol containing glacial acetic acid, **1c** formed a *tert*-butylcarbazone with mp 172–176° from chloroform–hexane.

Anal. Calcd for $C_{32}H_{32}N_2O_9$ (588.59): C, 65.30; H, 5.48; N, 4.76. Found: C, 65.05; H, 5.36; N, 4.70.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-allose (1b).—The imidazolidine derivative (**9a**, 500 mg, 0.8 mmol) was treated with *p*-toluenesulfonic acid monohydrate (350 mg) in a mixture of acetone and methylene chloride as during the preparation of **1c**. The crude product once again contained a little unreacted **9a** which was removed by rapid chromatography through a column of silicic acid using ether–hexane (2:1). The pure fractions were evaporated leaving 180 mg (52%) of **1b** as a chromatographically homogeneous, clear syrup: $[\alpha]^{23}D$ 62.5° (*c* 0.28, $CHCl_3$); nmr ($CDCl_3$) δ 9.64 ppm (d, $J_{1,2}$ = 1.5 Hz, CHO);[27] λ_{max}^{MeOH} 229 nm (ε 4800).

Anal. Calcd for $C_{27}H_{28}O_5$ (432.49): C, 74.98; H, 6.53. Found: C, 74.92; H, 6.54.

2,5-Anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allose (13).—The imidazolidine derivative (**12**) was treated with *p*-toluenesulfonic acid monohydrate exactly as above to give, following rapid chromatography on silicic acid, the chromatographically homogeneous aldehyde **13** as a clear syrup: $[\alpha]^{23}D$ 11.9° (*c* 0.5, $CHCl_3$); nmr ($CDCl_3$) δ 9.65 ppm (s, CHO).[27]

Anal. Calcd for $C_{16}H_{18}O_6 \cdot 0.5H_2O$ (315.31): C, 60.94; H, 6.07. Found: C, 60.65; H, 6.22.

Treatment of the crude aldehyde in ethanol with *tert*-butyl carbazate in the presence of acetic acid for 1 hr at room temperature gave the crystalline *tert*-butylcarbazone with mp 118–120° from chloroform–hexane in 57% yield.

Anal. Calcd for $C_{21}H_{28}N_2O_7$ (420.45): C, 59.99; H, 6.71; N, 6.66. Found: C, 60.29; H, 6.71; N, 6.58.

Registry No.—**1** (R = H; X = O), 39037-97-3; **1b**, 37699-02-8; **1c**, 39037-99-5; **1c** *tert*-butylcarbazone, 39038-00-1; **3**, 23316-67-8; **5**, 39050-05-0; **6**, 150-61-8; **7**, 39038-02-3; **8**, 39038-03-4; **9a**, 38821-04-4; **9b**, 39037-09-7; **10**, 30002-87-0; **11**, 29868-36-8; **12**, 39037-12-2; **13**, 39037-13-3; **13** *tert*-butylcarbazone, 39037-14-4; 2,2-dimethoxypropane, 77-76-9; *p*-toluenesulfonic acid, 104-15-4.

(26) The yield of unchromatographed product, which is better than 90% pure, is almost quantitative. This material generally is used in subsequent reactions.

(27) The free aldehydes (**1c**, **1b**, and **13**) do not give well-resolved nmr spectra. Since the aldehyde protons inevitably integrate for less than one proton, this is probably due to the ease with which these compounds form aldehyde hydrates. Similar facile hydration of sugar aldehydes has been frequently encountered. See, *e.g.*, D. Horton and J. D. Wander, *Carbohyd. Res.*, **16**, 477 (1971).

C-Glycosyl Nucleosides. III.[1] A Facile Synthesis of the Nucleoside Antibiotic Showdomycin

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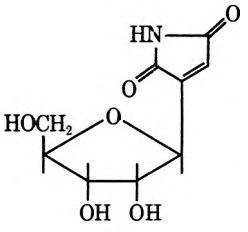
The reaction of 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose with sodium cyanide and hydrogen peroxide gives 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonamide (**6**) and its D-glycero-D-altro isomer (**5**). Methanolysis of these substances gives the corresponding methyl heptonates which can be oxidized using DMSO and DCC in the presence of dichloroacetic acid to methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (**9**). Reaction of this keto ester with carbamoylmethylenetriphenylphosphorane leads directly to the tribenzyl ether of showdomycin. Removal of the benzyl groups can be achieved either by boron trifluoride catalyzed acetolysis followed by acidic hydrolysis, or by treatment with boron trichloride at −78°. The showdomycin so obtained is identical with the natural product. Several model reactions are described to clarify the steric course of the reactions between α-keto esters and carbamoylmethylenetriphenylphosphorane.

The *C*-glycosyl nucleoside antibiotic showdomycin was first isolated from *Streptomyces showdoensis* by Nishimura, *et al.*[3] On the basis of spectroscopic studies, chemical transformations, and ultimately X-ray crystallographic examination, showdomycin was shown to be 2-(β-D-ribofuranosyl)maleimide (**1**).[4] Since the compound shows quite significant antibacterial[3] and antitumor[5] activities it has been the subject of numerous biochemical studies that have recently been reviewed.[6]

A synthesis of showdomycin has been briefly reported by Kalvoda, *et al.*,[7] involving, as the key intermediate, the keto ester **2** which was ingeniously prepared *via*



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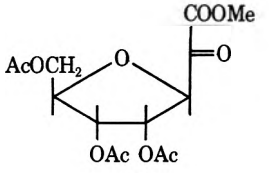


2

ozonolysis of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,4,6-trimethoxybenzene. As yet details and yields of this process have not been disclosed but the conversion of **2** into showdomycin required a six-step sequence.

In the accompanying paper[1] we have described efficient routes for the preparation of derivatives of 2,5-anhydro-D-allose in which the hydroxyl groups are protected as benzoyl or acetyl esters, benzyl ethers, or isopropylidene acetals. In this paper we describe the ready conversion of these compounds into keto esters similar to **2** and a much simplified, two-step conversion of one of these substances into showdomycin.

In conceiving a synthetic route to showdomycin one must bear in mind that, while this compound is very stable under acidic conditions, it is very labile in base,[3,4] owing, at least in part, to a rapid Michael type of addition of the 5′-hydroxyl group to the maleimide double bond.[4a] In view of this alkaline instability of the final product, and the necessity for a fairly vigorous acidic step during our proposed sequence, we decided to use benzyl ethers for protection of our sugar moiety.

The readily available 1,3-diphenyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazolidine (**3**) was therefore treated under reflux with Dowex 50 (H^+) resin in aqueous tetrahydrofuran to hydrolyze the imidazolidine ring and liberate 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**4**) in 95% yield. The latter compound was previously liberated from **3** by treatment with *p*-toluenesulfonic acid monohydrate in a mixture of acetone and methylene chloride at room temperature, but under these conditions minor amounts of unreacted **3** were found in the final product.[1] Using the resin method the free aldehyde **4** was obtained as a chromatographically homogeneous syrup that was used directly in the next step (Scheme I).

In previous work on the synthesis of the nucleoside moiety of the polyoxin group of nucleoside antibiotics[8] and their analogs,[9] we have made extensive use of the cyanohydrin reaction as a means of homologating nucleoside 5′-aldehydes. In this work we have found that such cyanohydrins are frequently somewhat difficult to deal with because of their tendency to revert partially to the original aldehydes. To offset this we have shown that such cyanohydrin reactions can be made totally irreversible by immediate addition of hydrogen peroxide to the reaction mixture, thus giving the corresponding hydroxy amides. The same approach was used in the present work. Thus, the reaction of **4** with sodium cyanide and potassium carbonate was immediately followed by addition of hydrogen peroxide giving a roughly equal mixture of 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonamide (**6**) and its D-glycero-D-altro epimer (**5**) in a combined yield of 93%. By chromatography on a column of silicic acid the epimeric hydroxy amides could be quite readily separated, giving the pure, less polar and more polar isomers in yields of 45 and 39%, respectively. A definitive assignment of stereochemistry to these two isomers by chemical degradation does not appear to be too easy at this time. It is likely that such an assignment could be made on either the hydroxy amides or

(1) For part II, see H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **38**, 1836 (1973).

(2) Syntex Postdoctoral Fellow, 1971–1973.

(3) H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, *J. Antibiot., Ser. A*, **17**, 148 (1964).

(4) (a) Y. Nakagawa, H. Kano, Y. Tsukuda, and H. Koyama, *Tetrahedron Lett.*, 4105 (1967); (b) K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Nat. Acad. Sci.*, **57**, 548 (1967).

(5) S. Matsuura, O. Shiratori, and K. Katagiri, *J. Antibiot., Ser. A*, **17**, 234 (1964).

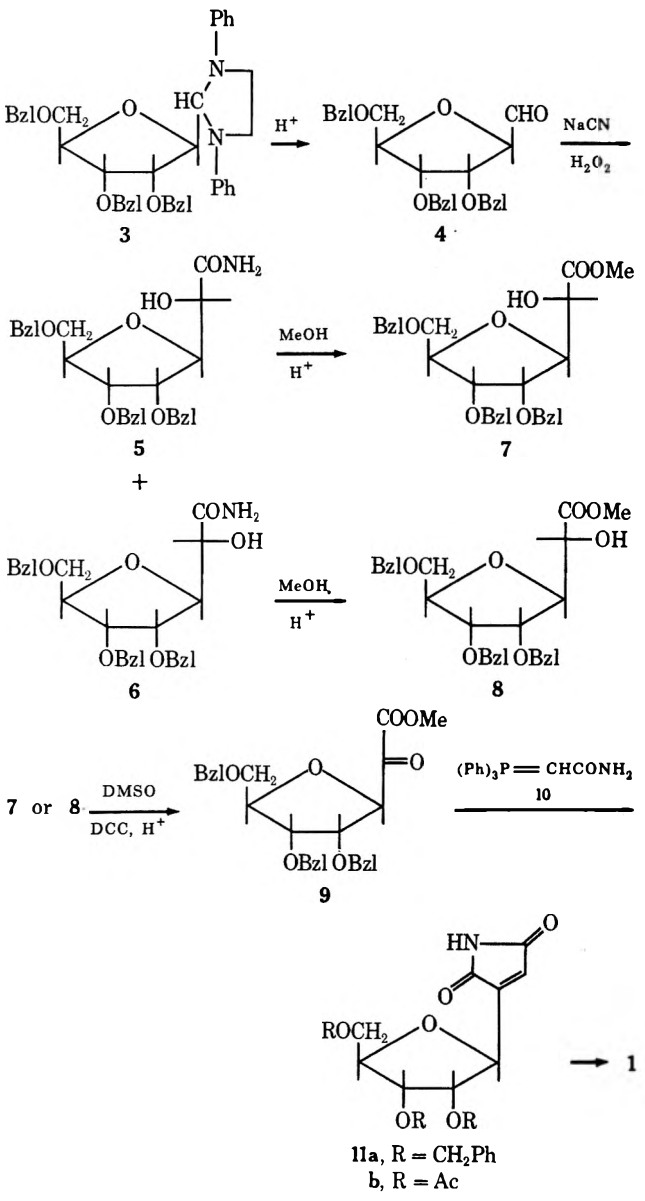
(6) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 393.

(7) L. Kalvoda, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, 2297 (1970).

(8) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971).

(9) M. D. Edge, N. P. Damodaran, G. H. Jones, and J. G. Moffatt, unpublished work.

SCHEME I



the related hydroxy acids by circular dichroism[10] or other optical techniques, but such methods would presumably demand prior removal of the benzyl ether chromophore. Since for our present purpose a distinction between the two isomers is unnecessary, we have chosen to postpone this assignment of configuration until a later date.

Our original plan was to oxidize the hydroxy amides **5** and **6** to the corresponding keto amide and then to treat the latter with carbomethoxytriphenylphosphorane, giving a maleamic acid ester that could be cyclized to the maleimide **11a**. This route was, however, frustrated by the difficulties attending the oxidation of the hydroxy amides. The use of oxidants such as chromic oxide in acetic acid[11] led to complex mixtures, whereas mild methods such as the use of dimethyl sulfoxide and acetic anhydride[12] gave only the acetate ester of the hydroxy amide. The use of the DMSO–DCC oxidation reaction[13] is essentially precluded by the known reaction of amides with these agents.[14]

Because of these difficulties, each hydroxy amide (**5** and **6**) was then individually transformed into the corresponding hydroxy ester by treatment under reflux with anhydrous methanol in the presence of Dowex 50 (H^+) resin. In this way homogeneous methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate (**8**) and its D-glycero-D-altro epimer (**7**) were prepared in yields of 70–75%. While both **7** and **8** were analytically pure syrups, they could be readily differentiated by both tlc and by their nmr spectra. As has been the case in most of the intermediates in this work, the methylene protons of the benzyl ethers are superimposed upon most of the sugar protons and preclude a detailed analysis of this region. The methyl ester protons in **7** and **8** are, however, cleanly separated and permit a quantitative estimation of epimeric purity. It is interesting to note that the less polar hydroxy amide (**5** or **6**) gives rise to the more polar of the hydroxy esters (**7** or **8**). For the reasons cited above, the assignment of relative stereochemistry at C_2 in **7** and **8** must await further work.

Several different methods were examined for the oxidation of **7** and **8** to the keto ester methyl 3,-6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (**9**). By far the best results were obtained using the DMSO–DCC method with dichloroacetic acid as the proton source. By this method both **7** and **8** were converted essentially quantitatively to the keto ester **9** within 30 min at room temperature. Examination of the crude reaction mixture by tlc showed essentially a single carbohydrate containing spot together with some incompletely removed dicyclohexylurea and some *N*-dichloroacetyl-*N*,*N*′-dicyclohexylurea, both known by-products of the oxidation reaction using dichloroacetic acid.[13] The keto ester proved to be extremely labile and attempts to remove the by-products by either column or preparative thin layer chromatography on silicic acid led to partial decomposition. The oxidation step itself, however, appears to be quite clean and, since the urea-type by-products do not apparently interfere with subsequent steps, we routinely prepare **9** immediately prior to use and treat it without further purification.

Our previous work with nucleoside 5′-aldehydes[15] and with 5-ketohexofuranosyluronic acid derivatives as potential precursors to polyoxins[16] has taught us to be cautious of possible epimerization adjacent to the carbonyl group in such compounds. To convince ourselves that no such epimerization at C_3 had taken place during preparation of **9**, we directly reduce the carbonyl group in the normally worked up product using sodium borohydride in dimethoxyethane. The product from this reduction appeared by tlc to contain only the epimeric hydroxy esters **7** and **8** together with the re-

(10) (a) J. C. Craig and W. E. Pereira, *Tetrahedron*, **26**, 3457 (1970); (b) L. I. Katzin and E. Gulyas, *J. Amer. Chem. Soc.*, **92**, 1211 (1970).

(11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 145.

(12) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).

(13) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965). (b) For a review of these methods, see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., 1971, p 1.

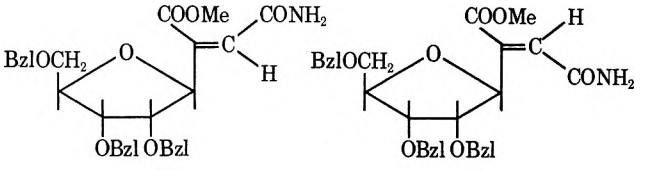
(14) U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3391 (1971).

(15) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, CARB 16.

(16) Unpublished experiments of N. P. Damodaran, G. H. Jones, and J. G. Moffatt.

sidual urea products known to be present in the keto ester. The latter were removed by chromatography on silicic acid giving a tlc-pure mixture of **7** and **8** in an overall yield of 76% through the oxidation and reduction sequence. Examination of this mixture by nmr spectroscopy showed only signals corresponding to a mixture of **7** and **8** with the less polar isomer now predominating in a 3:1 ratio. This combination of tlc and nmr data would appear to allay any fear that epimerization of the labile keto ester **9** had taken place. The attempted selective reduction of **9** using sodium borohydride in methanol was not successful owing apparently to concomitant reduction of the ester grouping. The products of this reduction, or of the reduction of the hydroxy esters **7** and **8**, appeared as a pair of rather polar materials giving a positive test with the periodate–benzidine spray[17] for vicinal diols.

The keto ester **9** reacted very rapidly at room temperature with 1 equiv of carbamoylmethylenetriphenylphosphorane (**10**)[18] in chloroform to give a single major product with a polarity less than **9** together with considerable amounts of polar by-products. Chromatography of the mixture on a column of silicic acid led to the isolation of this crystalline product in an overall yield of 43% from the hydroxy esters **7** and **8**. The nmr and mass spectra of this substance clearly showed the disappearance of the methyl ester group and the presence of a single NH proton which was coupled to a vinyl proton. These results can be explained by spontaneous cyclization of an intermediate cis-oriented maleamic acid ester (**12**) to the corresponding maleimide (**11a**) which is the tribenzyl ether of showdomycin. Alternatively, the cyclization could take place at the level of the betaine precursor of **12** and for the



12 **13**

moment we cannot distinguish between these two possibilities.

Only traces of a more polar product with the mobility expected of the acyclic product (**12**) or its trans oriented isomer (**13**) could be found and no pure materials were isolated from the polar by-products which also contained triphenylphosphine oxide. It is not clear whether these by-products are the result of decomposition of the labile keto ester **9**, to a general nucleophilic instability of the maleimide ring,[19] or to further reactions of **11a** with the phosphorane **10**. Such reactions of imides with even highly stabilized phosphoranes are known[20] and model experiments (see below) have shown that the yields of maleimides from α-keto esters and **10** are markedly reduced if an excess of **10** is used. In addition, it could be shown by tlc that treatment of pure **11a** with **10** in chloroform led to fairly rapid conversion of **11a** into unidentified polar products.

(17) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

(18) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 3874 (1959).

(19) For a review on cyclic imides, see M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, **70**, 439 (1970).

(20) W. Flitsch and B. Müter, *Chem. Ber.*, **104**, 2847, 2852 (1971).

Completion of the synthesis of showdomycin then only required removal of the benzyl ether groups from **11a**. The usual approach *via* catalytic hydrogenolysis was not, however, feasible since the maleimide ring of showdomycin is rapidly reduced in the presence of palladium catalysts.[4] The alternative use of sodium in liquid ammonia is also precluded by the extreme base lability of showdomycin.[3,4b] Two solutions to this problem have been found. Our first approach involved the acetolysis of the benzyl ethers with acetic anhydride in the presence of boron trifluoride etherate at room temperature.[21] Under these conditions a fairly smooth reaction occurred giving what is considered to be 2′,3′,5′-tri-*O*-acetylshowdomycin (**11b**).[4a,7] Without purification, the latter was then subjected to treatment with 0.15 *M* methanolic hydrochloric acid at room temperature for 18 hr to remove the acetyl groups. Even on the very small scale upon which this reaction was conducted, crystalline showdomycin (**1**) was obtained in an overall yield of 33% from **11a**. The second, and more direct, approach was based on the well-established cleavage of carbohydrate methyl[22] and benzyl[23] ethers using boron trihalides. Treatment of **11a** with boron trichloride in methylene chloride at −78° followed by destruction of the excess reagent with methanol led quite smoothly to complete debenzylation. Subsequent chromatographic purification led to beautifully crystalline showdomycin in a yield of 69%. The synthetic product was physically and spectroscopically identical with an authentic sample of showdomycin[24] and also showed a spectrum of antibacterial activity identical with that of the natural product.[25] The above route thus appears to offer a direct and reasonably efficient route for the synthesis of showdomycin.

The spontaneous cyclization of the intermediate **12** (or of its betaine precursor) to the maleimide **11a** suggests that the reaction of carbamoylmethylenephosphoranes with α-keto esters might constitute a generally useful route for the preparation of substituted maleimides.[19] To check this the reaction of methyl pyruvate (**14a**) with **10** was examined under conditions similar to those used for preparing **11a**. The reaction proceeded rapidly at room temperature to give two major crystalline products in addition to triphenylphosphine oxide. The desired cyclized product, citraconimide (**17a**)[26] was only obtained in 9% yield while the major product, isolated in 53% yield, proved to be the acyclic methyl 2-methylfumaramate (**16a**) (Scheme II).[27]

There was no indication of the presence of the maleamate **15a**. The formation in this case of the fumaramate **16a** as the predominant product is clearly a consequence of steric factors. Thus when the substituent R in **14** is a small methyl group, the Wittig reac-

(21) Acetolysis of carbohydrate ethers with sulfuric acid and acetic anhydride has been described by R. Allerton and H. G. Fletcher, *J. Amer. Chem. Soc.*, **76**, 1757 (1954). Recently the very rapid acetolysis of a homoallylic benzyl ether using boron trifluoride has also been described by E. J. Corey and P. Grieco, *Tetrahedron Lett.*, 107 (1972).

(22) See, *e.g.*, T. G. Bonner, E. J. Bourne, and S. McNally, *J. Chem. Soc.*, 2929 (1960).

(23) H. Ohrui, H. Kuzuhara, and S. Emoto, *Tetrahedron Lett.*, 4267 (1971).

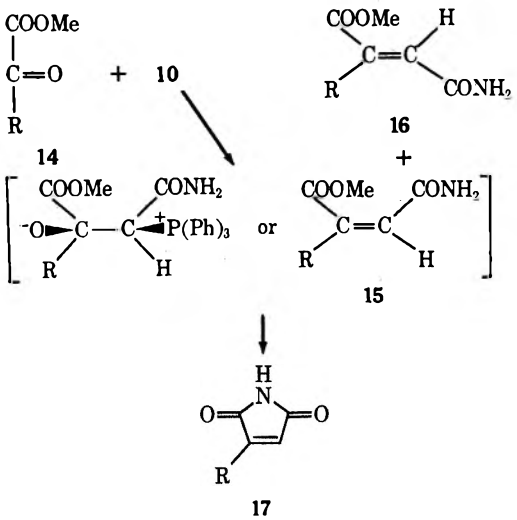
(24) We gratefully acknowledge receipt of a generous sample of showdomycin from Shionogi Research Laboratories, Osaka, Japan.

(25) The biological testing was done through the kind cooperation of Dr. K. Katagiri of Shionogi Research Laboratories.

(26) G. Ciamician and M. Dennstedt, *Gazz. Chim. Ital.*, **12**, 501 (1882).

(27) R. Anschütz, *Justus Liebigs Ann. Chem.*, **353**, 169 (1907).

SCHEME II

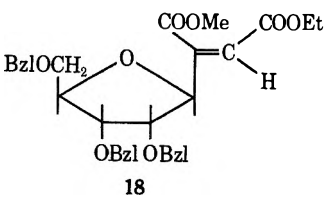


17

a, R = CH_3; b, R = C_6H_5

tion proceeds so as to place the two bulkiest substituents (COOMe and $CONH_2$) in a stable trans relationship.[28] On the other hand, with the keto ester **9** the bulky, benzylated furan ring becomes the major steric influence and becomes oriented trans to the carbamoyl group. The resulting maleamate (**12**) then undergoes spontaneous cyclization to **11a**. Once again, it cannot be ruled out that cyclization occurs at the betaine level preceding actual formation of **12**. An intermediate course was taken in the reaction of **10** with methyl phenylglyoxalate (**14b**). This reaction, which was expectedly somewhat slower than the others and required brief heating in chloroform, led to roughly equal amounts of 2-phenylmaleimide (**17b**, 26%)[29] and the previously undescribed β-carbomethoxy-*cis*-cinnamamide (**16b**, 30%). In this case there is apparently little difference between the phenyl and carbomethoxy groups with regard to the steric control that they provide to the reaction.

The same type of steric control is clearly provided in the reaction of the acetylated keto ester **2** with carboethoxymethylenetriphenylphosphorane since the product of this reaction was shown to be a 10:1 mixture of isomers with the cis diester predominating.[7] The reaction of **9** with carboethoxytriphenylphosphorane also proceeded so as to give essentially a single isomer. By chromatography on silicic acid a homogeneous product, which by analogy with the results of the Czech workers[7] is considered to have the maleate structure **18**, was isolated in 65% yield. This product has not, however, been examined further.



18

From the results above it is clear that the reaction of α-keto esters **14** with carbamoylmethylenetriphenylphosphorane provides a direct route to 2-substituted maleimides providing that the substituent R on **14** is reasonably bulky. The method would appear to offer an interesting route to analogs and homologs of showdomycin and we hope to describe our efforts in these directions at a later date.

(28) For a general discussion of the stereochemistry of the Wittig reaction, see J. Reucroft and P. Sammes, *Quart. Rev.*, **25**, 135 (1971).

(29) C. S. Rondestvedt and O. Vogl, *J. Amer. Chem. Soc.*, **77**, 2313 (1955).

Experimental Section

General Methods.—Thin layer chromatography was carried out using silica gel GF on glass plates obtained from Analtech, Inc., Newark, Del. Preparative tlc was done using 1.3-mm layers of Merck silica gel HF on 20 × 100 cm glass plates and column chromatography using Merck silica gel with 0.05–0.20-mm particles. Nmr spectra were determined using a Varian HA-100 spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. Mass spectra were obtained using an Atlas CH-4 spectrometer fitted with a direct inlet system. Elemental analyses and most physical measurements were obtained by the Analytical Laboratories of Syntex Research. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson and to Dr. L. Tőkés for their cooperation with nmr and mass spectrometry.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-allose (4).—Dried Dowex 50 (H^+) resin (6.5 g) was added to a solution of 1,3-diphenyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazolidine (**3**, 1.25 g, 2.0 mmol)[1] in a mixture of tetrahydrofuran (130 ml) and water (65 ml). The resulting mixture was stirred under reflux for 4 hr, the reaction being monitored by tlc using ether–hexane (2:1). Since some unreacted **3** persisted, the resin was removed by filtration and the filtrate was retreated with fresh Dowex 50 (H^+) resin as above. The mixture was then filtered and the resin was washed with tetrahydrofuran. The combined filtrates were evaporated and dried *in vacuo* leaving 821 mg (95%) of **4** that was chromatographically homogeneous and identical with the material previously described.[1]

3,6-Anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*altro*-heptonamide (6) and Its D-Glycero-D-altro Isomer (5).—A solution of sodium cyanide (1.5 g) and potassium carbonate (1.5 g) in water (20 ml) was added to a cooled (10°) solution of **4** (821 mg, 1.9 mmol) in dioxane (30 ml) and the mixture was then stirred at room temperature for 30 min. The solution was then cooled in ice and stirred while 30% hydrogen peroxide (5.5 ml) was added. After 1 hr the mixture was added to 500 ml of ice–water and the precipitate was collected, washed with cold water, and dried over phosphorus pentoxide giving 840 mg (93%) of a mixture of **5** and **6**. This material was chromatographed on a 4 × 50 cm column of silicic acid using ethyl acetate–chloroform (1:1) to effect a clean separation. The less polar isomer was crystallized from aqueous methanol giving 410 mg (45%) of **5** or **6** with mp 141.5–142°; $[\alpha]^{23}D$ 125.6° (*c* 0.18, $CHCl_3$); ν_{max} (KBr) 1650, 1640 cm^{-1} ($CONH_2$); nmr ($CDCl_3$), δ 3.4–4.8 (m, 13, sugar protons and $ArCH_2O$), 4.15 (br s, 1, C_2OH), 5.64 and 6.62 (br s, 1, $CONH_2$), 7.24 ppm (m, 15, Ar).

Anal. Calcd for $C_{28}H_{31}NO_6$ (477.57): C, 70.42; H, 6.54; N, 2.93. Found: C, 70.43; H, 6.31; N, 2.99.

The more polar isomer (355 mg, 39%) was obtained as a syrup that was homogeneous and free of the other isomer by tlc using $CHCl_3$–EtOAc (1:1) or ether–hexane (2:1) and that crystallized upon storage with mp 79–84° (it was, however, difficult to recrystallize from a solvent); $[\alpha]^{23}D$ 74.7° (*c* 0.11, $CHCl_3$); ν_{max} (KBr) 1660 cm^{-1} ($CONH_2$); nmr ($CDCl_3$) δ 3.51 (dd, 1, $J_{6,7a}$ = 2 Hz, J_{gem} = 10 Hz, C_{7a} H), 3.79 (dd, 1, $J_{6,7b}$ = 2.5 Hz, J_{gem} = 10 Hz, C_{7b} H), 3.9–4.8 (m, 11, C_2–C_6 H and $ArCH_2O$), 4.1 (br s, 1, C_2OH), 5.45 and 6.52 (br s, 1, $CONH_2$), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{28}H_{31}NO_6$ (477.57): C, 70.42; H, 6.54; N, 2.93. Found: C, 70.49; H, 6.64; N, 2.86.

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate (8) and Its D-Glycero-D-altro Isomer (7).—Dried Dowex 50 (H^+) resin (2.5 g)[30] was added to a solution of the less polar hydroxy amide (**5** or **6**, 380 mg, 0.8 mmol) in dry methanol (20 ml) and the mixture was stirred under reflux, the reaction being monitored by tlc using EtOAc–$CHCl_3$ (1:1). After 6 hr a further portion of the resin (2.5 g) was added and after a total of 8 hr the resin was removed by filtration and washed with methanol. Evaporation of the solvent left a syrup that was purified by chromatography on a column of silicic acid using

(30) Freshly regenerated Dowex 50 (H^+) resin was carefully washed with methanol, then with ether, and dried in a vacuum oven at 40° for 24 hr.

ether–hexane (2:1) giving 277 mg (70%) of a homogeneous hydroxy ester (7 or 8) as a syrup: $[\alpha]^{23}D$ 40.9° (*c* 0.11, $CHCl_3$); nmr ($CDCl_3$) δ 3.3–4.7 (m, 13, sugar protons and $ArCH_2O$), 3.66 (s, 3, OMe), 7.27 ppm (s, 15, Ar).

Anal. Calcd for $C_{29}H_{32}O_7$ (492.58): C, 70.72; H, 6.55. Found: C, 70.76; H, 6.52.

The more polar hydroxy amide (290 mg, 0.6 mmol) was treated in the same way as above to give 215 mg (74%) of a hydroxy ester (7 or 8) that was homogeneous by tlc using ether–hexane (2:1) and was less polar than its isomer above: $[\alpha]^{23}D$ 20.3° (*c* 0.13, $CHCl_3$); nmr δ 3.3–4.7 (m, 13, sugar protons and $ArCH_2O$); 3.73 (s, 3, OMe), 7.27 ppm (s, 15, Ar).

Anal. Calcd for $C_{29}H_{32}O_7$ (492.58): C, 70.72; H, 6.55. Found: C, 70.29; H, 6.64.

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (9).—Dichloroacetic acid (0.041 ml, 0.5 mmol) was added to an ice-cooled, stirred solution of 7, 8, or a mixture of these compounds (493 mg, 1 mmol) and dicyclohexylcarbodiimide (515 mg, 2.5 mmol) in a mixture of anhydrous dimethyl sulfoxide (5 ml) and benzene (5 ml). After 30 min at room temperature the mixture was cooled to 0° and a concentrated aqueous solution of oxalic acid (1.5 mmol) was added. The mixture was kept at room temperature for 20 min, diluted with ethyl acetate (50 ml), and filtered. The filtrate was washed five times with water and the organic phase was dried (Linde 4A Molecular Sieve) and evaporated to a syrup. The latter was dissolved in ethanol (5 ml) and a small amount of dicyclohexylurea was removed by filtration. Evaporation of the solution left the keto ester 9 as a syrup that was contaminated by minor amounts of dicyclohexylurea and *N*-dichloroacetyl-*N*,*N'*-dicyclohexylurea. Attempted purification of 9 by chromatography on silicic acid led to partial decomposition and accordingly the material was used directly in the next steps: ν_{max} (film) 1730 (sh), 1750 cm^{-1}, and no hydroxyl band.

Borohydride Reduction of 9.—Sodium borohydride (30 mg) was added to an ice-cooled solution of 9 (prepared from 0.2 mmol of a mixture of 7 and 8) in 1,2-dimethoxyethane (1 ml) and the mixture was stirred at room temperature for 15 min. The mixture was diluted with chloroform (5 ml), washed four times with water, dried, and evaporated leaving a syrup. The latter was chromatographed on a column of silicic acid using ether–hexane (2:1) to remove residual urea by-products and gave 75 mg (76% overall from the hydroxy ester) of a mixture of 7 and 8 with the less polar isomer predominating in a 3:1 ratio. The nmr spectrum of this mixture was identical with that of a mixture of 7 and 8 and showed no evidence of other isomers.

A comparable reduction of 9 (or of a mixture of 7 and 8) using sodium borohydride in methanol led to reduction of the ester grouping and gave two more polar products showing a positive test for vicinal diols with the periodate–benzidine spray.[17]

2-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)maleimide (11a).—A solution of carbamoylmethylenetriphenylphosphorane (10, 320 mg, 1 mmol)[18] and 9 (from 1 mmol of a mixture of 7 and 8) in dry chloroform (15 ml) was stirred at room temperature for 30 min. The solvent was then evaporated and the residue was chromatographed on a 3.5 × 25 cm column of silicic acid using a gradient of 33 to 50% ether in hexane. Crystallization of the major product from ether–hexane gave 215 mg (43% from the hydroxy esters) of 11a with mp 64–65°; $[\alpha]^{23}D$ 96° (*c* 0.55, $CHCl_3$); ν_{max} (KBr) 1775, 1720, 1635 cm^{-1}; nmr ($CDCl_3$) δ 3.51 (dd, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3 Hz, $C_{5'a}$ H), 3.74 (dd, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}$ H), 3.9 (m, 2, $C_{2'}$ H and $C_{3'}$ H), 4.2–4.7 (m, 7, $ArCH_2$ and $C_{4'}$ H), 4.96 (dd, 1, $J_{1',2'}$ = $J_{1',3}$ = 2 Hz, $C_{1'}$ H), 6.54 (dd, 1, $J_{1',3}$ = $J_{3,NH}$ = 2 Hz, C_3 H), 7.25 (m, 15, Ar), 7.7 ppm (br s, 1, NH); ORD (MeOH) multiple Cotton effect $[\Phi]^{pk}_{320}$ 22,000°, $[\Phi]_{238}$ 0°, $[\Phi]^{tr}_{261}$ − 18,500°, $[\Phi]_{295}$ 0°, and $[\Phi]^{pk}_{308}$ 4500°; mass spectrum (70 eV, 150°) *m/e* 499 (M^+), 408 ($M - C_7H_7$).

Anal. Calcd for $C_{30}H_{29}NO_6$ (499.57): C, 72.13; H, 5.85; N, 2.80. Found: C, 72.59; H, 5.89; N, 2.84.

2-(β-D-Ribofuranosyl)maleimide (1) (Showdomycin). A.—A solution of boron trichloride (6.0 g, 50 mmol) in methylene chloride (20 ml) at −78° was added to a solution of 11a (300 mg, 0.6 mmol) in methylene chloride (5 ml) and the mixture was stored at −78° for 30 hr and then at −50° for 2 hr. A mixture of methanol (25 ml) and methylene chloride (25 ml) at −78° was then added and the temperature was allowed to slowly rise to −20°. After storage overnight at −20° the solvents were evaporated *in vacuo* and the residue was coevaporated with methanol four times. The final residue was chromatographed on a 2 × 20 cm column of silicic acid using ethyl acetate–acetone (7:3). The major peak was crystallized from acetone–benzene giving 95 mg (69%) of 1 as colorless needles with mp 154.5–156° (lit. mp 153–154,[3] 152–153,[7] 160–161°[4a]). The melting point was not depressed upon admixture with an authentic sample of showdomycin[24] and the two samples showed identical spectroscopic and antibacterial[25] behavior.

B.—Boron trifluoride etherate (0.05 ml) was added to an ice-cooled solution of 11a (25 mg) in acetic anhydride (0.5 ml). The resulting solution was stirred at 5° for 1 hr and then at room temperature for 18 hr with addition of a further portion of boron trifluoride (0.1 ml) after 6 hr. The mixture was then partitioned between water and chloroform and the organic phase was dried and evaporated to a syrup that contained the tri-*O*-acetate (11b). This was dissolved in methanol (10 ml) and a 3 *N* solution of hydrochloric acid in methanol (0.5 ml) was added. After storage at room temperature for 18 hr the solution was evaporated and the residue chromatographed on a column of silicic acid as described in A. Crystallization of the major peak from acetone–benzene gave 3.8 mg (33%) of 1 identical with that above.

Reaction of Methyl Pyruvate with Carbamoylmethylenetriphenylphosphorane (10).—A solution of 10 (319 mg, 1 mmol)[18] and methyl pyruvate (102 mg, 1 mmol) in dry chloroform (5 ml) was stirred at room temperature for 20 min and then evaporated to dryness. The residue was chromatographed on a 2 × 20 cm column of silicic acid using chloroform–ethyl acetate (1:1) giving three main fractions. Crystallization of the least polar compound gave 10 mg (9%) of citraconimide (15) with mp 109–110° (lit.[26] mp 109–110°); nmr ($CDCl_3$) δ 2.06 (d, 3, *J* = 2 Hz, CH_3), 6.3 (m, 1, CH), 7.7 ppm (br s, 1, NH). The second compound was triphenylphosphine oxide while the most polar fraction contained 75 mg (53%) of methyl 2-methylfumaramate (16a) with mp 118–119° from chloroform–hexane (lit.[27] mp 117°); λ^{MeOH}_{max} 221 nm (ε 10,000); ν_{max} (KBr) 1725, 1705, 1675, 1620 cm^{-1}; nmr ($CDCl_3$) δ 2.26 (d, 3, *J* = 2 Hz, CH_3), 3.79 (s, 3, COOMe), 5.80 (br s, 2, $CONH_2$), 6.80 ppm (m, 1, CH).

Reaction of Methyl Phenylglyoxalate (14b) with 10.—A solution of 10 (319 mg, 1 mmol)[18] and 14b (164 mg, 1 mmol) in dry chloroform (3 ml) was heated under reflux for 30 min and then evaporated to a syrup which was chromatographed on a 3 × 25 cm column of silicic acid. Elution with hexane–ether (2:1) gave a little unreacted 14b, followed by a substance that was crystallized from chloroform–hexane giving 45 mg (26%) of 2-phenylmaleimide with mp 166–168° (lit.[29] mp 167–168°); nmr ($CDCl_3$) δ 6.69 (s, 1, CH), 7.3–8 ppm (m, 5, Ar).

Elution with chloroform–ethyl acetate (1:1) gave triphenylphosphine oxide followed by a substance that was crystallized from chloroform–hexane giving 61 mg (30%) of β-carbomethoxy-*cis*-cinnamamide (16b) with mp 113.5–114.5°; λ^{MeOH}_{max} 278 nm (sh, ε 5200); ν_{max} (KBr) 1712, 1685, 1670, 1610 cm^{-1}; nmr ($CDCl_3$) δ 3.78 (s, 3, OMe), 5.2 and 5.6 (br s, 1, NH), 7.04 (s, 1, CH), 7.2–7.5 ppm (m, 5, Ar).

Anal. Calcd for $C_{11}H_{11}NO_3$ (205.22): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.31; H, 5.63; N, 6.75.

1-Methyl-4-ethyl 2-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)maleate (18).—Carboethoxymethylenetriphenylphosphorane (70 mg, 0.2 mmol) was added to a solution of 9 (from 0.2 mmol of a mixture of 7 and 8) in chloroform (2 ml) and then stirred for 2.5 hr at room temperature. After evaporation of the solvent the residue was purified by chromatography on a 2 × 30 cm column of silicic acid using ether–hexane (1:1) giving 73 mg (65%) of 18 that was homogeneous by tlc: $[\alpha]^{23}D$ 6° (*c* 0.2, $CHCl_3$); $\nu^{CHCl_3}_{max}$ 1700, 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.23 (t, 3, *J* = 7 Hz, CH_2CH_3), 3.46 and 3.61 (dd, J_{gem} = 11 Hz, $J_{4',5'a}$ = $J_{4',5'b}$ = 4 Hz, $C_{5'}$ H_2), 3.69 (s, 3, OCH_3), 3.8–4.3 (m, 2, $C_{3'}$ H and $C_{4'}$ H), 4.04 (dd, 1, $J_{1',2'}$ = $J_{2',3'}$ = 4 Hz, $C_{2'}$ H), 4.14 (q, 2, *J* = 7 Hz, CH_2CH_3), 4.47, 4.50, and 4.55 (s, 2, OCH_2Ph), 4.73 (dd, 1, $J_{1',2'}$ = 4 Hz, $J_{allylic}$ = 2 Hz, $C_{1'}$ H), 6.27 (d, 1, $J_{allylic}$ = 2 Hz, CHCOOEt), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{33}H_{36}O_8$ (560.65): C, 70.70; H, 6.47. Found: C, 70.56; H, 6.41.

Registry No.—**1**, 16755-07-0; **3**, 38821-04-4; **4**, 37699-02-8; **5**, 38821-06-6; **6**, 38821-07-7; **7**, 38821-08-8; **8**, 38821-09-9; **9**, 38821-10-2; **10**, 38821-11-3; **11a**, 38821-12-4; **14b**, 15206-55-0; **16a**, 38821-13-5; **16b**, 38821-14-6; **18**, 38821-15-7; dichloroacetic acid, 79-43-6; methyl pyruvate, 600-22-6; carboethoxymethylenetriphenylphosphorane, 21382-83-2.

New Alkaloids and Related Artifacts from *Cyclea peltata*[1a,b]

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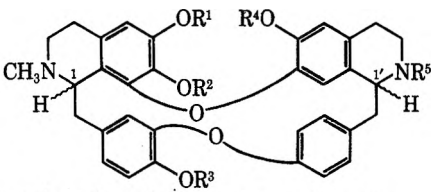
Five new bisbenzylisoquinoline alkaloids, cycleapeltine (**11**), cycleadrine (**5**), cycleacurine (**19**), cycleanorine (**8**), and cycleahomine chloride (**14**), have been isolated from *Cyclea peltata* Diels and their structures determined. Three related artifacts have also been isolated and the structures **16**, **26**, and **31** advanced on the basis of spectroscopic and chemical evidence.

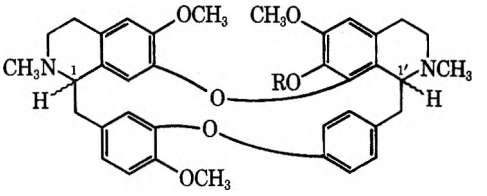
The bisbenzylisoquinoline alkaloid *dl*-tetrandrine was found to have a significant inhibitory activity against the Walker intramuscular carcinosarcoma 256 in rats, over a wide dosage range.[2] Subsequent studies revealed that the dextrorotatory enantiomer, tetrandrine (**1**), was equally active. Tetrandrine has undergone extensive preclinical toxicological studies and has been selected for clinical trial. The promising biological activity prompted the procurement by the National Cancer Institute of a large collection of roots of *Cyclea peltata* Diels,[3-5] for the isolation of kilogram quantities of tetrandrine. In view of the *in vivo* tumor-inhibitory activity of related alkaloids[2,6] as well, it was deemed of interest to examine the mother liquors of the large-scale extraction of tetrandrine as a potentially unique source of new alkaloid tumor inhibitors. We report here the isolation and structural elucidation of cycleapeltine (**11**), cycleadrine (**5**), cycleacurine (**19**), cycleanorine (**8**), and cycleahomine chloride (**14**), five new bisbenzyltetrahydroisoquinoline alkaloids from *Cyclea peltata*. In addition, three related artifacts have been isolated and structures **16**, **26**, and **31** advanced.

The extraction of 6000 lb of *Cyclea peltata* was carried out by a procedure modified only slightly from our initial laboratory work.[3,5] The bulk of tetrandrine (**1**) and the other major alkaloid, fangchinoline (**2**), were retained and the extraction mother liquors containing the water-soluble, methanol-soluble, and glycol-soluble alkaloids were sent to us for investigation.

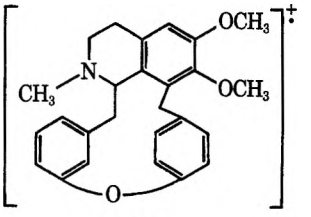
Acid extraction of an aliquot of the methanol-soluble alkaloids gave fraction D, which after column chromatography on alumina and fractional recrystallization eventually yielded large amounts of **1** and much smaller amounts of another crystalline alkaloid, cycleapeltine, $C_{37}H_{40}N_2O_6$ [mp 232–234°; $[\alpha]D$ − 106° ($CHCl_3$)]. The nmr spectrum of cycleapeltine exhibited two *N*-methyl signals at τ 7.47 and 7.53 and three *O*-methyl signals at 6.07, 6.27, and 6.71. Its mass spectrum indicated a fragmentation pattern characteristic of a "head to head" bisbenzyltetrahydroisoquinoline alkaloid with two diphenyl ether link-



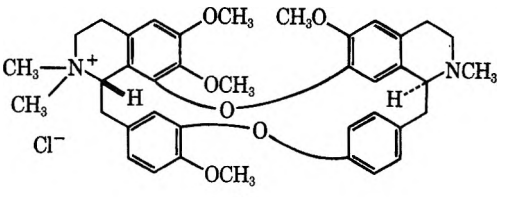
1, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$ (1-*S*, 1′-*S*)
2, $R^1 = R^3 = R^4 = R^5 = CH_3$; $R^2 = H$ (1-*S*, 1′-*S*)
3, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$ (1-*R*, 1′-*S*)
4, $R^1 = R^2 = R^4 = R^5 = CH_3$; $R^3 = H$ (1-*R*, 1′-*S*)
5, $R^1 = R^3 = R^4 = R^5 = CH_3$; $R^2 = H$
6, $R^1 = R^2 = R^3 = R^5 = CH_3$; $R^4 = H$
7, $R^2 = R^3 = R^4 = R^5 = CH_3$; $R^1 = H$
8, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = H$ (1-*S*, 1′-*S*)
9, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COOCH_3$ (1-*S*, 1′-*S*)



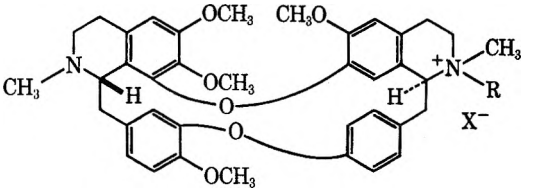
10, R = H (1-*R*, 1′-*R*)
11, R = H (1-*S*, 1′-*S*)
12, R = CH_3 (1-*S*, 1′-*S*)



13



14



15, R = CH_3; X = I
16, R = CH_2Cl; X = Cl

(1) (a) Tumor Inhibitors. LXXIX. Part LXXVIII: S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, **38**, 405 (1973). (b) This investigation was supported by grants from the National Cancer Institute (CA-11718 and CA-12059) and a contract with the Division of Cancer Treatment, National Cancer Institute (NIH 71-2099). (c) National Institutes of Health Postdoctoral Fellow, 1971–1972.

(2) (a) S. M. Kupchan, 7th Pan American Congress of Pharmacy and Biochemistry, Buenos Aires, Argentina, Dec 1966; *Chem. Eng. News*, **44**, 64 (1966). (b) J. L. Hartwell and B. J. Abbott, *Advan. Pharm. Chemother.*, **7**, 117 (1969).

(3) S. M. Kupchan, N. Yokoyama, and B. S. Thyagarajan, *J. Pharm. Sci.*, **50**, 164 (1961).

(4) The *Cyclea peltata* roots (6000 lb) were collected in India in January 1967 by Meer Corp.

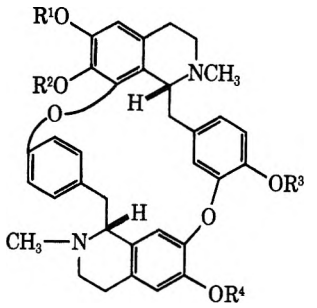
(5) The large-scale extraction and fractionation was carried out by Dr. J. A. Ellard, Monsanto Research Corp., Dayton, Ohio, under a contract with Drug Research and Development, Division of Cancer Treatment, National Cancer Institute. We thank Dr. Harry B. Wood, Jr., NCI, for making the mother liquors available to us.

(6) (a) S. M. Kupchan, T.-H. Yang, G. S. Vasilikiotis, M. H. Barnes, and M. L. King, *J. Org. Chem.*, **34**, 3884 (1969); (b) S. M. Kupchan and A. J. Liepa, *Chem. Commun.*, 599 (1971).

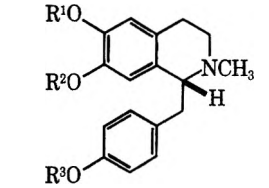
ages.[7] All of these data are in accord with those reported for limacusine (**10**) except that the optical rotation is of the opposite sign,[8] suggesting that cycleapeltine (**11**) is the antipode of **10**. Accordingly, treatment of **11** with methanolic diazomethane yielded a product identical with the known *O*-methylrepandine (**12**).[9]

Acid extraction (with subsequent neutralization to pH 7.0–7.5) of an aliquot of the glycol-soluble alkaloids (fraction A) gave fraction E, which after column chromatography on alumina yielded more **1** and a slightly more polar oil. Thin layer chromatography of this oil on alumina yielded **2** and an optically inactive isomeric alkaloid, cycleadrine, isolated as its bishydriodide salt (mp 223–224°). Treatment of this salt with aqueous ammonia liberated the free base, $C_{37}H_{40}N_2O_6$, mp 160–162°. The nmr spectrum of cycleadrine exhibited two *N*-methyl signals at τ 7.57 and 7.75 and three *O*-methyl signals at 6.12, 6.12, and 6.27. Its mass spectrum indicated a fragmentation pattern characteristic of a "head to head" bisbenzyltetrahydroisoquinoline alkaloid with two diphenyl ether linkages. The base-induced bathochromic uv shift suggested a phenolic functionality. Treatment of the free base with methanolic diazomethane yielded a product identical with isotetrandrine (**3**),[9a,b,10] apart from its optical inactivity. Of the four possible de-*O*-methylisotetrandrine isomers, only berbamine (**4**) is known and the reported data[10] excluded it from further consideration. Distinction between the remaining three isomers, **5**, **6**, and **7**, could be made by examination of the spectra data. The mass spectral rearrangement[7] ion **13** is of value. As the observed ion **13** was at *m/e* 417 (11%), structure **6** could be excluded, since the C:D ring isoquinoline nucleus that was lost during the rearrangement would have had to contain a methoxyl group. The choice between structures **5** and **7** was based on the nmr chemical shift of the high-field methoxyl signal. A methoxyl group at the **7** position usually appears near τ 6.80.[9c] As the highest field methoxyl signal in cycleadrine is only at τ 6.27, cycleadrine could be assigned structure **5** in the form of a mixture of two antipodal diastereomers of **2**.

Basification to pH 12 of the acid extract of fraction A gave fraction F, which after separation on an anionic ion exchange column and subsequent tlc on alumina yielded a third alkaloid, cycleacurine, isolated as its bishydrobromide salt, mp 293–296°. Treatment of this salt with aqueous sodium bicarbonate liberated the amorphous free base, $C_{35}H_{36}N_2O_6$, mp 205–208°, $[\alpha]_D$ − 202° (CH_3OH). The nmr spectrum (DMSO-d_6) of cycleacurine exhibited two *N*-methyl signals at τ 7.52 and 7.82 and a single *O*-methyl signal at 6.25. Its mass spectrum indicated a fragmentation pattern characteristic of a "head to tail" bisbenzyltetrahydroisoquinoline alkaloid with two diphenyl ether linkages.[11] The solubility properties as well as a base-induced bathochromic uv shift suggested the presence of



17, $R^1 = R^2 = R^3 = R^4 = CH_3$
18, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$
19, $R^2 = R^3 = R^4 = H$; $R^1 = CH_3$
20, $R^2 = R^3 = R^4 = CH_2CH_3$; $R^1 = CH_3$



21, $R^1 = CH_2CH_3$; $R^2 = R^3 = H$
22, $R^1 = CH_3$; $R^2 = R^3 = CH_2CH_3$
23, $R^2 = CH_3$; $R^1 = R^3 = H$
24, $R^3 = CH_3$; $R^1 = R^2 = H$

several phenolic functionalities. Treatment of the free base with methanolic diazomethane yielded a product which was shown to be the antipode of the known di-*O*-methyl-*d*-curine, **17**.[12]

To locate the methoxyl position in cycleacurine, it was necessary to identify the phenol groups. For this purpose, tri-*O*-ethylcycleacurine was prepared by treatment of the free base with methanolic diazoethane. The methoxyl chemical shift in this derivative was at τ 6.15, suggesting that it occupied one of the C-6 positions.[9a] Cycleacurine would then have either structure **18** or **19**. The choice of structure **19** was based on the structures of the products of sodium–liquid ammonia cleavage of the triethyl derivative. The course of sodium–liquid ammonia reductive cleavage of curine derivatives is well established.[13] Treatment of tri-*O*-ethylcycleacurine with sodium in liquid ammonia yielded only two major products, as expected. The phenolic product contained an *O*-ethyl group and could therefore be assigned structure **21**. The nonphenolic product was then expected to have structure **22**. That the nonphenolic product was **22** and not **23** or **24** followed from its spectral data. The mass spectral base peak corresponding to loss of the benzyl group was at *m/e* 220, indicating that the isoquinoline nucleus contained the methoxy group and only one ethoxyl group. The methoxyl chemical shift in the nonphenolic product was at τ 6.16, clearly indicative of the C-6 location.[9] The nonphenolic cleavage product could then be assigned structure **22** and cycleacurine structure **19**.

The methanol eluate from ion exchange chromatography of fraction F was passed through a column of ion exchange resin (chloride form) and then chromatographed on a column of neutral alumina.

Cycleanorine (**8**), the least abundant of the compounds studied, was isolated from the later column fractions by preparative tlc and subsequent crystal-

(7) J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. Chem. Soc., Perkin Trans. 1*, 592 (1972).

(8) M. Tomita and H. Furukawa, *Tetrahedron Lett.*, 4293 (1966).

(9) (a) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1896 (1961); (b) M. Tomita, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Lett.*, 857 (1966); (c) I. R. C. Bick, E. S. Ewen, and A. R. Todd, *J. Chem. Soc.*, 695 (1953).

(10) I. R. C. Bick, P. S. Clezy, and W. D. Crow, *Aust. J. Chem.*, **9**, 111 (1956).

(11) J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. Chem. Soc., Perkin Trans. 1*, 599 (1972).

(12) L. J. Haynes, E. J. Herbert, and J. R. Plimmer, *J. Chem. Soc. C*, 615 (1966).

(13) I. R. C. Bick and P. S. Clezy, *J. Chem. Soc.*, 3893 (1953).

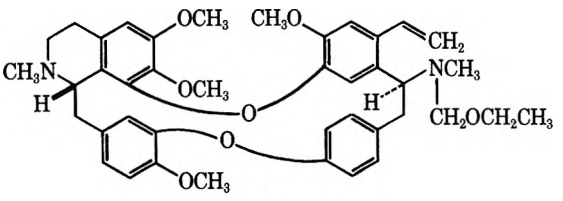
lization, mp 171–172°, $[\alpha]D$ +308° ($CHCl_3$). The molecular formula $C_{37}H_{40}N_2O_6$ was advanced on the basis of elemental analysis and high-resolution mass spectrometry. The nmr spectrum showed signals corresponding to one *N*-methyl (τ 7.67) and four *O*-methyl groups (τ 6.12, 6.30, 6.67, and 6.78). The close similarity of the aromatic region of the spectrum to that of tetrandrine (**1**) suggested that cycleanorine (**8**) might be a *N*-demethyl analog of **1**. This was confirmed by reductive N-methylation of **8** with formaldehyde and sodium borohydride,[14] which afforded **1** in fair yield. The assignment of position of the *N*-methyl group in **8** follows from the presence of an ion at *m/e* 431 in the mass spectrum, which can be attributed to an ion of structure **13**.[7]

The structure of cycleanorine (**8**) was confirmed by synthesis from tetrandrine (**1**), through the intermediacy of the monocarbamate **9** which on alkaline hydrolysis gave **8**.[15]

Cycleahomine chloride (**14**) was also isolated by preparative tlc of the later column fractions and purified by crystallization, mp 190–194°, $[\alpha]D$ +103° ($CHCl_3$). The empirical formula $C_{33}H_{45}N_2O_6Cl$ was advanced on the basis of elemental analysis. The nmr spectrum showed signals corresponding to one free *N*-methyl (τ 7.63), two quaternary *N*-methyl (τ 6.46 and 6.70), and four *O*-methyl (τ 6.06, 6.28, 6.62, and 6.70) groups. The pattern of the ten aromatic proton resonances was again almost superimposable on the spectrum of tetrandrine (**1**), suggesting that cycleahomine was one of the two possible monomethyl quaternary salts of tetrandrine. This was confirmed by conversion of cycleahomine chloride (**14**) to tetrandrine bismethiodide[16] by treatment with an excess of methyl iodide.

Monomethylation of tetrandrine with 1 equiv of methyl iodide did not give cycleahomine iodide but the isomeric compound **15**, which could be distinguished from the natural product on the basis of its nmr spectrum. In accord with the selective monocarbamation of tetrandrine noted above, quaternization of the 6,7-dioxygenated isoquinoline nitrogen of tetrandrine was evidently favored.

The compound **16**, present in large amounts in the earlier column fractions, was purified by preparative tlc on alumina and subsequent crystallization from acetone, mp 213–217°, $[\alpha]D$ + 156° ($CHCl_3$), and the empirical formula $C_{39}H_{44}N_2O_6Cl_2$ assigned on the basis of elemental analysis. In the nmr spectrum signals corresponding to one free *N*-methyl (τ 7.63), one quaternized *N*-methyl (τ 6.70), and four *O*-methyl groups were apparent, together with a multiplet at τ 5.4 (2 H) which could not be immediately assigned. Treatment with potassium *tert*-butoxide and 1-propanethiol in dimethylacetamide at room temperature converted **16** to cycleanorine (**8**) in good yield, indicating that **16** was a derivative of tetrandrine (**1**) quaternized on the nitrogen of the 6,7-dioxygenated isoquinoline moiety. That the quaternizing substituent was in fact a chloromethyl group could be inferred from the empirical formula of **16**. In refluxing ethanolic sodium ethoxide **16** smoothly underwent Hofmann elimination to yield the unstable styrene **25**. The nmr spectrum of **25** showed, in addition to the ABX pattern typical of a styrene grouping [dd (1 H), τ 2.12, J_{trans} = 18, J_{cis} = 11 Hz; d (1 H), τ 4.48, J_{trans} = 18 Hz; d (1 H), τ 4.82, J_{cis} = 11 Hz], an AB quartet at τ 5.66 ($\Delta\nu$ 25 Hz, J = 9 Hz) which can be attributed to the system $-NCH_2O-$ and a triplet (τ 8.73, J = 6 Hz) corresponding to the OCH_2CH_3 system. From the



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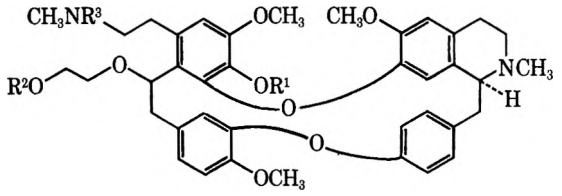
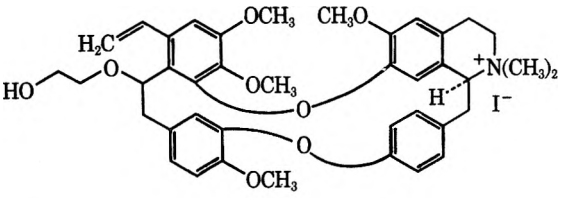


26, $R^1 = R^2 = R^3 = H$
27, $R^1 = R^2 = R^3 = COCH_3$
28, $R^1 = R^2 = H$; $R^3 = CH_3$



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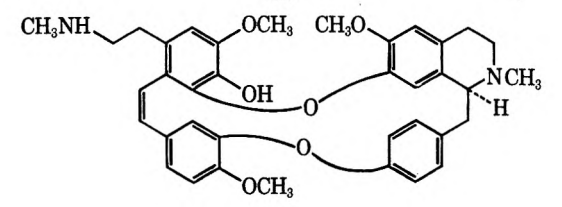

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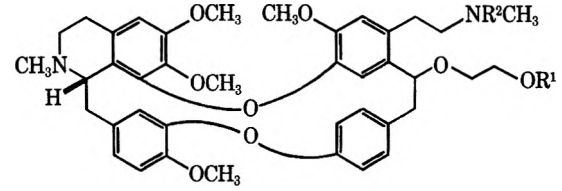
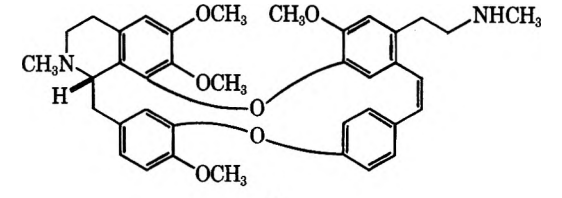


31, $R^1 = R^2 = H$
32, $R^1 = R^2 = COCH_3$
33, $R^1 = H$; $R^2 = CH_3$



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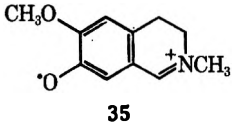

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(14) M. Tomita, K. Fujitani, Y. Masaki, and Y. Okamoto, *Chem. Pharm. Bull.*, **16**, 70 (1968).

(15) M.-M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972).

(16) C.-K. Chuang, C.-Y. Hsing, Y.-S. Kao, and K.-J. Chang, *Chem. Ber.*, **72**, 519 (1939).

nmr and the mass spectrum (M^+ at *m/e* 680), it is apparent that the chlorine of the chloromethyl group is replaced by ethoxide under the conditions used for the elimination.

In view of the fact that tetrandrine (**1**) was the principal component of the alkaloidal extract of *Cyclea peltata* and of the large quantity of dichloromethane used in the extraction, it is perhaps not surprising that significant quantities of **16** were isolated. Methylene halides are known to react with tertiary amines to give quaternary ammonium salts[17] and a number of alkaloids[18] have been shown to give chloromethyl chlorides under conditions similar to those of the extraction procedure used in this instance. Indeed, tetrandrine (**1**) was found to react very slowly with dichloromethane at room temperature to afford **16**.

The compound **26** was purified from the appropriate column fractions by succcessive crystallizations from benzene and ethanol, mp 177–179°, $[\alpha]D$ −237° ($CHCl_3$). The molecular formula $C_{39}H_{46}N_2O_8$ was advanced on the basis of elemental analysis and confirmed by high-resolution mass spectrometry. The uv spectrum showed a maximum at 284 nm (ϵ 12,100) and a bathochromic shift indicative of a phenolic chromophore was observed upon addition of sodium hydroxide. The nmr spectrum showed signals corresponding to two free *N*-methyl groups (τ 7.64 and 7.74), three *O*-methyl [τ 6.14 (6 H) and 6.27 (3 H)] groups, and ten aromatic protons.

On treatment with acetic anhydride in pyridine **26** afforded a noncrystalline triacetyl derivative **27**, the ir spectrum of which showed bands corresponding to a phenolic acetate (5.70 μ), an aliphatic acetate (5.78 μ), and an acetamide (6.12 μ) group. Reductive methylation yielded a single *N*-methyl derivative **28**, indicating the presence of a secondary amino group in **26**. Permethylation of **26** with methyl iodide in methanol containing sodium carbonate yielded the corresponding bismethiodide, which did not exhibit a base shift in the uv, indicating that the free phenolic hydroxyl had been methylated. This compound smoothly underwent Hofmann elimination with methanolic sodium methoxide to yield the product **29**, the nmr of which showed signals corresponding to two quaternary *N*-methyl groups [τ 6.80 (6 H)] and four *O*-methyl groups (τ 6.07, 6.18, 6.50, and 6.65) together with two one-proton doublets at 4.37 (J = 17 Hz) and 4.63 (J = 10 Hz) which could be attributed to a styrene group. The styrene structure of **29** suggested the presence of the system $ArCH_2CH_2NHCH_3$ in **26**. On heating with aqueous hydrochloric acid **26** afforded as the major product the stilbene **30**, high-resolution mass spectrometry of which indicated a molecular formula $C_{37}H_{40}N_2O_6$.

Since **16** had previously been shown to be an artifact formed during the isolation procedure, the facile loss of a $C_2H_6O_2$ unit from **26** on treatment with aqueous acid suggested that **26** might be regarded as having arisen from a monophenolic bisbenzyltetrahydroisoquinoline alkaloid through formal addition of glycol with concomitant opening of an isoquinoline ring. Since fangchinoline (**2**) is the only monophenolic bisbenzyltetrahydroisoquinoline alkaloid which has been isolated from *Cyclea peltata*[3] in significant amounts, it is the most probable precursor for formation of such an artifact. The presence of an ion in the high-resolution mass spectrum of **26** corresponding to the fragment **35** favors the structure **26** rather than that in which the 6,7-dioxygenated tetrahydroisoquinoline ring is opened.

A second artifact **31** isolated from the column fraction preceding that containing **26** was purified as its crystalline bisoxalate, which was decomposed with ammonium hydroxide to give the free base, mp 161–163°, $[\alpha]D$ +174° ($CHCl_3$). The molecular formula $C_{40}H_{48}N_2O_8$ was advanced on the basis of elemental analysis of the bisoxalate and supported by high-resolution mass spectrometry of the free base. The absence of a bathochromic shift in the uv spectrum [λ_{max}^{EtOH} 283 nm (ϵ 6780)] indicated that the compound was nonphenolic. In the nmr spectrum signals corresponding to two *N*-methyl groups (τ 7.36 and 7.42), four *O*-methyl (τ 6.11, 6.32, 6.60, and 6.82) groups, and ten aromatic protons were in evidence. With acetic anhydride in pyridine **31** yielded a noncrystalline diacetyl derivative **32**, which showed bands at 5.78 and 6.12 μ in the ir, corresponding to an aliphatic acetate and an acetamide group. The presence of a secondary amino function was again confirmed by reductive methylation, which gave the *N*-methyl derivative **33**. Treatment of **31** with aqueous acid gave a crystalline product **34**, the high-resolution mass spectrum of which suggested a molecular formula $C_{38}H_{42}N_2O_6$ (*i.e.*, a loss of $C_2H_6O_2$ from **31**). That **31** might be the *O*-methyl derivative of **26** was refuted by the dissimilarity of their respective permethylation products. However, the similarity of the aromatic region of the nmr spectrum of **31** to that of tetrandrine and the absence of an ion (*m/e* 191) in the mass spectrum of **31** corresponding to the fragment **35** suggests that the compound has the structure shown, and may have been formed by formal glycol addition and ring opening of tetrandrine (**1**).

In view of the isolation of significant amounts of the artifact **16** in the extracts, it is conceivable that this is an intermediate in the formation of the glycol adduct **31**, the latter being formed through direct substitution of the quaternary nitrogen. This course is favored over the intermediacy of the corresponding stilbene which might arise by Hofmann elimination *in situ*, since Hofmann elimination has been shown to give the styrene **25**. The formation of **26** from fangchinoline (**2**) might be expected to parallel that of **31** from tetrandrine (**1**).

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Values of $[\alpha]D$ were obtained on a Perkin-Elmer PE141 polarimeter and are approximated to the nearest degree. Ultraviolet spectra were determined on a Coleman EPS-3T recording spectrophotometer and infrared spectra on a Perkin-Elmer PE257 recording spectrophotometer. Nmr spectra were determined on a Varian HA-100 spectrometer in $CDCl_3$ (except where otherwise noted) using tetramethylsilane as the internal standard. Routine mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer and high-resolu- mass spectra on a AEI MS-902 mass spectrometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Commercially prepared tlc plates (E. M.

(17) (a) D. A. Wright and C. A. Wulff, *J. Org. Chem.*, **35**, 4252 (1970); (b) H. Bohme, M. Hilp, L. Koch, and E. Ritter, *Chem. Ber.*, **104**, 2018 (1971).

(18) R. Besselievre, N. Langlois, and P. Potier, *Bull. Soc. Chim. Fr.*, 1477 (1972).

Reagents) were used exclusively. For preparative tlc either aluminum oxide (type T, 1.5 × 200 × 200 mm) or silica gel (F-254, 2 × 200 × 200 mm) plates were used. Analytical tlc was carried out using silica gel (F-254, 0.25 mm) plates eluted with NEt_3–MeOH–$CHCl_3$ (5:10:85). Organic solutions were routinely dried with magnesium sulfate and evaporated to dryness on a rotary evaporator *in vacuo*.

Large-Scale Extraction of *Cyclea peltata*.[5]—The ground roots of *C. peltata* were extracted with isopropyl alcohol, the extract was filtered, and the filtrate was extracted first with heptane–toluene and then 0.5 *N* HCl. The acidic solution was adjusted to pH 8.6 with NH_4OH and extracted with CH_2Cl_2 and the organic layer was evaporated to a residue which was then partitioned between benzene and aqueous glycol (fraction A). On standing, fangchinoline (2) precipitated from the benzene layer and was removed by filtration. The filtrate was evaporated to a residue which was extracted successively with heptane (fraction B) and methanol (fraction C).

Isolation of Cycleapeltine (11).—An aliquot (2 l.) of fraction C was evaporated to a thick syrup, dissolved in $CHCl_3$, and reevaporated. This residue was redissolved in $CHCl_3$ (2 l.) and shaken with 5% aqueous citric acid (2 l.). The aqueous phase was separated, shaken with $CHCl_3$ (2 l.), and allowed to stand for 12 hr. After separation and decantation from a large amount of tar, the aqueous phase was basified with ammonium hydroxide and extracted with $CHCl_3$ (2 × 500 ml). The $CHCl_3$ extract was evaporated to yield fraction D. This was applied to an alumina column (2 kg, Woelm, basic, activity I) and eluted with $CHCl_3$ until the eluent showed only traces of tetrandrine (1). The combined $CHCl_3$ eluents were evaporated to a residue which was dissolved in acetone and boiled, and hexane was added until crystals began to separate. After 24 hr the crystals were filtered and washed briefly with acetone–hexane (1:2). The solid, approximately 20 g, was stirred with EtOAc–$CHCl_3$–MeOH (6:3:1, 200 ml) with a gradual increase in the temperature until the mass of fine needles had dissolved and only a heavy crystalline residue of plates remained. These were filtered, crystallized from EtOAc, and recrystallized from EtOH–$CHCl_3$ to give 1.30 g of cycleapeltine (11): mp 232–234°; $[\alpha]^{25}D$ −106° (*c* 1.0, $CHCl_3$); nmr τ 7.47, 7.53 (2 s, 6 H, $2NCH_3$), 6.07, 6.27, 6.71 (3 s, 9 H, 3 OCH_3); mass spectrum *m/e* (rel intensity) 608 (52), 381 (67), 367 (33), 191.5 (22), 191 (100); uv $\lambda_{max}^{95\%\ EtOH}$ 282 nm (ϵ 5200).

Anal. Calcd for $C_{37}H_{40}N_2O_6$: C, 73.00; H, 6.57; N, 4.61. Found: C, 72.89; H, 6.66; N, 4.63.

Isolation of Cycleadrine (5).—An aliquot (2 l.) of fraction A was extracted with $CHCl_3$ (4 × 500 ml). The combined $CHCl_3$ extracts were washed with 5% aqueous sodium chloride (1.5 l.) and evaporated to a viscous syrup. The syrup obtained in the above manner from 10 l. of fraction A was dissolved in $CHCl_3$ (2 l.) and shaken with 5% aqueous citric acid (2 l.). The aqueous phase was separated, filtered, adjusted to pH 4.0–4.5 by gradual addition of ammonium hydroxide, and extracted with $CHCl_3$ (2 × 1 l.). The aqueous phase was then adjusted to pH 7.0–7.5 by further addition of ammonium hydroxide and again extracted with $CHCl_3$ (2 × 1 l.). This $CHCl_3$ extract was evaporated to yield approximately 8.0 g of a dark brown foamy residue, fraction E.

Thirty grams of fraction E were dissolved in a small amount of $CHCl_3$ and applied to an alumina column (1.4 kg, Woelm, basic, activity I) and eluted with $CHCl_3$ until the eluent showed only traces of tetrandrine (1). The column solvent was then changed to 1% MeOH–$CHCl_3$ and elution continued until only traces of fangchinoline (2) were seen in the eluate. The combined 1% MeOH–$CHCl_3$ fractions were then evaporated to a residue (1.6 g). This residue was separated by preparative tlc on alumina using chloroform as the eluent. The faster moving major component (R_f ~0.5) was recovered and evaporated to a residue. This residue was dissolved in MeOH (5 ml) and hydroiodic acid (0.8 g, 47% aqueous) was added, followed by addition of EtOAc (10 ml). The mixture was warmed gently on a water bath for 10 min and then stirred at ambient temperatures under nitrogen for 24 hr. The solid was filtered, washed briefly with 5% MeOH–EtOAc, and recrystallized from aqueous EtOH to yield 0.8 g of cycleadrine bishydriodide, mp 223–224°, $[\alpha]^{25}D$ 0° (*c* 1.0, H_2O).

Anal. Calcd for $C_{37}H_{40}N_2O_6 \cdot 2HI$: C, 51.40; H, 4.90; N, 3.24; I, 29.36. Found: C, 51.19; H, 5.21; N, 3.19; I, 29.08.

Cycleadrine bishydriodide (0.8 g) was dissolved in ammonium hydroxide (10 ml) and extracted with ether (4 × 10 ml). The combined ether extracts were washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated to a white residue which was recrystallized from acetone–hexane to give 0.5 g of cycleadrine (5): mp 160–162°; $[\alpha]^{25}D$ 0° (*c* 1.0, $CHCl_3$); nmr τ 7.57, 7.75 (2 s, 6 H, 2 NCH_3), 6.12, 6.12, 6.27 (3 s, 9 H, 3 OCH_3); mass spectrum *m/e* (rel intensity) 608 (64), 417 (11), 381 (80), 367 (32), 191.5 (25), 191 (100); uv $\lambda_{max}^{95\%\ EtOH}$ 282 nm (ϵ 6400).

Anal. Calcd for $C_{37}H_{40}N_2O_6$: C, 73.00; H, 6.57; N, 4.61. Found: C, 72.97; H, 6.54; N, 4.58.

Isolation of Cycleacurine (19).—The pH 7.0–7.5 aqueous layer from the cycleadrine (5) isolation was made strongly basic by further addition of ammonium hydroxide and extracted with $CHCl_3$ (2 × 1 l.). The $CHCl_3$ extract was evaporated to yield approximately 80 g of a dark brown residue, fraction F. A portion of fraction F (20 g) was dissolved in MeOH (100 ml) and added to a 250-g ion exchange column (Dowex I-X8; ^-OH form, prepared by stirring the ion exchange resin first in 3% hydrochloric acid and then in 5% aqueous potassium hydroxide and washing with MeOH). The MeOH solution was passed slowly through the column and elution was continued with MeOH until the eluate was colorless. Evaporation of the methanol eluate yielded a residue (17 g), fraction G. Then the column was eluted with 5% HOAc–MeOH until the eluate was colorless. The acid eluate was evaporated to a residue (2.2 g), dissolved in water (20 ml), basified with ammonium hydroxide, and extracted with $CHCl_3$ (2 × 50 ml). The $CHCl_3$ extract was evaporated to a residue, subjected to preparative tlc, and eluted with MeOH–Et_3N–$CHCl_3$ (10:15:75). The major component (R_f ~0.5) was recovered and dissolved in MeOH (5 ml), and hydrobromic acid (1.0 g, 48% aqueous) was added followed by addition of EtOAc (10 ml). The mixture was warmed gently on a water bath for 10 min and then stirred at ambient temperatures under nitrogen for 24 hr. The solid was filtered, washed briefly with 5% MeOH–EtOAc, and recrystallized from aqueous EtOH to yield 0.25 g of cycleacurine bishydrobromide as its monohydrate, mp 293–296°.

Anal. Calcd for $C_{35}H_{36}N_2O_6 \cdot 2HBr \cdot H_2O$: C, 55.28; H, 5.30; N, 3.68. Found: C, 55.57; H, 5.39; N, 3.78.

Cycleacurine bishydrobromide (0.25 g) was added to 10% aqueous sodium bicarbonate (10 ml) and stirred at ambient temperatures for 24 hr. The solid was filtered, washed with water, and recrystallized from acetonitrile to yield 0.18 g of cycleacurine as its bishydrate: mp 205–208°; $[\alpha]^{25}D$ −202° (*c* 1.0, CH_3OH); nmr (DMSO-d_6) τ 7.52, 7.82 (2 s, 6 H, 2 NCH_3), 6.25 (s, 3 H, OCH_3); mass spectrum *m/e* (rel intensity) 580 (52), 298 (100), 297 (54), 283 (29); uv $\lambda_{max}^{95\%\ EtOH}$ 284 nm (ϵ 6750).

Anal. Calcd for $C_{35}H_{36}N_2O_6 \cdot 2H_2O$: C, 68.40; H, 6.57; N, 4.83. Found: C, 68.30; H, 6.50; N, 4.55.

Fractionation of the Basic Alkaloids.—Fraction G (17 g) in MeOH (100 ml) was slowly passed through a column of Dowex I-X8 ion exchange resin (Cl^- form, 250 g), and the eluate was evaporated to a residue and column chromatographed on alumina (Merck neutral grade I, 410 g). Column fractions eluted with $CHCl_3$, 1–3% MeOH–$CHCl_3$, 3% MeOH–$CHCl_3$, 5% MeOH–$CHCl_3$, and 10% MeOH–$CHCl_3$ were combined to give fractions H, J, K, L, and M, respectively.

Isolation of 16.—Fraction H was evaporated to give a brown residue, essentially homogeneous by tlc, purification of which by preparative tlc on alumina, using 5% MeOH–$CHCl_3$ as eluent, afforded a colorless solid (0.7 g) which was crystallized from acetone to yield fine colorless needles: mp 213–217° dec; $[\alpha]^{25}D$ +156° (*c* 0.41, $CHCl_3$); uv λ_{max}^{EtOH} 283 nm (ϵ 7600); ir $\lambda_{max}^{CHCl_3}$ 3.42, 3.54, 6.25, 6.34, 6.66 μ; nmr τ 2.3–4.2 (10 H, ArH), 5.40 (m, 2 H, $-CH_2Cl$), 6.06 (br s, 6 H, 2 OCH_3), 6.25 (2 s, 6 H, 2 OCH_3), 6.70 (s, 3 H, NCH_3), 7.63 (s, 3 H, NCH_3).

Anal. Calcd for $C_{39}H_{44}N_2O_6Cl_2 \cdot 3^1/_2H_2O$: C, 61.00; H, 6.64; N, 3.65; Cl, 9.24. Found: C, 60.99; H, 6.05; N, 3.65; Cl, 8.93.

Isolation of 31.—Fraction K gave a brown residue (2.2 g) on evaporation which proved to be a mixture by tlc. Preparative tlc on alumina using 10% MeOH–$CHCl_3$ as eluent afforded the major component (0.5 g) essentially homogeneous by tlc. Treatment with aqueous oxalic acid and crystallization of the product from aqueous MeOH yielded **31** as its bisoxalate (200 mg), mp 207–209° dec.

Anal. Calcd for $C_{40}H_{48}N_2O_8 \cdot 2H_2C_2O_4 \cdot 2H_2O$: C, 58.66; H, 6.22; N, 3.11. Found: C, 58.68; H, 6.27; N, 3.12.

Treatment of the oxalate (100 mg) with ammonium hydroxide solution, extraction with $CHCl_3$, and evaporation of the organic extract gave the free base **31** (74 mg), which was crystallized from

methyl ethyl ketone as colorless needles: mp 161–163°; $[\alpha]^{25}D$ +174° (*c* 1.00, $CHCl_3$); uv λ_{max}^{EtOH} 283 nm (ϵ 6780); ir $\lambda_{max}^{CHCl_3}$ 3.41, 6.26, 6.33, 6.67, 8.90 μ; nmr τ 2.6–3.9 (8 H, ArH), 4.28 (s, 1 H, ArH), 4.95 (d, 1 H, *J* = 9 Hz, ArH), 6.11, 6.32, 6.60, 6.82 (4 s, 12 H, 4 OCH_3), 7.36, 7.42 (2 s, 6 H, 2 NCH_3); mass spectrum *m/e* (rel intensity) 684 (100), 622 (30), 198 (25). Mass calcd for $C_{40}H_{48}N_2O_8$, 684.3408; found, 684.3349.

Isolation of 26.—Fraction L was evaporated to dryness to give a brown residue (1.5 g) which was redissolved in benzene (100 ml) and on standing afforded **26** as pale yellow needles (150 mg), mp 151–153°.

Anal. Calcd for $C_{39}H_{46}N_2O_8 \cdot 2C_6H_6$: C, 74.00; H, 7.03; N, 3.39. Found: C, 74.33; H, 7.24; N, 3.40.

Recrystallization from EtOH gave **26** as colorless needles free of solvent: mp 176–178°; $[\alpha]^{25}D$ −237° (*c* 1.00, $CHCl_3$); uv λ_{max}^{EtOH} 284 nm (ϵ 12,100), shifted to 305 nm on addition of NaOH; ir λ_{max}^{KBr} 2.94, 3.10, 3.43, 6.25, 6.36, 6.70 μ; nmr τ 2.7–4.0 (10 H, ArH), 6.14 (s, 6 H, 2 OCH_3), 6.27 (s, 3 H, OCH_3), 7.64, 7.74 (2 s, 6 H, 2 NCH_3); mass spectrum *m/e* (rel intensity) 670 (88), 608 (65), 381 (70), 191.5 (25), 191 (100). Mass calcd for $C_{39}H_{46}N_2O_8$, 670.3251; found, 670.3249. Mass calcd for $C_{11}H_{13}NO_2$, 191.0945; found, 191.091.

Anal. Calcd for $C_{39}H_{46}N_2O_8$: C, 69.83; H, 6.91; N, 4.18. Found: C, 69.90; H, 6.90; N, 4.11.

Isolation of Cycleanorine (8).—On evaporation fraction M yielded a brown gum (2.0 g), which was shown by tlc to be a complex mixture. Preparative tlc on silica gel using NEt_3–MeOH–$CHCl_3$ (5:10:85) as eluent gave two major bands. The upper band was rechromatographed on alumina using 5% MeOH–$CHCl_3$ as eluent to give a tlc-homogeneous oil (10 mg) which yielded cycleahomine chloride (**14**, 5 mg) on crystallization from MeOH. The lower band was also purified by preparative tlc on alumina, using 10% MeOH–$CHCl_3$ as eluent, to give a colorless residue (20 mg) which afforded cycleanorine (**8**, 10 mg) as colorless needles from aqueous ethanol: mp 170–172°; $[\alpha]^{25}D$ +308° (*c* 0.52, $CHCl_3$); uv λ_{max}^{EtOH} 282 nm (ϵ 10,200); ir $\lambda_{max}^{CHCl_3}$ 3.42, 6.25, 6.33, 6.77 μ; nmr τ 2.6–3.1 (10 H, ArH), 6.12, 6.30, 6.67, 6.78 (4 s, 12 H, 4 OCH_3), 7.67 (s, 3 H, NCH_3); mass spectrum *m/e* (rel intensity) 608 (55), 431 (18), 381 (80), 191 (100).

Anal. Calcd for $C_{37}H_{40}N_2O_6$: C, 73.00; H, 6.62; N, 4.60. Found: C, 72.89; H, 6.64; N, 4.61.

Isolation of Cycleahomine Chloride (14).—The benzene mother liquors from the crystallization of **26** above were chromatographed on preparative alumina tlc plates using 5% MeOH–$CHCl_3$ to afford two major bands. Extraction of the higher R_f band gave **26** (100 mg). Extraction of the lower R_f band gave a yellow gum (35 mg) which gave cycleahomine chloride (**14**) as colorless prisms (12 mg) on crystallization from CH_2Cl_2–EtOAc: mp 190–194°; $[\alpha]^{25}D$ +103° (*c* 0.15, $CHCl_3$); λ_{max}^{EtOH} 284 nm (ϵ 12,000); ir $\lambda_{max}^{CHCl_3}$ 3.34, 3.41, 6.24, 6.32, 6.65 μ; nmr τ 2.6–4.0 (10 H, ArH), 5.5 (m, 1 H, $ArCHN^+$), 6.06, 6.28, 6.62 (3 s, 9 H, 3 OCH_3), 6.70 (br s, 6 H, OCH_3, $^+NCH_3$), 6.46 (br s, 3 H, $^+NCH_3$), 7.63 (s, 3 H, NCH_3).

Anal. Calcd for $C_{39}H_{45}N_2O_6Cl$: C, 69.60; H, 6.75; N, 4.20. Found: C, 69.18; H, 6.80; N, 4.31.

O-Methylation of Cycleapeltine (11) to *O*-Methylrepandine (12).—A solution of **11** (50 mg) in CH_3OH (5 ml) was treated with an excess of ethereal diazomethane at 0–5° for 4 days. Evaporation of the solution and preparative tlc of the residue on alumina with $CHCl_3$ as the eluent yielded **12** (46 mg),[9] crystallized from acetone–hexane: mp 208–210°; $[\alpha]^{25}D$ −71° (*c* 0.48, $CHCl_3$); nmr τ 7.43, 7.47 (2 s, 6 H, 2 NCH_3), 6.05, 6.28, 6.58, 6.97 (4 s, 12 H, 4 OCH_3); mass spectrum *m/e* (rel intensity) 622 (52), 431 (5), 395 (55), 381 (25), 198.5 (25), 198 (100), 175 (34), 174 (20).

O-Methylation of Cycleadrine (5) to Isotetrandrine (3).—Treatment of **5** (40 mg) in the above manner yielded **3** (40 mg): mp 180–182°; $[\alpha]^{25}D$ 0° (*c* 1.0, $CHCl_3$); nmr τ 7.41, 7.71 (2 s, 6 H, 2 NCH_3), 6.08, 6.24, 6.38, 6.88 (4 s, 12 H, 4 OCH_3); mass spectrum *m/e* (rel intensity) 622 (56), 431 (6), 395 (58), 381 (26), 198.5 (28), 198 (100), 175 (40), 174 (29); identical (melting point, nmr, mass spectrum) with an authentic sample.[9a,b]

O-Methylation of Cycleacurine (19) to Di-*O*-methyl-*l*-curine (17).—Treatment of **19** (30 mg) in the above manner yielded **17** (18 mg): mp 117–119°; $[\alpha]^{25}D$ −265° (*c* 1.0, $CHCl_3$); nmr τ 7.46, 7.67 (2s , 6 H, 2 NCH_3), 6.12, 6.14, 6.28, 6.31 (4 s, 12 H, 4 OCH_3); mass spectrum *m/e* (rel intensity) 622 (48), 312 (100); identical in melting point, nmr, and mass spectrum with authentic di-*O*-methyl-*d*-curine,[9a,12] but with opposite $[\alpha]D$.

O-Ethylation of Cycleacurine (19) to Tri-*O*-ethylcycleacurine (20).—Treatment of **19** (270 mg) in the above manner but with diazoethane yielded **20** (210 mg) which was subjected to degradative studies without further purification: nmr τ 7.35, 7.58 (2 s, 6 H, 2 NCH_3), 6.16 (s, 3 H, OCH_3), 8.46, 8.65, 8.69 (3 t, 9 H, *J* = 7 Hz, 3 OCH_3CH_3); mass spectrum *m/e* (rel intensity) 664 (100), 340 (76), 326 (87). Mass calcd for $C_{41}H_{48}N_2O_6$, 664.351; found, 664.356.

Sodium–Liquid Ammonia Cleavage of Tri-*O*-ethylcycleacurine (20).—Tri-*O*-ethylcycleacurine (100 mg) was dissolved in benzene–toluene (2:1, 12 ml). Liquid ammonia (80 ml) was added, followed by sodium metal (0.3 g). The mixture was stirred for 1 hr and then allowed to warm up to ambient temperature overnight. The residue was dissolved in water (10 ml) and extracted with ether (6 × 10 ml). The combined ether layers were dried (Na_2SO_4), evaporated to a residue, applied to two 200 × 200 × 1.5 mm alumina plates, and eluted with $CHCl_3$. Aside from a small residue, only two components were apparent: the nonpolar (nonphenolic) product and the polar (phenolic) product. These were recovered.

The nonphenolic product **22** resisted crystallization and was characterized as a pale yellow oil: nmr τ 3.11 (AB quartet, $\Delta\nu$ 23 Hz, 4 H, *J* = 8 Hz, para-disubstituted benzene), 3.45, 3.94 (2 s, 2 H, 1,2,4,5-tetrasubstituted benzene), 5.99, 6.20, (2 q, 4 H, *J* = 6.5 Hz, 2 OCH_2CH_3), 6.16 (s, 3 H, OCH_3), 7.44 (s, 3 H, NCH_3), 8.54, 8.60 (2 t, 6 H, *J* = 6.5 Hz, 2 OCH_2CH_3); mass spectrum *m/e* (rel intensity) 355 (<0.1), 220 (100), all other peaks less than 5; mass spectrum (chemical ionization, Ar/H_2O) *m/e* (rel intensity) 356 (56), 221 (100). Mass calcd for $C_{22}H_{29}NO_3 + H^+$, 356.225; found, 356.223.

The phenolic product, **21**, also failed to crystallize and was similarly characterized as a pale yellow oil: nmr τ 3.27 (AB quartet, $\Delta\nu$ 29 Hz, 4 H, *J* = 8 Hz, para-disubstituted benzene), 3.47, 3.57 (2 s, 2 H, 1,2,4,5-tetrasubstituted benzene), 4.79 (br s, 2 H, ArOH), 5.93 (q, 2 H, *J* = 6.5 Hz, OCH_2CH_3), 7.51 (s, 3 H, NCH_3), 8.52 (t, 3 H, *J* = 6.5 Hz, OCH_2CH_3); mass spectrum *m/e* (rel intensity) 313 (<0.1), 206 (100), all other peaks less than 5; mass spectrum (chemical ionization, Ar/H_2O) *m/e* (rel intensity) 314 (62), 207 (100). Mass calcd for $C_{19}H_{23}NO_3 + H^+$, 314.175; found, 314.176.

N-Methylation of Cycleanorine (8).—To a cooled solution of cycleanorine (20 mg) in MeOH (0.5 ml), aqueous formaldehyde (37%, 0.2 ml) was added and the solution was stirred at 5° for 0.5 hr. Sodium borohydride (50 mg) was added cautiously over a further 0.5 hr, the solution was allowed to come to room temperature, and water (2 ml) was added. Extraction of the solution with $CHCl_3$ (10 ml) and evaporation of the solvent gave a crystalline residue which was subjected to preparative tlc on alumina using $CHCl_3$ as eluent. Extraction of the major band followed by crystallization from acetone–hexane afforded tetrandrine (**1**, 10 mg) as colorless needles, identical (tlc, mixture melting point, ir) with an authentic sample.

Demethylation of Tetrandrine (1).—To a solution of tetrandrine (3 g) in dry dimethoxyethane (125 ml) an excess of methyl chloroformate (6 ml) was added and the mixture was left at room temperature for 12 hr. The solution was neutralized by addition of NH_4OH and evaporated to dryness and the residue was subjected to preparative tlc on silica gel using 8% MeOH–$CHCl_3$ as eluent. Extraction of the major band gave the crude monocarbamate **9**, which was crystallized from CH_2Cl_2–EtOH as colorless needles (0.81 g), mp 219–220°.

Anal. Calcd for $C_{39}H_{42}N_2O_8$: C, 70.25; H, 6.35; N, 4.20. Found: C, 70.06; H, 6.49; N, 4.22.

The carbamate **9** (0.5 g) was dissolved in a solution of KOH in glycol (10%, 10 ml) and heated at 185° for 1 hr. The cooled solution was made acidic with aqueous HCl, basified after 5 min with NH_4OH, and extracted with $CHCl_3$ (2 × 10 ml). Evaporation of the organic extract followed by preparative tlc of the residue on alumina with 2% MeOH–$CHCl_3$ as eluent and subsequent crystallization from EtOH afforded cycleanorine (**8**) as colorless needles (250 mg), mp 170–172°, identical (tlc, mixture melting point, ir) with an authentic sample.

Tetrandrine Bismethiodide.—Cycleahomine chloride (5 mg) in MeOH (0.2 ml) was treated with methyl iodide (0.1 ml) at room temperature for 15 hr. Evaporation of the solvent and crystallization of the residue from MeOH afforded tetrandrine bismethiodide, mp 264–268° (lit.[16] mp 265–269°), identical (tlc, mixture melting point, ir, $[\alpha]D$) with an authentic sample.

Tetrandrine Monomethiodide (15).—Tetrandrine (50 mg) in MeOH (2 ml) was treated with methyl iodide (5 μl) and the solu-

tion was allowed to stand at room temperature for 12 hr. Evaporation of the solvent, preparative tlc of the residue on alumina with 5% MeOH–$CHCl_3$ as eluent, and subsequent crystallization from wet CH_2Cl_2–EtOAc afforded the monomethiodide **15** as colorless needles (10 mg): mp 208–211° dec; $[\alpha]^{25}D$ +163° (*c* 0.50, $CHCl_3$); uv λ_{max}^{EtOH} 281 nm (ε 12,500); ir $\lambda_{max}^{CHCl_3}$ 3.42, 6.26, 6.34, 6.68 μ; nmr τ 2.1–4.8 (10 H, ArH), 6.09 (br s, 6 H, $^+NCH_3$, OCH_3), 6.26, 6.59, 6.74 (3 s, 9 H, 3 OCH_3), 6.52 (br s, 3 H, $^+NCH_3$), 7.66 (s, 3 H, NCH_3).

Anal. Calcd for $C_{39}H_{45}N_2O_6I\cdot H_2O$: C, 59.85; H, 6.05; N, 3.58. Found: C, 60.08; H, 6.05; N, 3.59.

Dealkylation of 16.—To a solution of KO-*t*-Bu (1.1 g) and 1-propanethiol (1.1 g) in dimethyl acetamide (15 ml) was added **16** (0.5 g) and the mixture was stirred at room temperature for 18 hr. The mixture was poured into 2% aqueous HCl (25 ml), the solution was washed with ether (2 × 25 ml), and the washings were discarded. After heating at 80° for 5 min the solution was neutralized with NH_4OH and extracted with ether (2 × 25 ml) and the ether extract was evaporated to give a yellow oil (420 mg) which was subjected to preparative tlc on silica gel eluted with 15% MeOH–$CHCl_3$. The major band (R_f 0.1–0.2) afforded cycleanorine (**8**, 248 mg) as colorless needles from aqueous EtOH: mp 170–172°; $[\alpha]^{25}D$ +311° (*c* 0.52, $CHCl_3$); identical (tlc, mixture melting point, ir, nmr) with an authentic sample.

Hofmann Degradation of 16.—A solution of **16** (100 mg) in 4% ethanolic NaOEt (10 ml) (prepared *in situ* by dissolving 100 mg of Na in 10 ml of EtOH) was heated at reflux for 1 hr, water (10 ml) was added, and the solution was extracted with $CHCl_3$ (2 × 20 ml). Evaporation of the solvent afforded a colorless glass (70 mg), homogeneous by tlc, which quickly decomposed on standing: nmr τ 2.12 (dd, 1 H, J_1 = 18, J_2 = 11 Hz, ArCH=), 2.6–3.8 (10 H, ArH), 4.48 (d, 1 H, *J* = 18 Hz, $=CH_2-$), 4.82 (d, 1 H, *J* = 11 Hz, $=CH_2-$), 5.54 (d, 1 H, *J* = 9 Hz, NCH_2O), 5.79 (d, 1 H, *J* = 9 Hz, NCH_2O), 6.09, 6.24, 6.58, 6.68 (4 s, 12 H, 4 OCH_3), 7.38, 7.70 (2 s, 6 H, 2 NCH_3), 8.73 (t, 3 H, *J* = 6 Hz, $-CH_2CH_3$); mass spectrum *m/e* (rel intensity) 680 (3), 634 (100), 619 (60), 497 (58).

Preparation of 16.—Tetrandrine (1 g) in CH_2Cl_2 (100 ml) was allowed to stand for 6 days, the solvent was evaporated, and the residue was subjected to preparative tlc on alumina, using 10% MeOH–$CHCl_3$ as eluent, to afford two bands. The higher R_f band gave starting material (0.71 g) and the lower afforded **16** which was crystallized as colorless needles (12 mg) from EtOAc–isopropyl alcohol and was found to be identical (tlc, mixture melting point, ir) with **16** isolated above.

Acetylation of 26.—To **26** (20 mg) in pyridine (0.5 ml) was added acetic anhydride (0.2 ml) and the solution was allowed to stand at room temperature for 15 hr. Water (1 ml) was added and the mixture was extracted with $CHCl_3$ (2 × 5 ml). Evaporation of the organic extract afforded the triacetate **27** as a colorless glass (16 mg): ir λ_{max}^{KBr} 3.43, 5.70, 5.78, 6.12, 6.23, 6.35, 8.17 μ; nmr τ 2.5–4.0 (10 H, ArH), 6.11 (s, 3 H, OCH_3), 6.30 (s, 6 H, 2 OCH_3), 6.94 (s, 3 H, NCH_3Ac), 7.68 (s, 3 H, NCH_3), 7.89 (s, 3 H, OCH_3), 7.94 (s, 6 H, 2 $COCH_3$); mass spectrum *m/e* (rel intensity) 796 (30), 423 (25), 121 (100).

N-Methylation of 26.—This was carried out using the procedure described in the methylation of cycleanorine (**8**) above, to afford **28** as colorless needles from aqueous EtOH: mp 199–201°; $[\alpha]^{25}D$ −207° (*c* 1.00, $CHCl_3$); ir λ_{max}^{KBr} 2.95 (br), 3.43, 6.25, 6.34, 6.67 μ; nmr τ 2.5–2.9 (10 H, ArH), 6.10 (s, 6 H, 2 OCH_3), 6.23 (s, 3 H, OCH_3), 7.66 (br s, 9 H, 3 NCH_3); mass spectrum *m/e* (rel intensity) 684 (100), 622 (30).

Anal. Calcd for $C_{40}H_{48}N_2O_8$: C, 70.09; H, 7.18; N, 3.96. Found: C, 70.15; H, 7.07; N, 4.08.

Permethylation of 26.—To a solution of **26** (140 mg) in refluxing MeOH (10 ml) were added anhydrous K_2CO_3 (100 mg) and methyl iodide (0.5 ml) and the solution was allowed to cool to room temperature. A further 0.5 ml of methyl iodide was added and the solution was allowed to stand for 18 hr. Evaporation of the solvent and trituration of the residue with water afforded the crude methiodide (160 mg) which was crystallized from MeOH as colorless prisms (142 mg): mp 260° dec; uv λ_{max}^{EtOH} 280 nm (ε 14,700); ir λ_{max}^{KBr} 3.45, 6.26, 6.35, 6.70 μ; nmr (DMSO-d_6) τ 2.9–4.3 (10 H, ArH), 6.24, 6.32, 6.62, 6.76 (4 s, 12 H, 4 OCH_3), 6.74 (s, 15 H, 5 $^+NCH_3$).

Anal. Calcd for $C_{44}H_{58}N_2O_8I_2\cdot 2H_2O$: C, 51.00; H, 6.01; N, 2.71. Found: C, 50.63; H, 5.88; N, 2.74.

Hofmann Degradation of Permethylated 26.—The procedure used was essentially that employed in the degradation of **16** above. Permethylated **26** (112 mg) afforded upon reflux with 2.5% methanolic NaOMe for 18 hr a mixture of products (66 mg) from which the styrene **29** was crystallized from MeOH as colorless prisms (46 mg): mp 202–204°; uv λ_{max}^{EtOH} 263 nm (ε 16,200) and 292 (8310); ir λ_{max}^{KBr} 3.44, 6.22, 6.33, 6.68 μ; nmr ($CDCl_3$–CD_3CO_2D) τ 2.5–3.4 (12 H, ArH, $ArCHCH_2$), 4.37 (d, 1 H, *J* = 17 Hz, $ArCHCH_2$), 4.63 (d, 1 H, *J* = 10 Hz, $ArCHCH_2$), 6.07, 6.18, 6.50, 6.65 (4 s, 12 H, 4 OCH_3), 6.80 [br s, 6 H, $^+N(CH_3)_2$].

Anal. Calcd for $C_{40}H_{46}NO_8I\cdot H_2O$: C, 59.15; H, 5.92; N, 1.72. Found: C, 59.36; H, 5.97; N, 1.87.

Acid Degradation of 26.—A solution of **26** (104 mg) in 10% aqueous HCl (2 ml) was heated at steam bath temperature for 3 hr, and the cooled solution was made alkaline with NH_4OH and extracted with $CHCl_3$ (2 × 5 ml). Evaporation of the organic solvent and preparative tlc of the residue on alumina using 20% MeOH–$CHCl_3$ as eluent gave the stilbene **30** (35 mg), which was crystallized from MeOH as colorless prisms: mp 167–171°; uv λ_{max}^{EtOH} 281 nm (ε 2800); ir λ_{max}^{KBr} 3.43, 6.26, 8.95, 11.80 μ; nmr τ 2.5–3.9 (12 H, 10 ArH, 2 =CH–), 6.06, 6.20, 7.12 (3 s, 9 H, 3 OCH_3), 7.48, 7.70 (2 s, 6 H, 2 NCH_3); mass spectrum *m/e* (rel intensity) 608 (100), 191 (35). Mass calcd for $C_{37}H_{40}N_2O_6$, 608.289; found, 608.288.

Anal. Calcd for $C_{37}H_{40}N_2O_6\cdot {}^1/_2MeOH$: C, 72.10; H, 6.74; N, 4.49. Found: C, 71.74; H, 7.06; N, 4.70.

Acetylation of 31.—This was carried out in an identical manner with that of **26** above, and **31** (20 mg) yielded the diacetate **32** (12 mg) as a colorless glass: ir λ_{max}^{KBr} 3.60, 5.80, 6.05, 8.95 μ; nmr τ 2.6–4.0 (8 H, ArH), 4.9 (m, 2 H, ArH), 6.11, 6.34, 6.55, 6.76 (4 s, 12 H, 4 OCH_3), 7.78, 7.88 (2 s, 6 H, 2 NCH_3), 8.06, 8.08 (2 s, 6 H, 2 $COCH_3$); mass spectrum *m/e* (rel intensity) 768 (100).

N-Methylation of 31.—This was carried out using the procedure described in the methylation of cycleanorine (**8**) above. Thus the bisoxalate of **31** (400 mg) yielded **33** (291 mg) as colorless needles from EtOH: mp 170–171°; $[\alpha]^{25}D$ +180° (*c* 1.00, $CHCl_3$); uv λ_{max}^{EtOH} 282 nm (ε 8000); ir λ_{max}^{KBr} 3.42, 6.33, 7.87, 8.91 μ; nmr τ 2.6–3.8 (8 H, ArH), 4.14 (s, 1 H, ArH), 4.86 (d, 1 H, *J* = 8.5 Hz, ArH), 6.05, 6.19, 6.55, 6.72 (4 s, 12 H, 4 OCH_3), 7.30 (s, 3 H, NCH_3), 7.60 [s, 6 H, $N(CH_3)_2$]; mass spectrum *m/e* (rel intensity) 698 (100), 636 (48).

Anal. Calcd for $C_{41}H_{50}N_2O_8$: C, 70.46; H, 7.21; N, 4.01. Found: C, 70.22; H, 7.19; N, 4.06.

Permethylation of 31.—This was carried out in a similar manner to the permethylation of **26** above. Compound **31** (50 mg) afforded the corresponding bismethiodide (40 mg), which crystallized from MeOH as colorless prisms: mp 225–227° dec; uv λ_{max}^{EtOH} 281 nm (ε 2460); ir λ_{max}^{KBr} 3.43, 6.27, 6.34, 8.98 μ; nmr (DMSO-d_6) τ 1.80 (s, 1 H, ArH), 2.33 (m, 1 H, ArH), 5.80 (m, 1 H, ArH), 3.0–3.7 (5 H, ArH), 4.12 (m, 1 H, ArH), 5.10 (m, 1 H, ArH), 6.12, 6.16, 6.48, 6.65 (4 s, 12 H, 4 OCH_3), 6.60 (s, 15 H, 5 NCH_3^+).

Anal. Calcd for $C_{44}H_{58}N_2O_8I_2\cdot 2H_2O$: C, 51.00; H, 6.01; N, 2.71. Found: C 51.30; H, 5.93; N, 2.74.

Acid Degradation of 31.—The bisoxalate of **31** (50 mg) in 15% aqueous HCl (2 ml) was heated at steam bath temperature for 0.5 hr. The solution was allowed to cool, made alkaline with NH_4OH, and extracted with ether. Evaporation of the solvent and preparative tlc of the residue on alumina, using 10% MeOH–$CHCl_3$ as eluent, afforded the stilbene **34**, which was crystallized from MeOH as colorless needles (26 mg): mp 125–127°; uv λ_{max}^{EtOH} 290 nm (ε 1750), 325 (1590); ir λ_{max}^{KBr} 3.60, 6.18, 13.85 μ; nmr τ 2.6–3.6 (9 H, ArH), 2.98 (s, 1 H, ArH), 6.08, 6.73 (2 s, 6 H, 2 OCH_3), 6.19 (s, 6 H, 2 OCH_3), 7.40, 7.46 (2 s, 6 H, 2 NCH_3); mass spectrum *m/e* (rel intensity) 622 (100), 174 (10).

Registry No.—**1**, 518-34-3; **3**, 477-57-6; **5**, 38769-07-2; **5** 2HI, 38906-65-9; **8**, 38769-08-3; **9**, 38849-79-5; **11**, 38849-80-8; **12**, 4021-17-4; **14**, 38849-82-0; **15**, 38849-83-1; **16**, 38769-09-4; **17**, 1812-55-1; **19**, 38849-84-2; **19** 2HBr, 38769-11-8; **20**, 38769-12-9; **21**, 38769-13-0; **22**, 6681-71-6; **26**, 38769-15-2; **26** methiodide, 38849-85-3; **27**, 38769-16-3; **28**, 38769-17-4; **29**, 38769-18-5; **30**, 38769-19-6; **31**, 38769-20-9; **31** dioxalate, 38769-21-0; **31** dimethiodide, 38769-22-1; **32**, 38769-23-2; **33**, 38769-24-3; **34**, 38849-86-4.

The Isolation and Structural Elucidation of Liatrin, a Novel Antileukemic Sesquiterpene Lactone from *Liatris chapmanii*[1]

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The isolation and structural elucidation of liatrin, a novel sesquiterpene lactone from *Liatris chapmanii*, are reported. Liatrin has significant antileukemic activity in mice and possesses the unusual germacranolide *cis,cis*-diene structure **1**. Reduction of liatrin with sodium borohydride gave the diol **5**, which was converted to a crystalline mono-*o*-bromobenzoate (**6**). X-Ray crystallographic analysis of **6** established the structure of diol **5**. In the light of the structure of **5**, chemical and spectral evidence was adduced in support of structure **1** for liatrin.

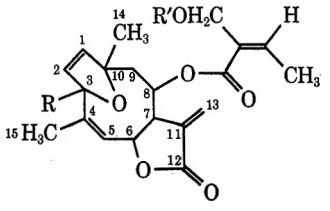
In the course of a continuing search for tumor inhibitors of plant origin, we found that chloroform extracts of *Liatris chapmanii* (Compositae)[2] showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[3] A preliminary communication[4] outlined the structural elucidation of liatrin. It is the purpose of this paper to present in detail the isolation and the structural elucidation of the active constituent, liatrin (**1**).

Fractionation of the chloroform extract (Chart I) was guided by assay against KB to give the most active fraction.[5] Activity was concentrated in the benzene-soluble fraction upon trituration with benzene. Partition of this fraction between acetonitrile–hexane concentrated the activity in the acetonitrile fraction. Rapid elution chromatography of the acetonitrile-soluble material on a deactivated alumina column with benzene–ethyl acetate (3:1, saturated with water) yielded two active fractions (G and H) which were combined and crystallized from cyclohexane–methylene chloride to afford liatrin (**1**). While the isolation of the active principle was guided by assay against KB, liatrin also showed significant *in vivo* antileukemic activity.[3,6]

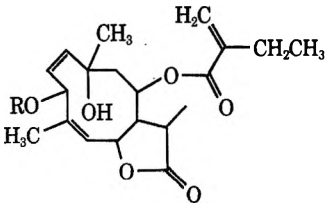
Liatrin (**1**) was assigned the molecular formula $C_{22}H_{26}O_8$ on the basis of elemental analysis and high-resolution mass spectrometry (Table I). The presence of high-intensity end absorption in the ultraviolet spectrum, bands at 5.67 and 6.03 μ in the infrared spectrum, and signals at τ 4.31 (d, J = 2.3 Hz) and 3.70 (d, J = 2.3 Hz) in the nmr spectrum of **1** suggested the presence of an α-methylene-γ-lactone group. The infrared spectrum also indicated the presence of free hydroxyl (2.92 μ), acetate (5.76 and 7.86 μ), and α,β-unsaturated ester (5.84 μ) groupings. Furthermore, the nmr spectrum showed a sharp one-proton singlet at τ 7.24 (exchangeable with D_2O) and a three-proton singlet at τ 7.94 corresponding to the hydroxyl and acetate methyl protons, respectively. The failure of **1** to undergo acetylation on treatment with acetic anhydride–pyridine suggested that the hydroxyl group was tertiary, and the one remaining oxygen atom in the molecular formula was assumed to be involved in an ether linkage. Further examination of the chemistry and spectra of liatrin (**1**) indicated that the tertiary hydroxyl and ethereal oxygen functions were present in the form of a cyclic hemiketal (see below).

TABLE I

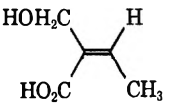
Compd	Ion	Calcd mass	Found mass
1	$C_{22}H_{26}O_8$	418.162	418.164
	$C_{15}H_{16}O_4$	260.104	260.104
	$C_7H_5O_2$	141.055	141.057
5	$C_{15}H_{19}O_4$	263.128	263.128
	C_5H_7O	83.049	83.049



1, R = OH; R′ = Ac
2, R = OH; R′ = H
3, R = OH; R′ = $COCH_2Br$
4, R = H; R′ = Ac



5, R = H
6, R = *o*-bromobenzoyl
7, R = *p*-bromobenzoyl



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Reduction of liatrin with sodium borohydride gave the crystalline diol **5**, which on treatment with *o*-bromobenzoyl chloride gave the crystalline mono-*o*-bromobenzoate derivative **6**. The structure, stereochemistry, and absolute configuration of **6**, and therefore of

(1) (a) Tumor Inhibitors. LXXXVI. Part LXXXV: S. M. Kupchan, M. Maruyama, R. J. Hemingway, J. C. Hemingway, S. Shibuya, and T. Fujita, *J. Org. Chem.*, in press. (b) This investigation was supported by grants from the National Cancer Institute (CA-11718 and CA-11760) and the American Cancer Society (IC-57), and a contract with the Division of Cancer Treatment, National Cancer Institute (NIH-NCI-C-71-2099).

(2) Whole plant was gathered in Florida in September 1964. The authors acknowledge with thanks receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture (USDA), Beltsville, Md., in accordance with the program developed with the USDA by the National Cancer Institute.

(3) Cytotoxicity and *in vivo* inhibitory activity were assayed under the auspices of the National Cancer Institute by the procedures described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(4) S. M. Kupchan, V. H. Davies, T. Fujita, M. R. Cox, and R. F. Bryan, *J. Amer. Chem. Soc.*, **93**, 4916 (1971).

(5) Cytotoxicity was assayed by differential agar diffusion by Professor D. Perlman, University of Wisconsin; *cf. J. Pharm. Sci.*, **58**, 633(1969).

(6) Liatrin showed significant antileukemic activity against the P-388 lymphocytic leukemia in mice, and cytotoxicity (ED_{50}) against KB cell culture at 1.5 μg/ml.

CHART I

FRACTIONATION OF THE CYTOTOXIC EXTRACT FROM *L. chapmanii*

Concentrated chloroform extract from *L. chapmanii*

A, 150 g

benzene trituration

benzene-soluble B, 125 g

benzene-insoluble C, 25 g

partition between acetonitrile and hexane

treatment with Norit

hexane solubles D, 60 g

acetonitrile solubles E, 60 g

deactivated alumina chromatography

fractions F-L

5, were determined unequivocally by X-ray crystallographic analysis.[7]

A view of the molecular structure found in the crystal is shown in Figure 1. Bond lengths and bond angles in the molecule are shown in Figure 2, as are the torsion angles defining the conformations of the five- and ten-membered rings.

The estimated standard deviations in the parameters, calculated from the elements of the least-squares matrices by the method of Hcdgson and Rollett,[8] lead to estimated standard deviations in bond lengths of C–C 0.035, C–O 0.025, and C–Br 0.016 Å, and in bond angles of not more than 2°, except for quantities involving the poorly defined terminal atoms C-33 and C-34, where the uncertainty is greater by a factor of at least 2.5. C-33 and C-34 appear quite clearly, but with reduced peak height, in normal electron-density maps, and in difference electron-density maps calculated with phases from which the contribution of the two atoms has been excluded the only structurally significant peaks are at the locations of the atoms. However, their thermal parameters, $B \cong 12.0$ Å,^{2} are much higher than those of the other atoms, and imply a substantial amplitude of vibration for each atom about its mean position. Because of this, C-33–C-34 is anomalously short, and the assumption of single-bond character rests also on chemical evidence.

Within these limits, the observed bond lengths have normal values. The valence angles within the ring of of the sp^3-hybridized carbon atoms of the ten-membered ring show the expected increase over the regular tetrahedral angle,[9] the mean value being 114.8°. The mean

(7) Positional parameters defining the crystal structure, the anisotropic thermal parameters of the atoms, and the observed and calculated structure amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-1853.

(8) L. I. Hodgson and J. S. Rollett, *Acta Crystallogr.*, **16**, 329 (1963).

(9) R. F. Bryan and J. D. Dunitz, *Helv. Chim. Acta*, **43**, 3 (1960).

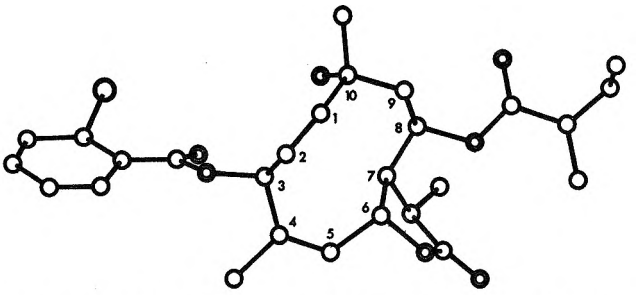

Figure 1.—Molecular structure of the *o*-bromobenzoate derivative 6 as found in the crystal. The central ring is numbered to correspond to the structural formula given in the text. Oxygen atoms are represented by double circles, and the bromine atom by the larger circle.

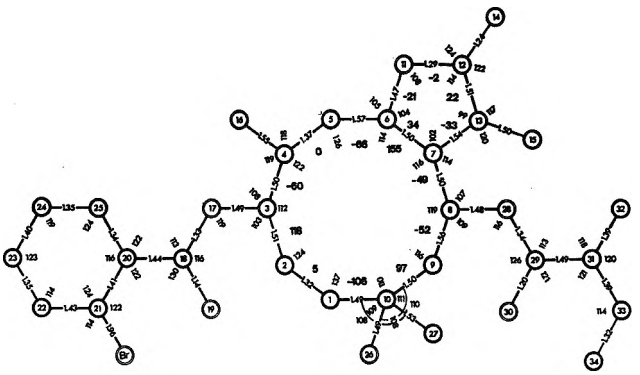

Figure 2.—Bond lengths and angles and torsion angles in the *o*-bromobenzoate 6.

of the observable extra-ring sp^3 angles is correspondingly reduced to 107.7°. The angle C-2–C-1–C-10 is greatly increased over the expected value for an sp^2 valence angle, presumably to relieve stress from the close approach of the hydroxyl group at C-10 to the hydrogen atoms at C-3 and C-7. Tables II and III show intra- and intermolecular contacts in the crystal.

TABLE II

SELECTED INTRAMOLECULAR CONTACTS (Å) WITHIN THE TEN-MEMBERED RING

C-1···C-6	3.28	C-3···C-10	3.28
C-2···C-5	3.07	C-3···O-26	2.97
C-2···C-6	3.16	C-4···C-7	3.27
C-3···C-6	3.08	C-6···C-9	3.12
C-3···C-7	3.33	C-7···C-10	3.17

TABLE III

SHORTER INTERMOLECULAR APPROACH DISTANCES (Å)[a]

Br···C-9^{I}	3.92	C-9···O-19^{II}	3.47
Br···O-28^{I}	3.59	O-14···O-26^{IV}	2.80
Br···C-31^{I}	3.98	C-15···O-17^{I}	3.43
C-1···O-19^{II}	3.47	C-22···O-30^{V}	3.40
C-2···C-15^{II}	3.71	C-23···O-30^{V}	3.48
C-2···O-26^{II}	3.50	C-27···O-32^{VI}	3.79
C-5···C-15^{III}	3.73		

[a] Contacts are between the first atom at x, y, z and the second atom in the symmetry-related position denoted by the Roman superscript: I = $x - 0.5, 1.5 - y, 1 - z$; II = $0.5 + x, 1.5 - y, 1 - z$; III = $0.5 + x, 1.5 - y, -z$; IV = $x, y, z - 1$; V = $1 - x, y - 0.5, 1.5 - z$; VI = $x, y, 1 + z$.

With the X-ray-defined structure of 6 (and hence of 5) in hand, liatrin could now be shown to have the unusual germacranolide *cis,cis*-diene structure 1 by

TABLE IV

NUCLEAR MAGNETIC RESONANCE DATA FOR *Liatris chapmanii* DERIVATIVES[a]

Compd	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-11	C-13	C-14	C-15	Side chain	Other
Liatrin (1)	3.64 d (5.6)	4.21 d (5.6)		4.35 dd (1.5, 6.5)	4.12 m	6.53 m	4.78 t (3.5)	7.63 d (3.5)		4.31 d (2.3)	8.61 s	8.09 m	3.51 q (7) 5.36 AB q (12)	7.24 s C-3 OH
										3.70 d (2.3)			7.94 s OAc 7.97 d (7)	
Deacetyl-liatrin (2)	3.57 d (5.4)	4.21 d (5.4)		4.34 dd[b]	4.03 m	6.50 m	4.79 t (3.6)	7.59 d (3.6)		4.27 d (2.0)	8.54 s	8.05 br s	3.60 q (7) 5.81 AB q (12)	
										3.69 d (2.0)			7.97 d (7)	
Bromo-acetate 3	3.65 d (5.6)	4.20 d (5.6)		4.38 dd[b]	4.15 m	6.55 m	4.80 t (3.5)	7.65 d (3.5)		4.31 d (2.0)	8.62 s	8.11 br s	3.44 q (7) 5.28 AB q (12)	7.37 C-3 OH
										3.71 d (2.0)			6.09 s (CH_2Br) 7.94 d (7)	
Deoxyliatrin (4)	4.26 dd (1.5, 6)	3.92 dd (2.5, 6)	4.89 dd (1.5, 2.5)	4.36 m	3.90 m	6.40 dt (2.4, 4.4)	4.76 t (4.0)	7.64 d (4.0)		4.32 d (2.4)	8.71 s	8.10 br s	3.51 q (7) 5.34 AB q (12)	No exchange-able signal
										3.72 d (2.4)			7.90 s (OAc) 7.90 d (7)	
Deoxyliatrin (4)[c]	4.73 dd (1.5, 6)	4.18 dd (2.5, 6)	5.20 m	4.52 br d (6.5)	3.78[b] m	6.58 m	4.8[b]	7.90 m		3.79 d (2.5)	8.50 s	8.14 s	3.94 q (7) 5.34 AB q (12)	
										4.81 d (2.5)			8.02 d (7)	
Diol 5									7.37 quintet (7.5)	8.91 d (7.5)	8.50 s	8.14 s	3.94 br s 4.45 br s	
													7.75 q (7.5)	
													8.95 t (7.5)	

[a] Values are given in τ units relative to tetramethylsilane as internal standard. Multiplicity of signals is designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad. Numbers in parentheses denote coupling constants in hertz. [b] Pattern obscured by other signals. [c] Measured in deuteriobenzene.

careful analysis of its chemical and spectral properties as described below. Liatrin (1) gave on acid hydrolysis an amorphous deacetylated product 2 which was reconverted to 1 on acetylation and could also be converted to a crystalline bromoacetate 3. Alkaline hydrolysis of 1 gave sarracinic acid (8),[10,11] identified by comparison of infrared spectra, melting point, and mixture melting point with those of an authentic sample.[12]

Closer examination of the nmr (Table IV) and mass spectra of liatrin (1), the deacetylation product 2, and the bromoacetate 3 indicated that 1 contained an acetylsarracinate ester moiety. For example, decoupling experiments on 1 revealed that a methyl proton doublet at τ 7.97 (J = 7 Hz) was coupled to a one-proton quartet at τ 3.51 (J = 7 Hz). In addition, the chemical shift of the methylene group centered at τ 5.36, 5.81, and 5.28 in the nmr spectra of 1, 2, and 3, respectively, showed that the acetyl group in 1 was attached to the hydroxyl group in the sarracinate ester. Additional corroboration of these results was found in the mass spectrum of 1, which contained a large peak at m/e 141, shown by high-resolution mass spectrometry to be due to the presence of the $C_7H_9O_3$ ion, whereas the mass spectrum of the bromoacetate 3 displayed a large double peak at m/e 221 and 219 ($C_7H_8O_3{}^{81}Br$, $C_7H_8O_3{}^{79}Br$). Finally, the presence of a peak in the high-resolution mass spectrum of 1 at m/e 260 corresponds to loss of acetylsarracinic acid from the molecular ion at m/e 418 and thus is representative of the sesquiterpene nucleus of 1.

The high-resolution mass spectrum of the borohydride reduction product 5 displayed peaks at m/e 263 and 83 due to the $C_{15}H_{19}O_4$ (sesquiterpene nucleus) and C_5H_7O (α-ethylacrylium) ions, respectively. This indicated that the acetylsarracinate side chain of 1 had undergone reductive elimination to give the α-ethyl acrylate group of the diol 5. Accordingly, the nmr spectrum of 5 revealed signals attributable to an ethyl group at τ 8.95 (3 H, t, J = 7.5 Hz) and 7.75 (2 H, q, J = 7.5 Hz), and a terminal methylene group at τ 3.94 and 4.45.

Treatment of liatrin (1) with dimethylamine borane afforded an oily deoxy compound 4, whose molecular formula, $C_{22}H_{26}O_7$, was assigned on the basis of mass spectrometry. The nmr spectrum of 4 was similar to that of liatrin (1), except that an AB type pattern at τ 3.64 (d, J = 5.6 Hz) and 4.21 (d, J = 5.6 Hz) in the spectrum of 1 was replaced by an ABX pattern at τ 3.92 (d, d, J = 2.5, 6 Hz), 4.26 (d, d, J = 1.5, 6 Hz), and 4.89 (d, d, J = 1.5, 2.5 Hz) in the spectrum of 4. Accordingly, the signals at τ 3.92 and 4.26, on irradiation at τ 4.89, collapsed to a pair of doublets (J = 6 Hz). In addition, 4 contained no D_2O-exchangeable protons. These facts suggested that the tertiary hydroxyl group of 1 had been replaced by a methine hydrogen in 4. The low chemical shift (τ 4.89) indicated that the methine hydrogen was probably attached to an ethereal carbon atom. The ease of replacement of the tertiary hydroxyl group of 1 by a hydrogen on treatment with dimethylamine borane, and the formation of the diol 5 on treatment of 1 with sodium borohydride,

(10) C. C. J. Culvenor and T. A. Geissman, *J. Org. Chem.*, **26**, 3045 (1961).

(11) J. D. Edwards, Jr., T. Matsumoto, and T. Hase, *J. Org. Chem.*, **32**, 244 (1967).

(12) The authors are indebted to Dr. J. D. Edwards, Jr., for a generous sample of authentic sarracinic acid.

are indicative of the presence of a hemiketal function in **1**.

Further evidence for the structure of **1** could be gained from the nmr spectrum of **4** in benzene-d_6 solution. Irradiation at τ 5.20, corresponding to the chemical shift of the methine hydrogen, collapsed a doublet of multiplets centered at τ 4.52 (J = 6.5 Hz) to a broad doublet, which could thus be assigned to the C-5 vinyl hydrogen. Consequently, the tertiary hydroxyl group in **1** and the new methine hydrogen in **4** could now be located at C-3 between the two olefinic bonds.

The crystalline diol **5** obtained from liatrin (**1**) on treatment with sodium borohydride in ethanol requires further comment. The presence of two hydroxyl groups in **5** was evident from the ready formation of both the mono-*o*-bromobenzoate **6** and the mono-*p*-bromobenzoate **7** derivatives, which, from their spectral characteristics, clearly contained one tertiary hydroxyl group. Three-proton singlets at τ 8.14 and 8.50 in the nmr spectrum of **5** indicated the presence of a vinyl methyl and a methyl attached to a carbon bearing oxygen, respectively. Consequently, one of the two tertiary methyl groups could be located in the sesquiterpene skeleton of **5**, geminal with a tertiary hydroxyl group. The appearance of a doublet at τ 8.91 (3 H, J = 7.5 Hz) and an apparent quintet at τ 7.37 (1 H, J = 7.5 Hz) in the nmr spectrum of **5**, which were shown to be coupled, indicated that reduction of the α-methylene-γ-lactone had occurred.

Examination of the high-resolution nmr spectrum of liatrin made possible elaboration of complete structure **1**. An AB quartet signal at τ 3.64 (d, J = 5.6 Hz) and 4.21 (d, J = 5.6 Hz) indicated the existence of an isolated cis double bond. Since this system was not coupled to any other protons, and appeared as part of an ABX system in the deoxy derivative **4**, it could be assigned to the C-1 and C-2 vinyl hydrogens, respectively. Chemical evidence had suggested the presence of a cyclic hemiketal, which on reduction with sodium borohydride gave the diol **5**. Clearly, from the X-ray derived structure of **5** the hemiketal in **1** must be in the form of a dihydrofuran. This was supported by the coupling constant for the C-1, C-2 vinyl hydrogens (5.6 Hz), which was in close agreement with that of unsaturated pentafuranosides described by Lemieux, *et al.*[13] A three-proton singlet at τ 8.61, indicative of a methyl group on carbon bearing oxygen, was then assigned to the C-10 methyl group.

Irradiation at τ 6.53 (1 H, m) caused the pair of doublets at τ 4.31 and 3.70 (each 1 H), previously assigned to the C-13 protons, to collapse to singlets.[14] The τ 6.53 multiplet could then be assigned to the C-7 proton. In addition, irradiation at τ 6.53 caused the multiplet at τ 4.12 (1 H) to collapse to a broad doublet. The same multiplet at τ 4.12 was collapsed to a doublet of doublets upon irradiation at τ 8.09 (3 H, br s). Thus the τ 4.12 signal could be assigned to the C-6 proton and the τ 8.09 signal to the C-4 methyl protons. Furthermore, irradiation of the C-4 methyl group caused a doublet of doublets at τ 4.35 (1 H, J = 6.5, 1.5 Hz) to collapse to a doublet (J = 6.5 Hz), which could thus be assigned to the C-5 vinyl proton.

(13) R. M. Lemieux, K. A. Watanake, and A. A. Pavia, *Can. J. Chem.*, **47**, 4413 (1969).

(14) Z. Samek, *Tetrahedron Lett.*, 671 (1970).

To complete the nmr assignments in **1** it was found that a two-proton doublet at τ 7.63 (J = 3.5 Hz) was coupled to a one-proton triplet at τ 4.78 (J = 3.5 Hz), allowing assignment of these signals to the C-9 methylene and C-8 methine protons, respectively. The formation of the diol **5** and the deoxy compound **4** from **1** on treatment with sodium borohydride and dimethylamine borane, respectively, can be explained as having involved reduction of the hemiketal in **1**.

The X-ray analysis of the *o*-bromobenzoate **6** established the stereochemistry as C-1, C-2, cis; C-3, *S*; C-4, C-5, cis; C-8, *R*; and C-10, *S*; the γ-lactone ring was found to be trans-fused to C-6, C-7.

Experimental Section

Melting points were determined on a Kofler block or a Mettler Model FP2 hot stage, and are corrected. Ultraviolet absorption spectra were determined on Beckman Model DK-2 and Coleman Hitachi Model EPS-3T recording spectrophotometers. Infrared spectra were determined on Beckman Model IR-9, Perkin-Elmer Model 257, and Perkin-Elmer Model 337 recording spectrophotometers. Nuclear magnetic resonance spectra were determined on a Perkin-Elmer Model R-20 spectrometer at 60 Mc/sec and on a Varian HA-100 spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard. Mass spectra were obtained from Hitachi Perkin-Elmer Model RMU-6A (RMU-6E) and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (tlc) was carried out on precoated plates supplied by E. Merck. The tlc-solvent system most commonly used was benzene–ethyl acetate–isopropyl alcohol (85:10:5, system A). Tlc plates were visualized with a mixture of concentrated sulfuric acid–25% vanillin in absolute ethanol (5:1). Evaporations were carried out at reduced pressure at less than 40°.

Isolation Procedure.—The dried ground roots, stems, leaves, and flowers (1.15 kg) of *L. chapmanii* were continuously extracted with chloroform in a Soxhlet apparatus for 48 hr and the chloroform extract was evaporated under reduced pressure to yield a dark green residue (A, 150 g). Fraction A was triturated with benzene (2.5 l.) for 8 hr and filtered, and the residue was again triturated with benzene (1 l.). The combined benzene extracts were evaporated to yield a dark brown gum (B, 125 g), which contained most of the KB activity present in the chloroform extract. Fraction B was partitioned between acetonitrile (1 l.) and hexane (1 l.). The acetonitrile layer was again extracted with hexane (4 × 750 ml) and the combined hexane layers were evaporated to give a green oil (D, 60 g). The acetonitrile layer was treated with Norit (20 g), and filtered to give a brown solution which was evaporated to yield a gum (E, 60 g). Fraction E showed significant KB activity. The acetonitrile solubles (E, 60 g) were chromatographed on 3 kg of Woelm neutral alumina (activity I) deactivated by the addition of 60 ml of distilled water. The column was packed in benzene saturated with water and eluted with benzene–ethyl acetate (3:1, saturated with water). A very fast flow rate (3.5–4 l./hr) was employed. Fractions were collected as follows: F (6 l., 1.4 g), G (4 l., 2.9 g), H (4 l., 2.6 g), I (3 l., 0.9 g), J (6 l., 1.6 g), K (7 l., 6.7 g), and a methanol wash L (8 l., 20.9 g). Tlc examination of these fractions on a silica gel plate showed that liatrin (**1**) (which gave an orange spot with the spray reagent described) was concentrated in fractions G and H. These fractions were combined and crystallized from methylene chloride–cyclohexane to give liatrin (**1**, 1.8 g) as colorless needles, mp 129–131°. Recrystallization from the same solvent gave material with mp 130–132°; $[\alpha]^{24.5}D$ −142.0° (c 1.93, chloroform); uv λ^{EtOH} end absorption, 220 nm (ϵ 19,420); ir λ_{max}^{KBr} 2.92, 3.37, 5.67, 5.76, 5.84, 6.03, 7.81, 8.67, and 9.71 μ; mass spectrum m/e (rel intensity) 418 (<1), 260 (6), 259 (12), 141 (30), 99 (20), 79 (15), 81 (70), 69 (15), 53 (16), and 43 (100).

Anal. Calcd for $C_{22}H_{23}O_8$: C, 63.15; H, 6.26. Found: C, 63.21; H, 6.22.

Sodium Borohydride Reduction of Liatrin (1).—Sodium borohydride (1.30 g) was gradually added over a period of 1 hr to a stirred solution of **1** (403 mg) in ethanol at −60 to −50°, and

then the bath temperature was kept at −20 to −5° for 3 hr. The mixture was poured into ice cold 5% hydrochloric acid (200 ml) to decompose excess reagent, then extracted with methylene chloride (3 × 50 ml). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated to give a gum (386 mg). The gum was crystallized from methylene chloride–cyclohexane to give 284 mg of diol **5**, which was purified by preparative thin layer chromatography and recrystallization from methylene chloride–cyclohexane to give colorless needles of **5**: mp 89.2–90.9°; uv λ^{EtOH} end absorption, 210 nm (ϵ 14,700); ir λ_{max}^{KBr} 2.92, 5.72, 5.83, and 6.15 μ; mass spectrum *m/e* (rel intensity) 346 ($M^+ - H_2O$, 4), 263 (20), 246 (32), 83 (100).

***o*-Bromobenzoylation of Diol 5.**—A solution of the diol **5** (80 mg) in anhydrous pyridine (8 ml) was treated with *o*-bromobenzoyl chloride (599 mg) at 0° for 30 min. The reaction mixture was diluted with methylene chloride and ice–water and then stirred for 30 min. The layers were separated and the water layer was extracted with methylene chloride. The combined organic layers were washed with 10% aqueous sodium carbonate solution, 1 *N* hydrochloric acid, and water, then dried over sodium sulfate and evaporated to dryness at reduced pressure. The solid residue obtained was crystallized from methylene chloride–cyclohexane to give the mono-*o*-bromobenzoate **6** (50 mg): mp 181.5–182.3°; ir λ_{max}^{KBr} 2.93, 5.69, 5.79, 5.88, 6.16, and 6.31 μ; mass spectrum *m/e* (rel intensity) 530, 528 ($M^+ - H_2O$, <1), 263 (12), 246 (10), 185, 183 (100), 83 (95).

Anal. Calcd for $C_{27}H_{31}BrO_7$: C, 59.24; H, 5.71; Br, 14.60. Found: C, 59.28; H, 5.76; Br, 14.68.

Deacetylliatrin (2).—A solution of liatrin (**1**, 203 mg) in water–dioxane (40:60, 15 ml) was treated with 6 *N* sulfuric acid (1 ml) at 5° for 25 days. Excess sodium bicarbonate solution was added and the reaction mixture was diluted with water (100 ml) and extracted with methylene chloride (3 × 100 ml). The combined organic layers were washed with water (200 ml), dried over sodium sulfate, and evaporated to yield a foam (185 mg) which was purified by preparative tlc on eight Silica Gel F254 plates using solvent system A. The medium R_f material was combined and extracted with methanol–methylene chloride (1:9). Evaporation of the solvents gave deacetylliatrin (**2**) as a gum: ir $\lambda_{max}^{CHCl_3}$ 2.76, 3.33, 3.39, 5.65, 5.80, 5.99, 6.20, 7.80, 8.70, and 9.80 μ; mass spectrum *m/e* (rel intensity) 260 (22), 259 (37), 191 (20), 149 (20), 99 (100), 97 (24), 81 (33), 69 (22), 53 (38), 43 (75), and 41 (55).

Bromoacetylation of Deacetylliatrin (2).—Deacetylliatrin (**2**, 60 mg) in anhydrous benzene (3 ml) was treated with anhydrous potassium carbonate (315 mg) and bromoacetic anhydride (10 drops) under nitrogen. The reaction mixture was intermittently stirred at 24° for 48 hr, then water (40 ml) was added and after 15 min the mixture was extracted with methylene chloride (3 × 33 ml). The combined organic layers were washed with water (50 ml), dried, and evaporated to dryness. The oily residue was purified by preparative tlc on four Silica Gel F254 plates (0.25 mm) using solvent system A. The high R_f band containing the desired bromoacetate was removed and extracted with methanol–methylene chloride (1:9). The solvent was evaporated and the residue was crystallized from methylene chloride–cyclohexane to give the bromoacetate **3** (15 mg) as colorless needles: mp 135–137°; ir λ_{max}^{KBr} 2.87, 3.37, 3.41, 5.69, 5.76 (sh), 5.80, 6.05, 7.85, 8.70, and 9.79 μ; mass spectrum *m/e* (rel intensity) 498, 496 (1), 260 (44), 259 (60), 242 (20), 221, 219 (32), 163 (22), 123, 121 (20), 99 (40), 97 (20), 81 (10), 53 (24), and 43 (32).

High resolution mass spectrum: calcd for $C_{22}H_{25}O_8{}^{79}Br$, 496.0733; found, 496.0721.

Acetylation of Deacetylliatrin (2).—Deacetylliatrin (**2**, 32 mg) in anhydrous benzene (2 ml) was treated with anhydrous potassium carbonate (170 mg) and acetic anhydride (5 drops) under nitrogen. The reaction mixture was stirred for 24 hr at 24°, after which time an additional quantity of acetic anhydride was added. After a further 24 hr, the reaction mixture was poured into water (30 ml). After 15 min the aqueous solution was extracted with methylene chloride (3 × 33 ml), and the combined organic layers were washed with water (50 ml), dried, and evaporated. The residue was dissolved in benzene and the benzene solution was evaporated, thereby removing the last traces of acetic acid. The crude product (41 mg) was chromatographed on two Silica Gel F254 plates (0.25-mm thickness) using solvent system A. The band corresponding to liatrin (**1**) was removed and extracted in the usual manner. Evaporation of the solvent and recrystallization of the residue from methylene chloride–cyclohexane gave liatrin (**1**, 17 mg), mp 132°, which was shown to be identical (tlc, ir, mass spectrum, mixture melting point) with authentic liatrin (**1**) described above.

Sarracinic Acid (8).—A solution of liatrin (**1**, 299 mg) in 5 *N* sodium hydroxide (25 ml), dioxane (35 ml), and water (45 ml) was heated at 60° for 30 min. After cooling, the reaction mixture was adjusted to pH 8.5 with hydrochloric acid, concentrated to approximately 40 ml, and basified with 10% sodium carbonate. The aqueous layer was extracted with chloroform to remove any neutral material, then acidified with hydrochloric acid and saturated by the addition of solid sodium chloride. Extraction with ether gave an acidic fraction which, after removal of solvent, was chromatographed on Cellulose F precoated tlc plates (0.1-mm thickness) using *sec*-butyl alcohol–2 *N* ammonium hydroxide (4:1) as development solvent. The acidic band (visualized by bromphenol blue spray reagent) was removed and extracted with methanol, and the solvent was evaporated. The residue was dissolved in ether and washed with 5% aqueous hydrochloric acid. The ether layer was washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated to a solid (25 mg). Recrystallization from ether–petroleum ether (bp 60–68°) gave sarracinic acid (**8**), mp 53.4–54.5°, which was shown to be identical (ir and mixture melting point) with an authentic sample of sarracinic acid.[12]

Deoxyliatrin (4).—To a solution of liatrin (**1**, 84 mg) in acetic acid (0.5 ml) was added dropwise a solution of dimethylamine borane (15 mg) in acetic acid (0.5 ml). The solution was heated over a steam bath for 5 min, cooled, neutralized with saturated potassium carbonate solution, and extracted with methylene chloride (3 × 10 ml). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on four Silica Gel F254 plates (0.5 mm thickness) using solvent system A. The major high R_f band was removed and extracted with methanol–methylene chloride (1:9) to afford, after evaporation of the solvent, pure deoxyliatrin (**4**) as an amorphous solid which failed to crystallize from several solvents. This material was homogeneous by tlc and displayed the following spectral data: ir $\lambda_{max}^{CHCl_3}$ 5.71, 5.82, 6.04, and 6.08 μ; mass spectrum *m/e* (rel intensity) 402 (4), 387 (20), 261 (14), 245 (55), 244 (50), 141 (70), 81 (70), 43 (100).

***p*-Bromobenzoylation of Diol 5.**—A solution of the diol **5** (47 mg) in anhydrous pyridine (1 ml) was treated with *p*-bromobenzoyl chloride (200 mg) at 25° under nitrogen in the dark for 24 hr. The reaction mixture was diluted with methylene chloride (10 ml) and added slowly to ice-cold 0.6 *N* sulfuric acid (50 ml). The aqueous solution was extracted with methylene chloride (2 × 100 ml). The combined organic layers were washed with 0.6 *N* sulfuric acid (2 × 50 ml) and with 10% aqueous sodium carbonate solution (2 × 50 ml), then dried over sodium sulfate. Removal of the solvent gave a gummy solid (100 mg) which was chromatographed on four Silica Gel F254 plates (2 mm) using solvent system A. The high R_f band, containing the desired *p*-bromobenzoate derivative, was removed, extracted with methanol–methylene chloride (1:3, 500 ml), and evaporated to give a gum (55 mg) which was further purified by preparative tlc on two alumina type T, F254 plates using chloroform as solvent. Extraction of the high R_f, uv-visible band and work-up in the usual manner gave a solid residue (27 mg). Crystallization from methylene chloride–Skelly B gave the *p*-bromobenzoate derivative **7** as needles: mp 156–158°; uv λ_{max}^{EtOH} 212 nm (ϵ 6230) and 245 (18,460); ir λ_{max}^{KBr} 2.90, 3.38, 5.63, 5.84, 6.14, 6.30, 7.82, 8.92, and 10.12 μ; mass spectrum *m/e* (rel intensity) 530, 528 ($M^+ - 18$, 2), 448, 446 (1), 430, 428 (1), 346 (2), 328 (2), 264 (5), 263 (18), 246 (21), 228 (11), 202, 200 (14), 185, 183 (100), 85 (15), 83 (60), 57 (37), and 55 (78).

Anal. Calcd for $C_{27}H_{31}BrO_7$: C, 59.24; H, 5.71; Br, 14.60. Found: C, 58.97; H, 5.83; Br, 14.64.

High resolution mass spectrum: calcd for M − 18, $C_{27}H_{29}{}^{81}BrO_6$, 530.1128; found, 530.1166.

X-Ray Crystallographic Structural Data.—Crystals of the *o*-bromobenzoate are colorless, transparent lathes elongated along the *c* axis. Intensity measurements were made, at room temperature, from a crystal 0.35 × 0.25 × 0.05 mm[3] mounted with *b* parallel to the ϕ axis of a Picker four-circle diffractometer controlled by an XDS Sigma 2 computer.[15] Monochromatic molybdenum K_α radiation was used with scintillation counting.

Within a single octant, 1530 independent reciprocal lattice points were surveyed out to $2\theta = 42°$, and scattered intensity significantly above background was found at 1150 of them. No

(15) R. C. Haltiwanger and R. F. Bryan, *J. Chem. Soc. B*, 1598 (1971).

loss of intensity was observed during the experiment as judged by regular monitoring of three reference reflections so that a single scale factor could be used. No corrections for absorption were deemed necessary.

Crystal Data for *o*-Bromobenzoate 6.—$C_{27}H_{31}BrO_7$ had formula weight 547.4, orthorhombic, a = 11.25 (2), b = 26.63 (4), c = 8.96 (2) Å, U = 2685 Å^3, D_m = 1.34 (by pycnometry with an aqueous ZnI solution), Z = 4, D_c = 1.35, F (000) = 1136. Space group $P2_12_12_1$. Precession photography, Mo K_α radiation, λ 0.7107 Å, μ 17 cm^{-1}.

Structure Determination and Refinement.—The structure was solved by the heavy-atom method in the usual way, and five cycles of Fourier refinement with a single, overall, isotropic thermal parameter, B = 4.0 Å^2, gave R = 0.22.

Further refinement of the structural parameters was by block-diagonal least-squares methods. With anisotropic thermal parameters assumed only for the bromine atom, R was 0.118 at convergence. Inclusion of the anomalous dispersion terms[16] for bromine in the structure factor calculations gave R = 0.123 and 0.116 for the two possible enantiomeric structures. By Hamilton's R-factor ratio test[17] a significant distinction is implied between the two absolute configurations at the 99.5% confidence level. The crystal was accidentally dislodged and lost during the measurement of intensity differences in Friedel pairs of reflections. The very few measurements made confirmed the correctness of the choice indicated by the ratio test.[18]

The least-squares refinement was continued for the favored enantiomorph, and with anisotropic thermal parameters assumed for all atoms R was 0.079 at convergence.

The scattering functions used were those for the neutral atoms.[19] The weighting scheme used was based on counting statistics with some allowance for errors of a nonstatistical nature in the stronger intensities.[20] All calculations were performed on an XDS Sigma 2 computer with programs written in this laboratory.

Registry No.—**1**, 34175-79-6; **2**, 38821-16-8; **3**, 38821-17-9; **4**, 38821-18-0; **5**, 34160-71-9; **6**, 34160-72-0; **7**, 34160-73-1; *o*-bromobenzoyl chloride, 7154-66-7; *p*-bromobenzoyl chloride, 586-75-4.

(16) D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).
(17) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(18) J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature (London)*, **168**, 271 (1951).
(19) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
(20) W. R. Busing and H. A. Levy, *J. Chem. Phys.*, **26**, 563 (1957); D. F. Grant, R. C. G. Killean, and J. L. Lawrence, *Acta Crystallogr., Sect. B*, **25**, 374 (1969).

Synthesis and Spectral Characterization of Some *C*-Alkylphospholes and Phospholecarboxylates[1]

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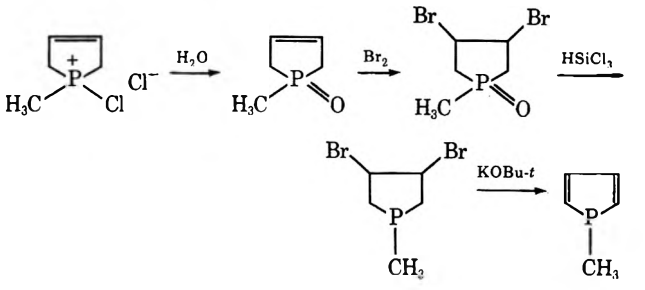
Ten phospholes, bearing either methyl, benzyl, or phenethyl substituents on phosphorus and methyl or carbomethoxy on carbon, have been synthesized by dehydrohalogenation of 3,4-dibromophospholanes or of 1-halophospholenium halides. The two esters prepared are the first phospholes with a reactive functional group. Significant differences were noted in the rates of reaction of phospholes to quaternization with alkyl halides; the fastest reacting phospholes (3,4-dimethyl derivatives) exhibited other differences, including (1) a small blue shift in the characteristic uv maximum of phospholes, (2) diminished allylic coupling between β CH_3 and an α proton, (3) a slight upfield shift of the α proton, and (4) a pronounced upfield shift of the ^{31}P signal. Steric or electronic effects, or a combination of these, are apparently leading to a diminution of electron delocalization from phosphorus in these derivatives. Some of the *P*-methyl phospholes had readily interpreted P–H coupling patterns, permitting experimental verification of computed values made earlier. It was possible to consider the ^{31}P value of the phosphole as derived from definite contributions for the ring fragment and for the P substituent. The phosphorus in phospholes is more strongly deshielded than in 2-phospholenes and in these more than in phospholanes. The carbomethoxy substituent caused quite strong additional deshielding, moderated, however, by steric interaction with a methyl substituent adjacent to it. The sensitivity of the ^{31}P value to conjugative effects is revealed by these observations.

In 1967, we announced[2] the synthesis of 1-methylphosphole, the first phosphole of sufficient structural simplicity to allow a meaningful evaluation[3] of properties of this ring system relative to those of the heteroaromatics thiophene, pyrrole, and furan. This study, as well as subsequent work of others,[4,5] has revealed that the phosphole ring has some of the properties associated with systems partaking of electron delocalization through p_π–p_π bonding. Following our initial work, we proceeded to pursue a synthetic program designed to provide appropriate phospholes for exploring further some unique features present in this system. Some of the results of this study are described in this paper.

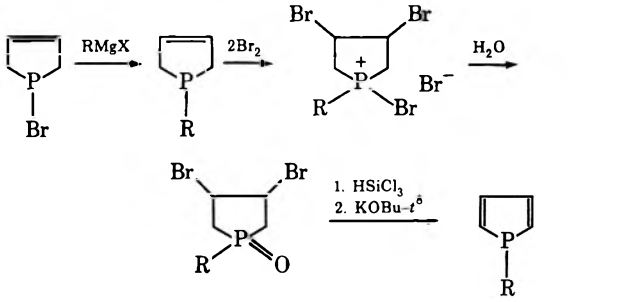
Synthesis.—The phospholene ring system, available from the cycloaddition of dienes and trivalent phosphorus halides,[6] serves as a useful starting point for construction of the phosphole system. Thus, 1-methylphosphole was prepared in our earlier work[2,3] by the following sequence.



(1) Taken from the Ph.D. dissertations of J. F. E. (1971) and S. G. B. (1972). Supported in part by Public Health Service Research Grant CA-05507 from the National Cancer Institute. The National Science Foundation provided funds toward the purchase of the Bruker spectrometer (Grant No. GP 10301), and the AEI spectrometer is sponsored by Special Facilities Grant No. FR-0330-01, National Institutes of Health.
(2) L. D. Quin and J. G. Bryson, *J. Amer. Chem. Soc.*, **89**, 5984 (1967).
(3) L. D. Quin, J. G. Bryson, and C. G. Moreland, *ibid.*, **91**, 3308 (1969).
(4) (a) W. Egan, R. Tang, G. Zon, and K. Mislow, *ibid.*, **92**, 1442 (1970); (b) *ibid.*, **93**, 6205 (1971); (c) A. Rauk, J. D. Andose, U. G. Frick, R. Tang, and K. Mislow, *ibid.*, **93**, 6507 (1971); (d) W. B. Farnham and K. Mislow, *Chem. Commun.*, 469 (1972).
(5) F. Mathey and R. Mankowski-Favelier, *Org. Magn. Resonance*, **4**, 171 (1972).
(6) W. B. McCormack, U. S. Patents 2,663,736 and 2,663,737 (Dec 22, 1953).

Our recent work has provided means for varying the substituent on phosphorus other than that offered by choice of reactants in the cycloaddition process, and has also given access to phospholes with a reactive functional group (*e.g.*, carboxylate). Some of our work has been aided by a new contribution of others to phosphole synthesis: the direct dehydrohalogenation[5] of the McCormack cycloadducts (halophospholenium halides).

Method A.—We have shown[7] that diene–PX_3 cycloadducts can be reduced (dehalogenated) to 1-halophospholenes. These have now been demonstrated to be useful intermediates for the synthesis of dibromophospholane oxide precursors of phospholes.



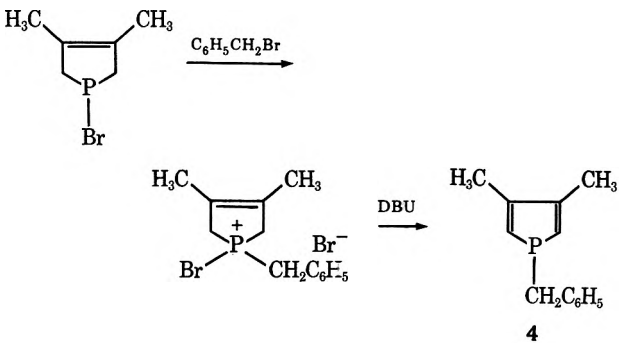
1, R = $CH_2C_6H_5$
2, R = $CH_2CH_2C_6H_5$
3, R = $CH_2CH_2C_6H_4$-*p*-Cl

The first reaction permits the synthesis of a wide variety of P-substituted phospholenes through the Grignard reaction. Addition of 1 mol of bromine to the phospholene occurred selectively at phosphorus; a second 1 mol added to the double bond. The resulting tetrabromo compound could then be hydrolyzed smoothly to the 3,4-dibromo *P*-oxide, which as in our previous work[3] was converted in two steps to the phosphole. One phosphole (1-benzyl, **1**) was also prepared by our earlier[3] route, starting with benzylphosphonous dibromide.

A side reaction, noted previously,[3] leads to contamination of the phosphole with some of the 3-phospholene. Its removal from the phosphole presents no difficulty; the latter is of greatly reduced basicity,[3] and remains in an organic solvent while the 3-phospholene is extracted with 1–2 *N* hydrochloric acid. The 3-phospholene apparently arises from debromination of the 3,4-dibromo system, by either the trichlorosilane[9] or by the phosphine formed in the reduction.[10]

Method B.—The 1-halo-3-phospholenes possess another property of value in phosphole synthesis; phosphorus is of sufficient nucleophilicity that an alkyl group can be added through reaction with an alkyl halide.

Phosphorus halides are generally much less reactive to alkyl halides than are tertiary phosphines, although examples of the alkylation of other phosphinous

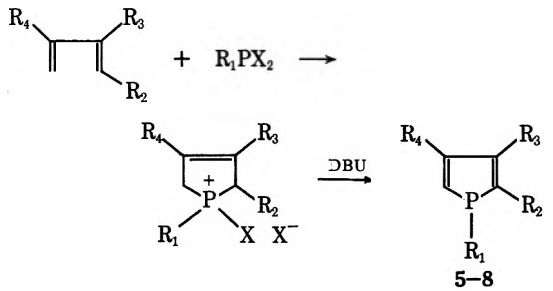


4

halides are known.[11,12] We found that particularly reactive alkyl halides (*e.g.*, benzyl and methyl halides; *n*-butyl bromide failed to react) were required to form phosphonium salts with our cyclic phosphinous bromides. These salts have the same structure as the diene–$RPBr_2$ cycloadducts, and can be converted to phospholes by the steps of our 1-methylphosphole synthesis. Alternatively, dehydrobromination by DBU[5,13] (method C) is possible, and was employed successfully in the synthesis of **4**.

Method B is preferred to method A for the synthesis of 3,4-dimethylphospholes, for the 3,4-dibromo-3,4-dimethylphospholane oxides required in method A are quite susceptible to decomposition *via* dehydrohalogenation.[14]

Method C.—The direct dehydrohalogenation of halophospholenium halides to phospholes[5,13] proceeds with modest yield, but the simplicity of the method makes it attractive where the halides can be readily obtained. We have used it in the synthesis of phospholes **5–8** (10–20% yield).



5–8

Compd	R_1	R_2	R_3	R_4
5	$CH_2C_6H_5$	H	CH_3	H
6	CH_3	CH_3	H	H
7	CH_3	H	CH_3	H
8	CH_3	H	CH_3	CH_3

Method D.—Phospholenecarboxylic esters have been prepared for the first time by the sequence in eq 1 and 2.

The anion from the phospholene oxide is delocalized and is attacked by the electrophile at two sites. Subsequently, rearrangement to the conjugated acids occurs. Sufficient difference in chemical properties of the 2- and 3-phospholene oxide systems existed to allow their separation in useful quantity. The utility of the silane method of oxide reduction is extended by our observation that the presence of an ester function offers no apparent complication. Some other aspects of the synthesis and properties of the products

(7) D. K. Myers and L. D. Quin, *J. Org. Chem.*, **36**, 1285 (1971).

(8) Diazabicycloundecane (DBU) has been successfully used for the corresponding reaction in the synthesis of 1-phenylphosphole [G. Märkl and R. Potthast, *Tetrahedron Lett.*, 1755 (1968)], but it has not given as satisfactory results as *tert*-butoxide in our syntheses.

(9) Trichlorosilane in the presence of triethylamine has been found to debrominate some vicinal dibromides (*e.g.*, *trans*-1,2-dibromocyclohexane): L. D. Quin, R. L. Wells, and R. Maher, unpublished results.

(10) I. J. Borowitz, D. Weiss, and R. K. Crouch, *J. Org. Chem.*, **36**, 2377 (1971).

(11) S. T. McNeilly and J. A. Miller, *J. Chem. Soc. C*, 3007 (1971).

(12) A. P. Stewart and S. Trippett, *ibid.*, 1263 (1970).

(13) F. Mathey, *C. R. Acad. Sci.*, **269**, 1066 (1969).

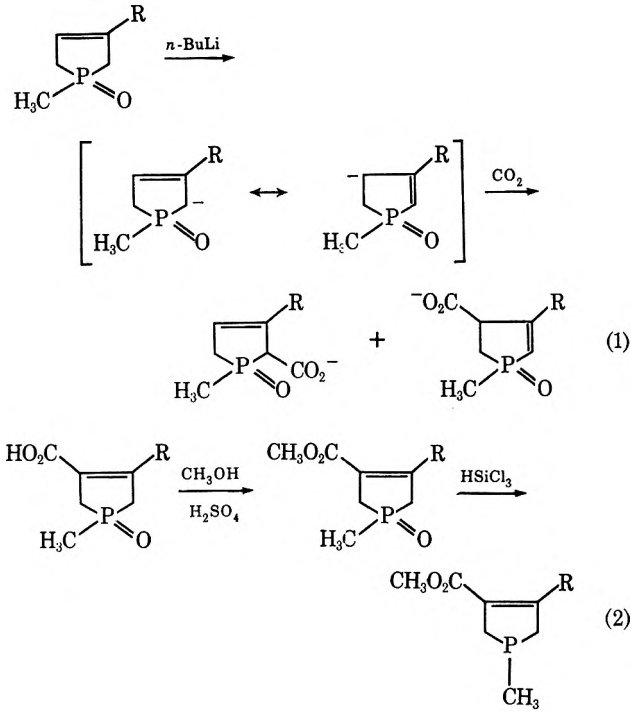
(14) L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).

TABLE I

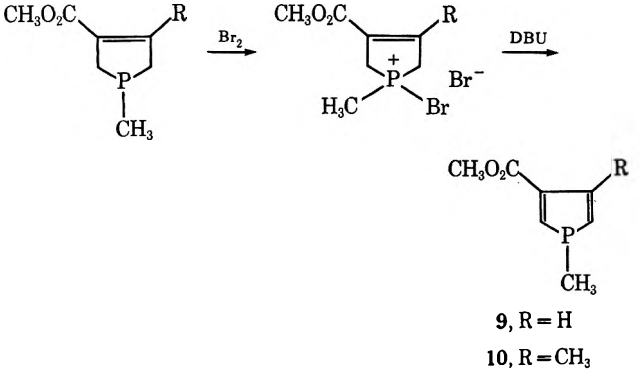
PHOSPHOLES PREPARED AND THEIR SALTS

Phosphole	Synthetic method	Mp, °C	Formula	Quaternary salts C, % Calcd	C, % Found	H, % Calcd	H, % Found	P, % Calcd	P, % Found
1-$PhCH_2$ (1)[a]	A	199–201[b,c]	$C_{18}H_{18}BrP$	62.62	62.58	5.26	5.31	8.97	8.74
1-$PhCH_2$-3-Me (5)	C	173–176[b,d]	$C_{19}H_{20}BrP$	63.52	62.99	5.61	5.45	8.62	8.78
1-$PhCH_2$-3,4-diMe (4)	B	261–264[b,d]	$C_{20}H_{22}BrP$	64.35	64.35	5.94	6.23	8.30	8.43
1,2-diMe (6)	C	177–179[c,e]	$C_7H_{12}IP$	33.09	33.02	4.76	4.88	12.19	12.14
1,3-diMe (7)	C	193–195[c,e]	$C_7H_{12}IP$	33.09	32.76	4.76	4.66	12.19	11.95
1,3,4-triMe (8)	C	181–183[d,e,f]	$C_8H_{14}IP$	35.84	35.80	5.26	5.47	11.55	11.55
1-$Ph(CH_2)_2$ (2)	A	187–189[b,c]	$C_{19}H_{20}BrP$	63.52	63.24	5.61	5.62	8.62	8.27
1-*p*-$ClC_6H_4(CH_2)_2$ (3)	A	116–118[e,g]	$C_{13}H_{15}ClIP$[c]	42.83	42.75	4.15	4.23	8.49	8.32
1-Me-3-COOMe (9)	D	*h*							
1,4-diMe-3-COOMe (10)	D	*h*							

[a] Calcd for $C_{11}H_{11}P$: C, 75.85; H, 6.37; P, 17.78. Found: C, 75.49; H, 6.74; P, 17.50. [b] Benzyl bromide salt, prepared at room temperature in benzene solution and recrystallized from methanol-ethyl acetate. [c] Dimer.[22] [d] Monomer. [e] Methyl iodide salt, from room temperature reaction in benzene; recrystallized from methanol-ether. [f] Lit.[5] mp 178–180°. [g] The nmr spectrum of a solution of this salt slowly changed to that of the dimer.[22] This implies that the initial solid is monomeric, or largely so. [h] Phosphole decomposition interfered with quaternization. These were characterized by high-resolution mass spectrometry (see Experimental Section).



are more appropriate for discussion elsewhere;[15] the phospholenes were of importance in the present program as precursors of phospholecarboxylates, the first phospholes known with a reactive functional group.



9, R = H

10, R = CH_3

The synthesis depends on the selective addition of bromine to phosphorus, giving salts which are of the same structure as would be formed from the cycloaddition reaction. Phospholes were then obtained by DBU dehydrohalogenation.[16] This general method may have much wider synthetic utility; other substituents can be placed on the phospholene oxide ring *via* their carbanions,[17] and the resulting products may lend themselves to phosphole synthesis as above.

Properties and Reactivity of the Phospholes.—The ten phospholes prepared in this study are listed in Table I with some of their properties. All were purified by distillation;[18] however, the two esters proved to be unstable at room temperature and within a few hours after distillation formed a solid brown mass. On prolonged exposure to high temperature other phospholes showed instability. Thus, in refluxing xylene, 1-benzyl-3,4-dimethylphosphole was about half decomposed after 25 hr, forming insoluble matter of indefinite nature. The phospholes were in general readily oxidized by atmospheric oxygen.

The phospholes were quaternized[22] with alkyl halides to form crystalline salts, useful for analysis (Table I). Distinct differences in the rates of quaternization were noted. 1-Benzylphosphole formed a salt with benzyl bromide very slowly (28% yield after 11 days), while in only 2 days the 3-methyl derivative gave an 83% yield, and the 3,4-dimethyl derivative a quantitative yield. This reactivity difference, noticed also by others,[5] is reflected in rates of complexation as well; neither 1-methyl- nor 1-benzylphospholes undergo

(15) L. D. Quin and S. G. Borleske, manuscript in preparation.

(16) Preliminary communication: L. D. Quin and S. G. Borleske, *Tetrahedron Lett.*, 299 (1972).

(17) F. Mathey and J. P. Lampin, *C. R. Acad. Sci.*, **270**, 1531 (1970); J. P. Lampin, F. Mathey, and B. Bartet, *Bull. Soc. Chim. Fr.*, 317 (1971).

(18) 1-Benzylphosphole (**1**) proved to be a solid (mp 34–34.5°) and was subjected to X-ray analysis. Compounds **2** and **3** were synthesized for continuation of our X-ray studies, but both proved to be liquids. Some results of the analysis of **1** have been published;[19] full details will appear elsewhere.[20] The X-ray analysis of another phosphole (1,2,5-triphenyl-) was published later;[21] the molecular parameters for this more complex derivative show no special effects attributable to delocalization.

(19) P. Coggon, J. F. Engel, A. T. McPhail, and L. D. Quin, *J. Amer. Chem. Soc.*, **92**, 5779 (1970).

(20) P. Coggon and A. T. McPhail, manuscript in preparation.

(21) W. P. Ozbirn, R. A. Jacobson, and J. C. Clardy, *Chem. Commun.*, 1062 (1971).

(22) In a separate paper, properties of these salts, some of which are dimeric, are discussed: L. D. Quin, S. G. Borleske, and J. F. Engel, *J. Org. Chem.*, **38**, 1954 (1973).

TABLE II

PROTON AND PHOSPHORUS NMR SPECTRA OF PHOSPHOLES

Phosphole	$\delta(^{31}P)$ ppm[a]	$\delta(^1H)$, ppm (J_{PH}, Hz)[b]				
		PCH_2R	CCH_3	2 H	3 H	4 H	5 H
1	−8.0	3.01 (s)[c]		Complex multiplet, 6.31–7.29			
2	−5.8	2.21–2.61 (m)[d,e]		Complex multiplet, 6.67–7.70			
3	−5.9	1.85–2.5[c,d]		Complex multiplet, 6.36–7.37			
4	+3.0	2.97 (s)[c]	1.96 (3)	6.31 (37.2)			6.31 (37.2)
5	−11.5	3.02 (s)[c]	2.03 (3)	Complex multiplet, 5.87–7.21			
6	+7.3	1.36 (1.5)[e]	2.28 (11)			Multiplet, 5.8–7.1	
7	+6.9	1.45 (1.3)[e]	2.31 (3.3)	6.52 (41)		6.93 (12.5)	7.01 (40)
8[i]	+20.2	1.22 (2)[e]	2.03 (3)	6.42 (41)			6.42 (41)
9	−3.0	1.92 (s)[f,g]		8.3 (34.5)		7.8 (17)	7.3 (38)
10	+12.6	1.96 (s)[f,h]	2.93 (3)	8.44 (33)			7.03 (39)

[a] All values are relative to external 85% H_3PO_4; 9 and 10 were run in $CDCl_3$ solution while all others were neat. [b] ^1H–^1H constants are given in Table III. [c] Neat with internal TMS. [d] Overlapped by benzylic CH_2. [e] Neat with external TMS. [f] In $CDCl_3$ with external TMS. [g] CH_3O at δ 4.26 (s). [h] CH_3O at δ 4.37 (s). [i] Reference 5.

the well-known phosphine reaction of complexation with nickel chloride, but 3,4-dimethyl-1-benzylphosphole reacts rapidly to give a typical complex.[23] These reactivity differences can be taken to imply that greater phosphine-like character (diminished electron delocalization from phosphorus) results from introduction of methyls in the two β positions. Other consequences of this substitution pattern will be noted in this paper and it is clear that effects are felt not only in chemical reactivity but in physical properties as well. Whether the influence of the substituents is electronic or steric in nature, or a combination of these, is not clear at this time. The direction of the effect is consistent with the electron-releasing characteristic of methyl,[5] but some observations will be noted that indicate that repulsive interactions occur between the adjacent methyls. If these repulsions caused some distortion of the ring carbons from planarity, or if the position of phosphorus relative to this plane (in **1**, it is out of this plane by 0.18 Å[19]) were modified slightly, then the extent of orbital overlap between the π electrons and the p orbital of phosphorus could differ slightly in the 3,4-dimethyl case. Knowledge of the behavior of phospholes with a variety of substituents seems called for to assess the relative importance of the two influences.

Spectral Properties of Phospholes.—In our study of 1-methylphosphole, some unique ultraviolet, ^1H nmr, and ^{31}P nmr spectral properties were observed. Our continued study has shown that these properties, described in the discussion to follow, are general characteristics of the phosphole system.

Uv Spectra.—In its uv spectrum, a maximum was observed for 1-methylphosphole at 285 nm (log ε 3.89, isooctane). This absorption has been found in every phosphole that we have since examined. The maximum is sensitive to conjugating substituents; the carbomethoxy group caused a pronounced shift (22 nm) to higher wavelength, a strong indication that the maximum is associated with the π electrons of the ring. Placement of a methyl on the other β carbon of the ester (as in **10**) produced a blue shift of 7 nm, in accord with steric inhibition of the conjugation. Relative to a 3-methylphosphole (**5**), the maximum for a 3,4-dimethylphosphole (**4**) is blue shifted by 5 nm. Normally, alkyl substitution in conjugated systems produces red shifts; a blue shift is common, however, when steric interaction is strong between adjacent substituents and affects conjugation, as in ortho-disubstituted benzenes. The blue-shifted uv maximum for the 3,4-dimethylphosphole case therefore is indicative of the repulsions having some effect on conjugation in the ring.

Proton Nmr Spectra.—The olefinic proton nmr spectrum (AA'BB'X) of 1-methylphosphole required computer assistance for interpretation.[3] The presence of substituents on the ring carbons has greatly facilitated the interpretation of the spectra; in many cases, olefinic signals were spread out so that spectra of first-order quality were obtained and chemical shifts and coupling constants could be measured by inspection. This was especially true where $-COOCH_3$ was present (**9** and **10**), for it added strong deshielding to adjacent CH. A methyl substituent, as in **7** and **8**, caused a useful upfield shift of adjacent CH. Phospholes with a benzyl substituent have less readily interpreted spectra, since the protons of the phenyl and the phosphole rings overlapped. The methyl effect did help in this regard, however, and in 1-benzyl-3,4-dimethylphosphole (**4**) the protons at the 2,5 positions were cleanly separated from the phenyl protons.

With the spectra of ten phospholes available (Table II), we have been able to consider in some detail the more unique properties of phospholes. (1) The ring protons, clearly in the "aromatic" region, are sensitive to substituent effects just as are those of benzene, thiophene, etc. Comparison of chemical shifts with those of olefinic protons in 2-phospholenes shows some additional deshielding, as might be expected from operation of a ring current [*cf.* δ 5.74–6.40 in 1-benzyl-2-phospholene to δ 6.31–7.29 in 1-benzylphosphole (**1**), and δ 5.90 in 1,3-dimethyl-2-phospholene[24] to δ 6.52 for the α proton in 1,3-dimethylphosphole]. (2) Values for ^{31}P–^1H coupling in 1-methylphosphole were calculated to be 38.5 Hz, an extraordinary size, and 13.8 Hz. These were assigned to the α and β protons, respectively, although the opposite assignments generally hold for phosphines. As seen especially by **4** and **8** in Table II, these assignments are now fully confirmed. Furthermore, as we have reported elsewhere,[7,14] $^2J_{PH}$ for the α proton in 2-phospholenes is of the same large size. It is not yet possible to account for this effect; it may prove to be a consequence

(23) L. D. Quin, J. G. Bryson, and J. F. Engel, *Phosphorus*, **2**, 205 (1973).

(24) L. D. Quin, J. J. Breen, and D. K. Myers, *J. Org. Chem.*, **36**, 1297 (1971).

of the bonding characteristics (C–P bond order greater than 1 through delocalization), or it may depend on the spatial relation of the α proton to the lone pair as in other cyclic phosphines. That a large value of $^2J_{PH}$ (38 Hz) has been recently reported[25] for phosphabenzene (phosphorin) should be noted in this regard. X-Ray analyses of 1-benzylphosphole[19] and of 2,6-dimethyl-4-phenylphosphorin[26] confirm the reduction in C–P bond length in these systems (1.78 and 1.74 Å, respectively) relative to saturated phosphines (*e.g.*, 1.846 Å in trimethylphosphine[27]). (3) Phosphorus coupling occurs with protons on substituents of the ring. Methyl or benzyl protons attached to phosphorus have quite small (1.3–2.0 Hz) or even unobservable values[3] for $^2J_{PH}$. *C*-methyl protons are more strongly coupled, especially at the α position. Thus, $^3J_{PH}$ for 1,2-dimethylphosphole is 11 Hz; this is a particularly large value but not unexpected from the magnitude of coupling with a proton at the α position. Similar values for α methyls have been observed by others.[4b,28] $^4J_{PH}$, as for the β methyl of 1,3-dimethylphosphole, is much smaller (3.3 Hz). These position-specific coupling constants are an aid in structure elucidation as well as spectra interpretation. (4) From the calculated spectrum[3] of 1-methylphosphole, proton–proton coupling constants were obtained. The directly measured constants of the present study are totally consistent with these values (Table III).

TABLE III

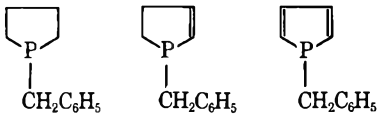
RING PROTON–PROTON COUPLING CONSTANTS[a] (HERTZ) IN PHOSPHOLES AND THIOPHENES

	$J_{H_2H_4}$	$J_{H_2H_5}$	$J_{H_4H_5}$ (or H_2H_3)
Phospholes			
1-Me[b]	1.1	3.0	7.2
1,3-diMe (**7**)	1.3	2.5	7.5
1-Me-3-COOMe (**9**)	1.5	2.5	7.5
1,4-diMe-3-COOMe (**10**)		3.0	
Thiophenes			
Unsubstituted[c]	1.0	2.9	4.7
3-Me[d]	*e*	3.0	4.9
3-COOMe[d]	1.3	2.9	5.1

[a] $J_{H_\alpha CH_3}$ values follow: for **5**, **6**, and **7**, 1.5 Hz; for **4**, **8**, and **10**, *ca.* 0.5 Hz. [b] See ref 3. [c] L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 307. [d] R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, 16, 515 (1961). [e] Not reported.

Furthermore, the values are not greatly different from those found for the corresponding thiophenes. A comparison of values for the carboxylates of the two ring systems is included in Table III. That a similarity in values should exist for these systems is not unexpected, for X-ray studies[19] have shown that bond angles and lengths in the two systems are similar and that the phosphole ring atoms deviate only slightly from coplanarity (at phosphorus). Agreement with values for pyrrole and furan would not be expected (and are not observed), for the smaller heteroatom in these rings leads to quite different molecular parameters. (5) Allylic coupling has been observed between β CH_3 groups and the α protons, causing the CH_3 doublet (from ^{31}P coupling) to split again. The magnitude of this coupling is greatest (1.5 Hz) when only one β CH_3 group is present (as in **5** and **7**); it is less than 0.5 Hz when two β CH_3 groups are present (as in **4** and **8**). Allylic coupling is well known[29] to be sensitive to geometric factors and the smaller value for the 3,4-dimethyl derivatives may imply a deviation from coplanarity for the α proton and β methyl. The suspected steric interactions between 3- and 4-methyls could cause such a deviation. Another nmr manifestation of the 3,4-dimethyl effect is the upfield shift for the α proton from a 3-methylphosphole to a 3,4-dimethylphosphole (*e.g.*, from **7** to **8**, 0.1 ppm; a larger difference, 0.4 ppm, has been reported[5] for the *n*-butylphospholes). In searching for an understanding of the origin of the 3,4-dimethyl effect, it is of importance to consider its possible occurrence among other heterocyclics where d_π–p_π conjugation cannot be implicated.[5] It is then found, for example, that for pyrroles the effect is also present (3-methylpyrrole,[30a] δ 6.42; 3,4-dimethylpyrrole,[30b] δ 6.27). The proposal[5] that dimethyl substitution on phospholes increases the extent of d_π–p_π conjugation relative to p_π–p_π conjugation[5] receives no support from this observation.

Phosphorus Spectra.—The ^{31}P nmr signal for 1-methylphosphole was located at +8.7 ppm, a value showing considerable deshielding relative to an acyclic vinylphosphine (*e.g.*, ethyl divinylphosphine, +20.8 ppm).[3] No suitable cyclic vinylphosphines were available at that time to test for the effect of the cyclic structure, however. We have now prepared the series of cyclic derivatives shown below to permit evaluation of the effect of introduction of unsaturation into a five-membered ring.



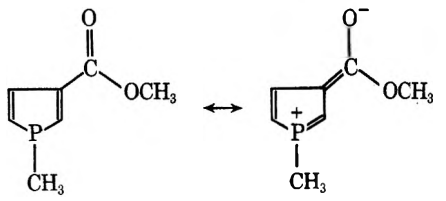
+14.4 ppm[31] 0.0 ppm −7.9 ppm

The results do reveal that both the phospholene and the phosphole possess a considerably more deshielded phosphorus than does the saturated cyclic phosphine, consistent with electron delocalization from phosphorus *via* p_π–p_π conjugation in both unsaturated systems.[24] However, an important influence on ^{31}P values is the bond angles about phosphorus,[32] and insufficient data are presently available to assess thoroughly the importance of this factor in the series above. Furthermore, conformational differences exist between saturated and unsaturated rings,[31] and these steric differences must also be taken into consideration. Nevertheless, that phospholes have the most deshielded phosphorus is, qualitatively, in ac-

(25) A. J. Ashe, III, *J. Amer. Chem. Soc.*, **93**, 3293 (1971).
(26) J. C. J. Bart and J. J. Daly, *J. Chem. Soc. A*, 567 (1970).
(27) L. S. Bartell and L. O. Brockway, *J. Chem. Phys.*, **32**, 512 (1960).
(28) G. Märkl and R. Potthast, *Angew. Chem., Int. Ed. Engl.*, **6**, 86 (1967).
(29) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 322.
(30) (a) H. Fukui, S. Shimokawa, S. Sohma, T. Iwadare, and N. Esume, *J. Mol. Spectrosc.*, **39**, 521 (1971); (b) R. A. Jones, T. M. Spotswood, and P. Cheuychit, *Tetrahedron*, **23**, 4469 (1967).
(31) J. J. Breen, J. F. Engel, D. K. Myers, and L. D. Quin, *Phosphorus*, **2**, 55 (1972).
(32) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, and J. R. Van Wazer, "Topics in Phosphorus Chemistry," Vol. 5, E. J. Griffith and M. Grayson, Ed., Wiley, New York, N. Y., 1967, Chapter 3.

cord with the concept of cyclic electron delocalization in this system. A theoretical discussion of this matter has been published recently.[5]

As seen in Table II, ^{31}P signals for other phospholes we have prepared also occur at low field. Three observations of significance can be made from these data. (1) A carbomethoxy group placed on the ring causes pronounced additional deshielding. This is easily interpretable on the basis of resonance involving this group and the ring, with further reduction of electron density on phosphorus. Indeed, this



effect may be taken as evidence supporting the delocalization explanation of deshielding at phosphorus in phospholes, since the deshielding is enhanced by a known conjugating group. (2) As in the phospholane and 3-phospholene series,[31] the phosphole ring appears to make a definite contribution to the ^{31}P value; subtracting the group contribution[33] (+21 ppm for CH_3, +4 ppm for $CH_2C_6H_5$) for the exocyclic substituent from the phosphole value leaves an increment for the ring contribution of −12 ppm in both 1-methyl- and 1-benzylphospholes. Similar constancy occurs for the ring contribution (−14 ppm) among derivatives of the 3-methylphosphole system, as well as for the 3,4-dimethylphosphole ring (−1 ppm). Such additive effects are of value[32,33] in calculating chemical shifts where experimental values are not available. (3) The ring contributions reveal a remarkable effect: one β methyl causes a small additional deshielding of P, but two β-methyl groups result in marked *shielding*[34] of phosphorus. The same effect has been noted for 1-phenyl- and 1-butylphospholes.[5] The upfield shift in the ^{31}P value may be explained on the basis of diminished electron delocalization from phosphorus, as have other manifestations of the 3,4-dimethyl effect. The fact that one β-methyl substituent causes the opposite effect (deshielding), however, makes it seem questionable that an explanation based solely on the electronic properties of methyl can suffice for this phenomenon. That steric effects which moderate conjugation in the system can influence ^{31}P shifts is seen from a consideration of the two phosphole esters **9** and **10**. In **9**, the conjugating carbomethoxy group causes additional deshielding of almost 12 ppm relative to 1-methylphosphole; placement of a methyl adjacent to carbomethoxy nullifies the effect through steric inhibition of conjugation, and even leads to shielding (by 4 ppm) relative to 1-methylphosphole.

We would also note in conclusion that ^{13}C nmr studies of phospholes have revealed the presence of steric interactions between vicinal methyls. It has been observed[36] that the upfield shift seen for substituents suffering steric crowding in benzene derivatives (*e.g.*, the methyls of *o*-ylene are upfield of those of *m*-xylene by 1.9 ppm[37]) occurs among phospholes. Thus, for **7**, the 3-CH_3 group resonates at 18.6 ppm (TMS 0), while the 3,4-dimethyl derivative **8** has a value of 17.8 ppm.

Experimental Section

General.—Melting points were taken on a Mel-Temp apparatus and are corrected, while boiling points are uncorrected. Proton nmr spectra were obtained with a Varian A-60 spectrometer or a Bruker HFX-10 spectrometer at 90 MHz. ^{31}P nmr spectra (referenced to external 85% H_3PO_4) were obtained with a Varian V-4300B spectrometer at 19.3 MHz; the Bruker instrument (36.43 MHz) was also used, under conditions of proton decoupling. Mass spectra were obtained on an AEI MS 903 mass spectrometer operated by the Research Triangle Mass Spectrometry Center. Gas chromatography (gc) was performed with a Varian Aerograph 202-1B dual column gas chromatograph using helium carrier gas and a 5 ft × 0.25 in. column packed with 20% SE-30 silicone oil on Chromosorb W. In specified cases, a similar column of 4% OV-17 on Chromosorb G was used. The flow rate was approximately 65–70 ml/min. Analyses were performed by commercial laboratories. All manipulations involving trivalent phosphorus compounds and other oxygen- or moisture-sensitive materials were done under a nitrogen atmosphere. Cycloadditions of dienes and phosphorus dihalides were performed by published procedures.[9] Reagents were commercially available except where noted by a reference to their preparation.

1-Benzyl-3-phospholene Oxide.—The adduct prepared from the benzylphosphonous dibromide[38] and butadiene adduct was hydrolyzed on ice and the aqueous layer was then extracted with four 100-ml portions of chloroform. The chloroform was stripped off and the residue was distilled to give 7.52 g of oxide, bp 151–155° (0.5 mm). Gc indicated only the 3-phospholene isomer to be present; pmr ($CDCl_3$, internal TMS) δ 5.84 (d, $^3J_{PH}$ = 28 Hz, HC=CH), 3.37 (d, $^2J_{PH}$ = 13.8 Hz, benzyl CH_2), 2.44 (d, $^2J_{PH}$ = 11 Hz, ring CH_2); ^{31}P nmr ($CDCl_3$) δ −63.2. Because of its hygroscopicity, analysis was deferred to the dibromo state (*vide infra*).

1-Benzyl-3-phospholene.—Benzylmagnesium chloride, prepared from 3.94 g (0.169 mol) of magnesium and 20.5 g (0.162 mol) of benzyl chloride in 150 ml of dry ether, was added dropwise to a well-stirred mixture of 24.4 g (0.148 mol) of 1-bromo-3-phospholene[7] and 25 ml of dry ether at 5°. A hard solid formed during the reaction. After being stirred for 1 hr at room temperature, the mixture was chilled and 100 ml of a 10% NH_4Cl solution was carefully added. The organic layer was separated and the aqueous layer was extracted three times with 20 ml of ether. The combined ether extracts were dried and distilled to give 21.1 g (81.1%): bp 80–82° (0.6 mm); pmr (neat) δ 5.79 (d, $^3J_{PH}$ = 7 Hz, HC=CH), 2.60 (s, benzyl CH_2), 2.14–2.50 (ABX, m, ring CH_2); ^{31}P nmr (neat) δ 23.4.

The phosphine was also prepared by reduction of 1-benzyl-3-phospholene oxide (7.60 g, 0.040 mol) in 125 ml of benzene (dried by distillation) with a solution of 21.4 g (0.158 mol) of trichlorosilane in 30 ml of benzene at 5°. Some gas evolution occurred. The reaction mixture was stirred for 45 min at room temperature, refluxed for 3 hr, and then cooled for hydrolysis with 125 ml of 25% NaOH solution. The benzene layer was removed and the aqueous layer was extracted twice with 15-ml portions of benzene. After drying the benzene extract, it was distilled to give 3.93 g of oxide [56.5%, bp 70–73° (0.4 mm)]. The spectra were identical with those for the first product. A sample quaternized with methyl bromide gave a salt of mp 185–186° with spectra identical with those of a specimen prepared by another route.[14]

1-Benzyl-2-phospholene Oxide.—A solution of 12.0 g (0.087 mol) of 1-chloro-2-phospholene oxide[7] in 50 ml of dry ether was

(33) S. O. Grim, W. McFarlane, and E. F. Davidoff, *J. Org. Chem.*, **32**, 781 (1967).

(34) Shielding by carbon γ to phosphorus is consistent with considerations of acyclic compounds,[35] and indeed is observed also in 3,4-dimethyl substitution in 3-phospholenes.[31] The precise nature of the steric effects would be expected to be quite dependent on the particular system involved, particularly where delocalization (as in the phospholes) and anisotropic effects (as in the 3-phospholenes) are also involved.

(35) L. D. Quin and J. J. Breen, *Org. Magn. Resonance*, in press.

(36) L. D. Quin, S. G. Borleske, and J. F. Engel, Abstracts, 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 30, 1972, No. ORGN-109.

(37) W. R. Woolfenden and D. M. Grant, *J. Amer. Chem. Soc.*, **88**, 1496 (1966).

(38) R. B. Fox, *ibid.*, **72**, 4147 (1950).

chilled in an ice bath and treated with benzylmagnesium chloride solution [prepared from 2.43 g (0.100 mol) of magnesium and 12.7 g (0.100 mol) of benzyl chloride in 115 ml of dry ether]. After stirring for 30 min at room temperature, the solution was again cooled and 100 ml of 15% NH_4Cl solution was slowly added. The ether layer was then removed and the aqueous layer was extracted four times with 50 ml of chloroform. The combined and dried ether and chloroform extracts were distilled, giving two fractions: (1) 3.23 g, bp 168–178° (0.3 mm); (2) 0.39 g, bp 179–186° (0.3 mm). Gc indicated the following ratios of 3-phospholene to 2-phospholene: (1) 1:99 and (2) 2:98. The yield of 2-phospholene oxide was 3.61 g (21.3%); pmr ($CDCl_3$, internal TMS) δ 5.9–6.65 (m, HC=CH), 3.29 (d, $^3J_{PH}$ = 15 Hz, benzylic CH_2), 1.6–2.7 (m, ring CH_2); ^{31}P nmr ($CDCl_3$) δ −67.7.

1-Benzyl-2-phospholene.—A solution of 3.30 g (0.017 mol) of 1-benzyl-2-phospholene oxide and 100 ml of benzene was dried by distilling off 20 ml of benzene. It was treated with 9.3 g (0.069 mol) of trichlorosilane in 15 ml of benzene, while being cooled with an ice–water bath. The mixture was brought to room temperature and then refluxed for 3 hr. The solution was again cooled and 125 ml of 20% NaOH was added cautiously. The organic layer was removed and the aqueous layer was extracted three times with 20 ml of benzene. The combined benzene portions, after being dried, were distilled, giving 1.40 g (46.2%): bp 80–83° (0.3 mm); pmr (CD_3COCD_3, internal TMS) δ 5.74–6.41 (m, HC=CH), 2.76 (broad s, benzylic CH_2), 1.5–2.6 (m, ring CH_2); ^{31}P nmr (CD_3COCD_3) δ 0.0. The benzyl bromide salt, formed in benzene and recrystallized from methanol–ethyl acetate, had mp 230–231°, ^{31}P nmr ($CDCl_3$) δ −61.8.

Anal. Calcd for $C_{18}H_{25}BrP$: C, 62.26; H, 5.80; Br, 23.01; P, 8.92. Found: C, 62.45; H, 5.53; Br, 23.33; P, 9.21.

1-Benzyl-3,4-dibromophospholane.—A solution of 1-benzyl-3,4-dibromophospholane oxide (17.4 g, 0.0493 mol) and 350 ml of benzene was dried by distilling off 90 ml of benzene. While at 0°, the solution was treated dropwise with 33.2 g (0.246 mol) of trichlorosilane. The ice bath was removed and within 30 min a homogeneous solution resulted. This solution was stirred for 1 hr at room temperature, whereupon slight cloudiness occurred. The solution was cooled to about 0° and 125 ml of 30% NaOH solution was added cautiously. Considerable foaming occurred. The benzene layer was then removed and the aqueous layer was extracted three times with benzene. The combined benzene portions were dried and filtered through glass wool to remove the drying agent. The total volume of benzene solution was 300 ml. A 10.0-ml aliquot required 45.30 ml of a 0.0245 *M* I_2 solution (standardized against As_2O_3), indicating 0.0333 mol (67.5%) of phospholane to be present. Another 10-ml aliquot was treated with an excess of methyl bromide and stirred for 46 hr. The resulting salt (0.05 g, 70.7% based on starting oxide) after recrystallization from methanol–ethyl acetate had mp 167–169°. The pmr and ir spectra were identical with those of the salt (mp 172°) obtained[3] by treating 3,4-dibromo-1-methylphospholane with benzyl bromide.

1-Benzyl-3,4-dibromophospholane Oxide.—To a well-stirred mixture of 21.1 g (0.120 mol) of 1-benzyl-3-phospholene and 100 ml of cyclohexane at 5° was added dropwise a solution of 38.0 g (0.24 mol) of bromine in 50 ml of cyclohexane. A hard, granular orange solid formed. After the addition was complete, the reaction mixture was stirred for 1 hr at room temperature and then filtered; the resulting orange solid was immediately hydrolyzed with ice, giving an orange, gummy substance. This gum was dissolved and removed from the aqueous layer by several extractions with chloroform (total volume about 1.2 l.). Removal of chloroform from the extracts left a solid residue which was recrystallized from isopropyl alcohol, giving 37.0 g (87.8%) of white needles, mp 158–159°.

Anal. Calcd for $C_{11}H_{13}Br_2OP$: C, 37.53; H, 3.72; Br, 45.40; P, 8.79. Found: C, 37.48; H, 3.86; Br, 45.03; P, 8.65.

The oxide was also obtained (89.9% yield) by addition of bromine to the phospholene oxide, following a published procedure.[14]

1-Benzylphosphole (1) by Method A.—A solution of 16.4 g (0.0488 mol) of 1-benzyl-3,4-dibromophospholane in 475 ml of benzene was treated with 22.6 g (0.200 mol) of potassium *tert*-butoxide over a 45-min period at room temperature. The reaction was mildly exothermic and was accompanied by rapid darkening of the solution. After an additional 3 hr, 10 g of ice was added and, after stirring for 45 min, the benzene layer was removed and then washed twice with 25 ml of saturated $NaHCO_3$ solution. Distillation gave 3.89 g at 76–81° (0.3 mm). Gc of this distillate showed two peaks in the ratio of 4:1; the minor peak was 1-benzyl-3-phospholene from its ^{31}P nmr chemical shift and gc retention time. It was removed by washing the crude product (in 10 ml of benzene) with four 10-ml portions of 2 *N* HCl, then with two 10-ml portions of saturated $NaHCO_3$ solution, and finally with 5 ml of water. The solution was dried ($MgSO_4$) and then distilled (71–72°, 0.2 mm) to give 2.22 g (26%) of 1. This liquid solidified upon standing, mp 34–34.5° (sealed capillary). Gc showed less than 2% of phospholene remaining; nmr, see Table II; uv (95% ethanol) λ_{max} 286 nm (log ϵ 3.56); benzyl bromide salt, see Table I. An attempt to prepare 1 by method C from the benzylphosphonous dibromide–butadiene adduct gave less than 2% of a crude product.

1-(2-Phenylethyl)-3-phospholene.—Using the procedure employed for the preparation of 1-benzyl-3-phospholene, β-phenethylmagnesium bromide [from 3.30 g (0.136 g-atom) of magnesium and 21.0 g (0.114 mol) of freshly distilled β-phenethyl bromide in 150 ml of dry ether] was added to 17.2 g (0.103 mol) of 1-bromo-3-phospholene[7] in 50 ml of dry ether. The product was worked up also as before. Distillation gave 14.3 g (76.4%): bp 85–94° (0.1–0.2 mm); pmr (neat, external TMS) δ 5.93 (d, $^3J_{PH}$ = 7 Hz, HC=CH); ^{31}P nmr (neat) δ +29.9. The salt formed with methyl bromide in benzene had mp 156–158° after two recrystallizations from methanol–ethyl acetate; pmr (CF_3COOH, external TMS) δ 5.97 (d, $^3J_{PH}$ = 28 Hz, HC=CH), 2.35 (d, $^2J_{PH}$ = 15 Hz, PCH_3).

Anal. Calcd for $C_{13}H_{18}BrP$: C, 54.75; H, 6.35; Br, 28.02; P, 10.86. Found: C, 54.36; H, 6.57; Br, 27.88; P, 10.87.

3,4-Dibromo-1-(2-phenylethyl)phospholane Oxide.—Using the procedure for the bromination of 1-benzyl-3-phospholene oxide, 1.3 g (0.068 mol) of 1-(2-phenylethyl)-3-phospholene in 125 ml of cyclohexane was treated with 21.9 g (0.137 mol) of bromine in 25 ml of cyclohexane. The product was recrystallized twice from aqueous methanol to give 20.6 g (82.3%) of a light tan solid, mp 116–117.5°.

Anal. Calcd for $C_{12}H_{15}Br_2OP$: C, 39.38; H, 4.13; Br, 43.66; P, 8.46. Found: C, 39.68; H, 4.33; Br, 43.60; P, 8.54.

3,4-Dibromo-1-(2-phenylethyl)phospholane.—Using the same procedure as employed for the 1-benzyl compound, 18.5 g (0.0508 mol) of 3,4-dibromo-1-(2-phenylethyl)phospholane oxide in 450 ml of dry benzene was reduced with 27.7 g (0.203 mol) of trichlorosilane. The total volume of benzene solution after work-up was 425 ml; a 5.00-ml aliquot required 20.70 ml of 0.0224 *M* I_2 solution, indicating 0.0394 mol (77.6%) of phospholane to have been formed.

The salt formed from another 10-ml aliquot with methyl bromide weighed 0.37 g (69.9%) and after three recrystallizations from methanol–ethyl acetate had mp 140–142°.

Anal. Calcd for $C_{13}H_{18}Br_3P$: C, 35.09; H, 4.08; Br, 53.87; P, 6.96. Found: C, 34.81; H, 4.01; Br, 53.78; P, 7.07.

1-(2-Phenylethyl)phosphole (2).—Using method A as employed for the preparation of 1, 13.3 g (0.039 mol) of 3,4-dibromo-1-(2-phenylethyl)phospholane in 410 ml of benzene was dehydrobrominated with 11.0 g (0.098 mol) of potassium *tert*-butoxide. Distillation gave 1.70 g of tan liquid, bp 91–93° (0.2 mm). Gc (170°) showed two peaks in a ratio of 3:2. The minor peak was shown to be 1-(2-phenylethyl)-3-phosphole by ^{31}P nmr and gc. After the acid wash, distillation gave 0.74 g (10.1%), bp 91–92° (0.2 mm), free of phospholene (gc): nmr, see Table II; uv (95% ethanol) 284 nm (log ϵ 3.93); benzyl bromide salt, see Table I.

1-(*p*-Chloro-2-phenylethyl)-3-phospholene.—Using the procedure employed for the 1-benzyl compound, *p*-chloro-β-phenethylmagnesium bromide [prepared from 5.84 g (0.240 g-atom) of magnesium and 45.6 g (0.209 ml) of freshly distilled *p*-chloro-β-phenethyl bromide[39] in 275 ml of dry ether] was added to 31.6 g (0.190 mol) of 1-bromo-3-phospholene[7] in 80 ml of dry ether. Distillation gave 22.6 g (53.4%) at 124–131° (1.2 mm): pmr (neat, external TMS) 6.12 (d, $^3J_{PH}$ = 8 Hz, HC=CH); ^{31}P nmr (neat) δ +28.6. The phospholene was used directly in the next step of the phosphole synthesis.

3,4-Dibromo-1-(*p*-chloro-2-phenylethyl)phospholane Oxide.—Using the same procedure as for the 1-benzyl compound, 20.4 g (0.091 mol) of 1-(*p*-chloro-2-phenylethyl)-3-phospholene in 150 ml of cyclohexane was treated with 29.0 g (0.182 mol) of bromine in 30 ml of cyclohexane. The product was recrystallized three times from aqueous methanol, giving 26.9 g (74.5%), mp 124–126°.

(39) R. W. Griffin, J. D. Gass, M. A. Berwick, and R. S. Shulman, *J. Org. Chem.*, **29**, 2109 (1964).

Anal. Calcd for $C_{12}H_{14}Br_2ClOP$: C, 35.99; H, 3.52; P, 7.73. Found: C, 35.78; H, 3.32; P, 7.73.

3,4-Dibromo-1-(*p*-chloro-2-phenylethyl)phospholane.—Using the same procedure as for the 1-benzyl compounds, 25.0 g (0.0628 mol) of 3,4-dibromo-1-(*p*-chloro-2-phenylethyl)phospholane oxide in 450 ml of dry benzene was reduced with 34.0 g (0.251 mol) of trichlorosilane. The total volume of the benzene solution was 470 ml; a 5.00-ml aliquot required 23.40 ml of 0.0232 *M* I_2 solution, indicating 0.0543 mol (81.3%) of phospholane to have been formed. The phospholane was not isolated from the benzene solution, but was used directly in the next step.

1-(*p*-Chloro-2-phenylethyl)phosphole (3).—Using method A as in the preparation of 1, 18.9 g (0.049 mol) of 3,4-dibromo-1-(*p*-chloro-2-phenylethyl)phospholane in 455 ml of benzene was dehydrobrominated with 14.3 g (0.127 mol) of potassium *tert*-butoxide. Distillation gave 3.91 g of a tan liquid, bp 123–135° (0.85 mm). Gc (170°) indicated two products in a 3:1 ratio, the minor one being 1-(*p*-chloro-2-phenylethyl)-3-phospholene. After the acid wash, distillation gave 1.91 g of **3** (17.3%), bp 118–122° (0.7 mm), containing only 2% of phosphole (gc): nmr, see Table II; uv (95% ethanol) λ_{max} 285 nm (log ϵ 3.85); benzyl bromide salt, see Table I.

Quaternization of 1-Bromo-3,4-dimethyl-3-phospholene. A. With Methyl Bromide.—A mixture consisting of 9.73 g (0.050 mol) of 1-bromo-3,4-dimethyl-3-phospholene, 5 ml (*ca.* 0.10 mol) of methyl bromide, and 25 ml of cyclohexane was placed in a brown, narrow-mouth bottle and the cap was then sealed. After 2 months, the precipitated white solid was collected, washed with *n*-pentane, and dried (5.4 g, 37.4%). A sample on hydrolysis gave the known[14] 1,3,4-trimethylphospholene oxide.

B. With Benzyl Bromide.—A mixture of 34.2 g (0.175 mol) of 1-bromo-3,4-dimethyl-3-phospholene, 30.6 g (0.18 mol) of benzyl bromide, and 80 ml of cyclohexane after standing for 5 weeks gave 37.5 g (58.8%) of salt, used directly in the synthesis of **4**.

1-Benzyl-3,4-dimethylphosphole (4).—To 32.7 g (0.090 mol) of 1-bromo-1-benzyl-3,4-dimethyl-3-phospholenium bromide from above in 250 ml of benzene at room temperature was added dropwise a solution of 29.0 g (0.190 mol) of DBU in 50 ml of benzene. The solution was stirred for 45 min and then refluxed for 3.5 hr. The solution was filtered through a sintered glass funnel and then distilled to give 8.77 g of tan liquid, bp 83–107° (0.3 mm). After an acid wash, a second distillation gave 5.23 g (28.6%), bp 92–94° (0.3 mm). Less than 2% 1-benzyl-3,4-dimethyl-3-phospholene[32] remained (gc): nmr, see Table II; uv (95% ethanol) λ_{max} 280 nm (log ϵ 3.26); benzyl bromide salt, see Table I.

1-Benzyl-3-methylphosphole (5).—Using the same procedure, 22.0 g (0.063 mol) of the benzylphosphonous dibromide–isoprene cycloadduct in 100 ml of benzene was dehydrobrominated with a solution of 21.0 g (0.133 mol) of DBU in 25 ml of benzene. The product was worked up as before. Final distillation gave 0.88 g (7.4%), bp 84–85° (0.3 mm). Gc indicated only the phosphole to be present: nmr, see Table II; uv (95% ethanol) λ_{max} 285 nm (log ϵ 3.58); benzyl bromide salt, see Table I.

1,2-Dimethylphosphole (6).—To 26.8 g (0.145 mol) of the cycloadduct[40] of CH_3PCl_2 and 1,3-pentadiene in 150 ml of petroleum ether (bp 30–60°) and 50 ml of methylene chloride was added 44 g (0.29 mol) of DBU in four portions over 10 min. The reaction was moderated with an ice bath. The mixture was stirred at 25° for 3.5 hr, insoluble material was separated, and then the upper (organic) layer was recovered, washed with water, and dried over $MgSO_4$. Distillation gave 2.2 g (14%) of **6**, bp 98–100° (500 mm). Gc (OV-17 at 100°) showed the presence of 6% of 1,2-dimethyl-3-phospholene.[40] Nmr data (Table II) were collected on the 1,2-dimethylphosphole without purification. The phosphole was analyzed as its methyl iodide salt (Table I).

1,3-Dimethylphosphole (7).—A slurry of 5.2 g (0.03 mol) of the cycloadduct[14] of CH_3PCl_2 and isoprene in 50 ml of petroleum ether and 10 ml of methylene chloride was treated with a solution of 9.35 g (0.06 mol) of DBU and 10 ml of methylene chloride; 30 ml of methylene chloride was then added to thin the slurry. The product was worked up as for **6**, giving 0.4 g (12%) of **7**, bp 110–112° (500 mm). Gc (OV-17 column at 100°) showed the presence of only one component. Nmr data are given in Table II. Analysis of the methiodide, recrystallized from methanol–ether, is given in Table I.

1,3,4-Trimethylphosphole (8).—The adduct[14] of 2,3-dimethylbutadiene and CH_3PCl_2 was placed in a mixture of 150 ml of dry petroleum ether and 40 ml of dry methylene chloride. With gentle stirring, 43 ml (66 g, 0.43 mol) of DBU was added in four portions over a 10-min period. The reaction and work-up were conducted as for **6**. Distillation gave 3.5 g (12.7%) of **8**, bp 135–136° (500 mm) [lit.[5] bp 60° (15 mm)]. Gc (OV-17 at 125°) showed 1% of 1,3,4-trimethyl-3-phospholene[14] to be present. Analysis of the methiodide, recrystallized from methanol–ether, is given in Table I; nmr data for **8** are in Table II.

1-Methyl-3-phospholene 1-Oxide 3-Carboxylic Acid and Its Methyl Ester.—To a solution of 200 ml of anhydrous tetrahydrofuran (THF) and 165 ml of 2.38 *M* *n*-butyllithium (0.39 mol) in hexane at −75° was added dropwise a solution of 41.6 g (0.36 mol) of freshly distilled 1-methyl-3-phospholene 1-oxide. A yellowish-orange color developed. Stirring was continued for 10 min and then the solution was transferred into a vigorously stirred Dry Ice–ether slurry, avoiding contact with the atmosphere. The reaction mixture (a white slurry) was stirred for several hours without temperature control, and then hydrolyzed with 500 ml of water. The aqueous solution was separated and acidified with 250 ml (wet volume) of Dowex 50-WX8 (H^+) ion exchange resin. After CO_2 evolution had ceased, the supernatant liquid was passed through a column (5 × 50 cm) of fresh resin to complete the acidification. The resin was eluted with water until the pH of the eluate was 6.5–7.0. The solution was evaporated *in vacuo;* the gummy yellow residue was dried further over P_2O_5 in a vacuum oven (40°, 1 mm, for 24 hr). The residue was dissolved in 150 ml of hot chloroform and placed in a freezer for 4–8 hr. From this solution 7.0 g of a white solid precipitated; reduction of the filtrate volume to 100 ml gave more solid. By a process of adding benzene and then reducing the solution volume, repeated several times, additional crops of solid were obtained (total 32.3 g, 56%). The product was a mixture of the desired compound (30%) and the isomeric 2-phospholene oxide 3-carboxylic acid (70%). They were not readily separated and the mixture was subjected directly to esterification with methanol containing concentrated sulfuric acid (2 drops to 50 ml for a 2-g sample). After 10 hr reflux, the methanol was stripped off and the residue was dissolved in water. The solution was neutralized with sodium bicarbonate and extracted three times with chloroform. The combined organic extracts were dried (Na_2SO_4) and stripped of solvent on a rotary evaporator. The residual oil was further dried at 1 mm. The isomer separation was then accomplished by placing the residue in benzene and after 7 days adding ether until a yellow oil (a polymer of the 2-phospholene derivative) dropped out of solution. The solution was decanted from the oil, and removal of the solvent gave the desired methyl 1-methyl-3-phospholene 1-oxide 3-carboxylate (80% from the corresponding acid). The isomers were also separable on a silica gel chromatographic column. The compound was not readily purified by distillation because of instability. The crude sample sufficed for spectral identification: pmr ($CDCl_3$, internal TMS) δ 6.96 (d, $^3J_{PH}$ = 31 Hz, C=CH), 3.79 (s, OCH_3), 2.82 (4 H, d, $^2J_{PH}$ = 11 Hz, ring CH_2), 1.73 (d, $^2J_{PH}$ = 13.5 Hz, PCH_3); ir (neat) $\nu_{C=O}$ 1720, $\nu_{C=C}$ 1630, ν_{CO} 1280, 1215, $\nu_{P=O}$ 1175 cm^{-1}.

Methyl 1-Methyl-3-phospholene-3-carboxylate.—A solution of 2.5 g (0.016 mol) of methyl 1-methyl-3-phospholene 1-oxide 3-carboxylate and 100 ml of benzene was first dried by distilling off 20 ml of benzene, and then cooled to 5° for dropwise addition of 6.7 g (0.05 mol) of trichlorosilane in 10 ml of benzene. After the addition was complete, the solution was stirred at 25° for 4 hr. The flask was placed in an ice bath and several pieces of ice were added to destroy excess trichlorosilane. To the white, gelatinous mixture, 50 ml of 40% sodium hydroxide solution was added slowly with stirring. The benzene layer was recovered, washed with 10 ml of water, and dried over sodium sulfate. Distillation gave 0.70 g (32%): bp 41–42° (0.1 mm); pmr ($CDCl_3$, external TMS) δ 7.34–7.58 (m, C=CH), 4.23 (s, OCH_3), 2.4–3.6 (4 H, m, CH_2), 1.45 (d, $^2J_{PH}$ = 3 Hz, PCH_3); ^{31}P nmr ($CDCl_3$) δ +33.5. The methiodide, recrystallized from isopropyl alcohol–ether, had mp 189–191°.

Anal. Calcd for $C_8H_{14}IO_2P$: C, 32.02; H, 4.70; P, 10.32. Found: C, 31.85; H, 4.99; P, 10.40.

Methyl 1-Methylphosphole-3-carboxylate (9).—A solution of 2.1 g (0.013 mol) of methyl 1-methyl-3-phospholene-3-carboxylate in 100 ml of petroleum ether cooled with an ice bath was treated dropwise with 2.1 g (0.013 mol) of bromine in 30 ml of methylene chloride. The precipitated phospholenium bromide (yellow) was allowed to settle and the solvent was decanted. The solid was then washed twice with 50-ml portions of petroleum ether,

(40) L. D. Quin and T. P. Barket, *J. Amer. Chem. Soc.*, **92**, 4303 (1970).

covered with 30 ml of benzene, and while at 0–5° treated with a solution of 4.0 g (0.026 mol) of DBU and 10 ml of benzene, added in three portions over a 10-min period. Slight darkening was observed; 40 ml of methylene chloride was added (10 min), during which time the slurry turned black. Vigorous stirring was continued at 0–5° for 3 hr. The mixture was filtered from a gummy solid and the filtrate was washed twice with 50-ml portions of deoxygenated water. Gc (SE-30, 150°) indicated the presence of one component with a retention time of 5 min; no need was indicated for acid washing. The dried (Na_2SO_4) solution was distilled at 20 mm to remove solvent. The black residue was then rapidly distilled directly into a receiver chilled by a Dry Ice–acetone bath. A total of 0.47 g (23%) of 9 was collected at 40–50° (0.1 mm). The liquid remained colorless in the Dry Ice–acetone bath, but darkened rapidly at 25° and precipitated black solid. The purity of the product (gc, 150°, 5 min retention time) exceeded 95%; the impurity was methyl 1-methyl-3-phospholene-3-carboxylate (4 min retention). The nmr data (Table II) were collected on the sample without further purification. Quaternization with methyl iodide was very slow and gave salt badly contaminated with the decomposition material. It could not be successfully analyzed. The mass spectrum of 9 showed a molecular ion of *m/e* 156.0334 (calcd for $C_7H_9O_2P$, 156.0341) (at 17.5% abundance, it was the base peak); uv (cyclohexane) λ_{max} 307 nm; ir (neat) ν_{CH} 3110, $\nu_{C=O}$ 1720, $\nu_{C=C}$ 1535, ν_{CO} 1250 and 1186; 1075 (s), 1062 (s), 888 (m), 793 (s), 740 (s), and 700 cm^{-1} (s).

1,4-Dimethyl-3-phospholene 1-Oxide 3-Carboxylic Acid and Its Methyl Ester.—A solution of 300 ml of THF, 30 ml of tetramethylethylenediamine, and 73 ml of 2.5 *M* *n*-butyllithium at −75° was treated with a solution of 21.4 g (0.17 mol) of 1,3-dimethyl-3-phospholene 1-oxide in 25 ml of THF. As for the previously prepared acid, the mixture was carbonated, acidified by the ion-exchange procedure, and crystallized from chloroform and benzene. The yield was 8.5 g (30%), consisting of 70% of the desired compound and 30% of the isomeric 1,3-dimethyl-2-phospholene 1-oxide 2-carboxylic acid. The unwanted isomer was readily removed by its greater solubility in chloroform; addition of 8 g of the mixture to about 50 ml of chloroform at room temperature completely removed the 2-phospholene and left the desired acid as a residue. Recrystallization from methanol–ether gave a sample of mp 193–195°: pmr (D_2O, external TMS) δ 3.3–3.6 (4 H m, CH_2), 2.68 (broad s, CCH_3), 2.27 (d, $^2J_{PH}$ = 14 Hz, PCH_3); no C=CH signal was present.

Anal. Calcd for $C_7H_{11}O_3P$: C, 48.26; H, 6.37; P, 17.74. Found: C, 48.06; H, 6.36; P, 17.63.

The methyl ester was prepared by treating a refluxing mixture of 3.0 g (0.017 mol) of the acid in 75 ml of *tert*-butyl alcohol containing 2.62 g (0.019 mol) of potassium carbonate with 2.43 g (0.019 mol) of dimethyl sulfate. After 5 hr of reflux, the mixture was filtered and solvent was stripped from the filtrate. The residue, in 75 ml of chloroform, was extracted with 20 ml of 0.5 *M* hydrochloric acid. The organic solution was dried (Na_2SO_4) and stripped to leave 2.4 g of an oil (76%): pmr ($CDCl_3$, external TMS) δ 4.2 (s, OCH_3), 3.1–3.5 (4 H, broad d, CH_2), 2.7 (s, CCH_3), 2.15 (d, $^2J_{PH}$ = 13.5 Hz); ^{31}P nmr (D_2O) δ −68.9; ir $\nu_{C=O}$ 1722, $\nu_{C=C}$ 1642, ν_{CO} 1300, 1230, $\nu_{P=O}$ 1175 cm^{-1}.

Methyl 1,4-Dimethyl-3-phospholene-3-carboxylate.—A solution of 0.60 g (0.003 mol) of methyl 1,4-dimethyl-3-phospholene 1-oxide 3-carboxylate and 100 ml of benzene was dried by distilling off 20 ml of benzene. A solution of 1.40 g (0.01 mol) of trichlorosilane and 10 ml of benzene was added dropwise over 15 min with ice-bath chilling. The reaction mixture was then stirred at 25° for 3 hr, and again cooled, and the excess trichlorosilane was destroyed by the addition of several pieces of ice and then 25 ml of 20% sodium hydroxide. The benzene layer was isolated, washed with 10 ml of H_2O, and dried over sodium sulfate. Distillation yielded 0.22 g (40%) of a colorless liquid: bp 73–74° (0.5 mm); pmr ($CDCl_3$, internal TMS) δ 3.75 (s, OCH_3), 1.8–3.2 (4 H, m, CH_2), 2.21 (s, CCH_3), 0.93 (d, $^2J_{PH}$ = 3 Hz, PCH_3); ^{31}P nmr (neat) δ +46.1. The methiodide (very hygroscopic), recrystallized from isopropyl alcohol–ether, had mp 144.5–145.5°.

Anal. Calcd for $C_9H_{16}IO_2P$: C, 34.41; H, 5.13; P, 9.86. Found: C, 34.13; H, 5.62; P, 9.67.

Methyl 1,4-Dimethylphosphole-3-carboxylate (10).—A solution of 1.11 g (0.0064 mol) of methyl 1,4-dimethyl-3-phospholene-3-carboxylate,[15] 5 ml of methylene chloride, and 90 ml of petroleum ether was treated with 1.14 g (0.0070 mol) of bromine in 10 ml of methylene chloride as in the synthesis of 9. The product was treated with a solution of 1.9 g (0.013 mol) of DBU in 20 ml of benzene. After work-up, gc (OV-17 at 150°) indicated the presence of the starting phospholene, the phosphole, and DBU. The solution was therefore washed very rapidly with 20 ml of cold 0.05 *M* HCl. The organic layer was dried over sodium sulfate, and the solvent was stripped off at 20 mm. The black residue was rapidly distilled under high vacuum directly into a receiver chilled by a Dry Ice–acetone bath. Methyl 1,4-dimethylphosphole-3-carboxylate (0.25 g, 23%) was collected at 67° (0.3 mm). The colorless liquid obtained was unstable at 25°, but solidified in, and could be preserved in, a Dry Ice–acetone bath. The purity of the product (gc) exceeded 98%, with an impurity of methyl 1,4-dimethyl-3-phospholene-3-carboxylate. The base peak in the mass spectrum was the molecular ion of *m/e* 170.0502 (calcd for $C_8H_{11}O_2P$, 170.0479) in 20.0% abundance; uv (cyclohexane) λ_{max} 300 nm; ir (neat) ν_{CH} 3110, $\nu_{C=O}$ 1725, $\nu_{C=C}$ 1560, ν_{CO} 1250 and 1190, 1035 (s), 886 (m), 774 cm^{-1} (m).

Registry No.—**1**, 29853-74-5; **1** benzyl bromo salt dimer, 38863-80-8; **2**, 38864-26-5; **2** benzyl bromo salt, 38864-27-6; **3**, 38864-28-7; **3** MeI, 38864-29-8; **4**, 38864-30-1; **4** benzyl bromo salt, 38864-31-2; **5**, 38864-32-3; **5** benzyl bromo salt, 38857-58-8; **6**, 38864-34-5; **6** MeI dimer, 38884-24-1; **7**, 38864-35-6; **7** MeI dimer, 38884-25-2; **8**, 37739-99-4; **9**, 36163-75-4; **10**, 38864-38-9; benzylphosphonous dibromide–butadiene adduct, 38864-39-0; 1-benzyl-3-phospholene oxide, 38864-40-3; benzyl chloride, 100-44-7; 1-bromo-3-phospholene, 28273-34-9; 1-benzyl-3-phospholene, 28278-53-7; 1-benzyl-3-phospholene methyl bromide salt, 1130-42-3; 1-chloro-2-phospholene oxide, 1003-18-5; 1-benzyl-2-phospholene oxide, 38864-45-8; 1-benzyl-2-phospholene, 28278-52-6; 1-benzyl-2-phospholene benzyl bromide salt, 38864-47-0; 1-benzyl-3,4-dibromophospholane oxide, 38864-48-1; 1-benzyl-3,4-dibromophospholane, 38864-49-2; 1-benzyl-3,4-dibromophospholane methyl bromide salt, 1130-42-3; β-phenethyl bromide, 103-63-9; 1-(2-phenylethyl)-3-phospholene, 38864-51-6; 1-(2-phenylethyl)-3-phospholene methyl bromide salt, 38864-52-7; 3,4-dibromo-1-(2-phenylethyl)phospholane oxide, 38864-53-8; 3,4-dibromo-1-(2-phenylethyl)phospholane, 38864-54-9; 3,4-dibromo-1-(2-phenylethyl)-phospholane methyl bromide salt, 38864-55-0; *p*-chloro-β-phenethyl bromide, 6529-53-9; 1-(*p*-chloro-2-phenyl; ethyl)-3-phospholene, 38864-56-1; 3,4-dibromo-1-(*p*-chloro-2-phenylethyl)phospholane oxide, 38864-57-2-3,4-dibromo-1-(*p*-chloro-2-phenylethyl)phospholane, 38864-58-3; 1-bromo-3,4-dimethyl-3-phospholene, 28273-33-8; 1-bromo-1-benzyl-3,4-dimethyl-3-phospholene bromide, 38906-68-2; benzyl phosphonous dibromide–isoprene adduct, 38864-60-7; cycloadduct of CH_3PCl_2 and 1,3-pentadiene, 38864-61-8; cycloadduct of CH_3PCl_2 and isoprene, 36044-15-2; cycloadduct of CH_3PCl_2 and 2,3-dimethylbutadiene, 38864-63-0; 1-methyl-3-phospholene 1-oxide 930-38-1; 1-methyl-3-phospholene 1-oxide 3-carboxylic acid, 38864-65-2; methyl 1-methyl-3-phospholene 1-oxide 3-carboxylate, 38864-66-3; methyl 1-methyl-3-phospholene-3-carboxylate, 36163-72-1; methyl 1-methyl-3-phospholene-3-carboxylate methyl iodide salt, 36163-73-2; 1,3-dimethyl-3-phospholene 1-oxide, 15450-79-0; 1,4-dimethyl-3-phospholene 1-oxide 3-carboxylic acid, 38864-70-9; 1,4-dimethyl-3-phospholene 1-oxide 3-carboxylic acid methyl ester, 38864-71-0; methyl 1,4-dimethyl-3-phospholene-3-carboxylate 38864-72-1; methyl 1,4-dimethyl-3-phospholene-3-carboxylate methyl iodide salt, 38864-73-2.

Base-Induced Rearrangement of Ethane-2-chloro-1-hydroxy-1,1-diphosphonic Acid

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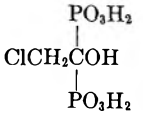
Ethane-2-chloro-1-hydroxy-1,1-diphosphonic acid is readily dehydrohalogenated on treatment with aqueous base. The rate of chloride loss displays a first-order dependency on the concentration of the parent diphosphonate, and is greatly influenced by the degree of neutralization of the parent acid. The product isolated after all chloride has been removed is $Na_2O_3PCH_2C(O)PO_3Na_2$, wherein one of the geminal phosphonate groups has undergone a 1,2 shift. This structure is deduced from ^{31}P, ^{1}H, and ^{13}C nmr spectra, and is consistent with ir and uv spectral patterns. Stabilities of various acid and salt forms of this new carbonyl phosphonate are discussed and its conversion to ethane-1-hydroxy-1,1,2-triphosphonic acid *via* addition to the carbonyl group is demonstrated.

Recent publications from these laboratories have described general methods of preparation of alkyl-1-hydroxy-1,1-diphosphonic acids[1,2] and their esters.[3] In exploring methods for converting one such compound, ethane-2-chloro-1-hydroxy-1,1-diphosphonic acid, to another, ethane-1-hydroxy-1,1,2-triphosphonic acid, the complex solution chemistry described in this paper was elucidated.

The preparation of ethane-2-chloro-1-hydroxy-1,1-diphosphonic acid (I) from chloroacetic acid and



I

P_4O_6 has been briefly described.[1] Phosphorus and proton nmr spectra are consistent with the assigned structure. The ^{31}P nmr spectrum (aqueous solution) consists of a triplet centered at δ −15.6 ppm (J_{H-P} = 11 Hz). The CH_2 protons appear as a triplet in the ^{1}H nmr spectrum centered at τ 5.38 ppm (J = 11.5 Hz).

The acid form of I is stable in water to a temperature of ~100°, whereupon slow decomposition begins (oxygen was not excluded from the system). The phosphorus-containing product of this decomposition is H_3PO_4. When I is titrated with aqueous base, dehydrohalogenation occurs. If I remained intact at high pH, the expected titration curve, based on the behavior of analogous diphosphonic acids,[1] would have end points at 2, 3, and 4 equiv of base. Titration curves A and B of Figure 1 indicate a normal first end point (2 equiv). This was substantiated by silver nitrate titration, which showed that no free Cl^- was present in solution at this point.

After 5 equiv of base had been added, the theoretical amount of Cl^- was present regardless of the rate of titration. The large difference in the amount of base required to reach the second end point (3.16 *vs.* 4.00 equiv) demonstrates a dependency of the rate of Cl^- loss on the speed of titration. Curve C is a reverse titration of the solution resulting from either A or B and suggests that a new compound has been formed with different acid–base properties.

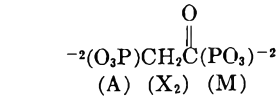
Simple rate studies revealed that the release of free chloride ion was first order with respect to I, independent of the chloride ion concentration but dependent on the ionic charge of I. The first-order rate expression, log [I], plotted *vs.* time was linear for over 80% of the reaction at pH values of 7.0, 9.0, and 10.0. The apparent first-order rate constant, k_{app}, was unaffected by the substitution of 0.1 *M* NaCl, as an ionic medium, for 0.1 *M* KNO_3. While k_{app} increased by only a factor of 1.3 as the pH was raised from 7.0 (k_{app} = 1.5 × 10^{-3} sec^{-1}) to 9.0 (k_{app} = 2.0 × 10^{-3} sec^{-1}), it increased by a factor of 3.7 (to k_{app} = 7.4 × 10^{-3} sec^{-1}) as the pH was increased from 9.0 to 10.0. This indicates that the dehydrohalogenation reaction is not simply base catalyzed, but proceeds by parallel pathways at different rates depending on the ionic form of the reactant ion. The apparent rate constant is a combination of the true rate constants for the individual ionic species.

The product of complete dehydrohalogenation is $Na_2O_3PCH_2C(O)PO_3Na_2$ (II). Evidence for this structure comes from elemental analysis, ^{31}P, ^{1}H, and ^{13}C nmr (Table I), and ir and uv spectroscopy.

TABLE I
NMR SPECTRAL DATA

Counter-ion in M_2O_3P-$CH_2C(O)$-PO_3M_2	^{31}P, δ (50%)	Mult	^{1}H, τ	Mult	^{13}C, δ	Mult
Na_4	−11.9	4	6.29	2	148.4	4
	−0.3	2			−8.7	4
H_4	−16.3	4	5.92	2		
	+3.8	2				

The splittings found in the nmr spectra of II and its corresponding acid are not what would be expected on the basis of first-order calculations. They are, however, interpretable as follows. Consider $Na_2O_3PCH_2C(O)PO_3Na_2$ as a compound in the AMX_2 system where A is the phosphorus attached to the $-CH_2-$, M is the phosphorus attached to the >C=O, and X_2 are the two methylene protons. The ^{31}P and ^{1}H nmr spectra are then consistent with coupling constants of J_{A-X} = 18–21, J_{A-M} = 16–18, J_{M-X} = <1 Hz.



(A) (X_2) (M)

(1) J. D. Curry, D. A. Nicholson, and O. T. Quimby, "Topics in Phosphorus Chemistry," Vol. 7, Wiley, New York, N. Y., 1972.

(2) J. B. Prentice, O. T. Quimby, R. J. Grabenstetter, and D. A. Nicholson, *J. Amer. Chem. Soc.*, **94**, 6119 (1972).

(3) D. A. Nicholson and H. Vaughn, *J. Org. Chem.*, **36**, 3843 (1971).

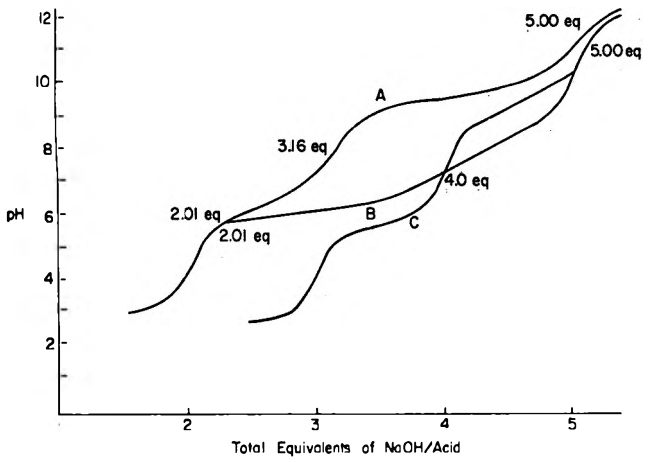
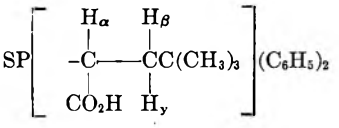


Figure 1.—Titration of $ClCH_2C(OH)(PO_3H_2)_2$ with NaOH: curve A, fast titration, 0.28 equiv/min, total time 10.5 min; curve B, slow titration, 0.037 equiv/min, total time 110 min; curve C, reverse titration of solution resulting from A or B.

Nucleus A appears as a quartet, *i.e.*, a 1–2–1 triplet from the X_2 splitting doubled by the M splitting such that the two 1–2–1 triplets add to form a 1–3–3–1 quartet. Nucleus M appears as a doublet split only by nucleus A. Nuclei X_2 also appear as a doublet split only by nucleus A. The M–X coupling is too weak to be observed in either ^{31}P to ^1H nmr.

Such a small coupling constant for PCCH is unusual but not without precedent. Although PCCH coupling constants are normally in the range of 15–19 Hz,[4] compounds are known wherein much smaller values have been observed. A noteworthy example has been described by Peterson.[5] In the phosphine sulfide

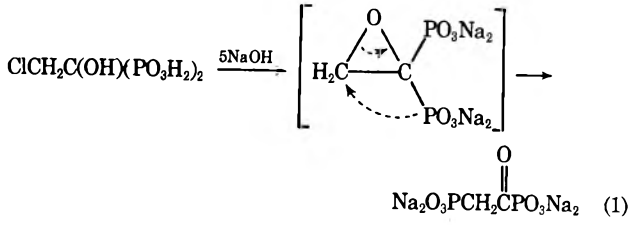


$J_{PCCH_\gamma} = 19$ Hz, while $J_{PCCH_\beta} = 2.5$ Hz.

The ^{13}C nmr spectrum further substantiates this interpretation. The resonance at −8.7 ppm with respect to CS_2 corresponds to that of a carbonyl carbon. It appears with a major splitting into a doublet caused by phosphorus M, and very minor further splitting by coupling with phosphorus A. This secondary splitting further shows small perturbations owing to phosphorus–phosphorus coupling. The methylene carbon appears at 148.4 ppm as a doubled doublet, the major splitting being due to phosphorus A and further splitting caused by phosphorus M. There is no observable ^{13}C–^{13}C coupling since the experiment was performed with natural abundance ^{13}C, requiring the averaging of 8000 scans to obtain the spectrum.

An infrared spectrum of II in D_2O showed methylene vibrations at 2860, 2920, and 2960 cm^{-1}, and strong absorption at 980 and 1635 cm^{-1}, assigned to a P–O stretch and the phosphonate-coupled carbonyl, respectively. An ultraviolet spectrum of II in aqueous solution exhibited an absorption band at 344 nm (ϵ ~90), which we ascribe to the carbonyl n → π^* transition.

Equation I describes a possible route to II. Rearrangements of α,β-epoxyalkylphosphonate esters have



been extensively studied by Churi[6] and his observations are consistent with the above 1,2 migration of phosphorus. Phosphorus nmr experiments were designed in an attempt to detect the epoxide intermediate suggested in eq 1. Sufficient NaOH was added to an nmr tube containing aqueous I to bring the pH to 7.0. Immediate scanning of these solutions failed to provide any evidence for the intermediate; all resonances detected were assignable to either I or II (Na_2 salts). Our conclusion is that whatever intermediate is involved in this rearrangement is short-lived with respect to the nmr time scale or is not formed in sufficient concentration to be detected by ^{31}P nmr.

When the neutralization in eq 1 was carried out with ammonium hydroxide, the solid tetraammonium salt precipitated from aqueous solution as well-formed, hydrated crystals. Ion exchange or titration to a pH of 1–2 allowed the isolation of the corresponding acid. The free acid was slow to crystallize but was obtained as either the monohydrate[7] from concentrated aqueous solutions or as the anhydrous acid from acetic acid solution.

The free acid, $H_2O_3PCH_2C(O)PO_3H_2$, is much more stable toward hydrolysis than would be expected based on the known instability of 1-ketophosphonates.[8] The rate of decomposition has not been thoroughly studied, but this acid was found to be stable in aqueous solution for 2–3 hr at 70°. It was completely decomposed when refluxed in aqueous solution for 48 hr. The fully neutralized salt, II, is stable for long periods of time to hot aqueous base. In this respect it is reminiscent of tetrasodium carbonyldiphosphonate.[9]

Using the general conditions outlined for the reaction of acylating agents and P(III) sources,[1,2] it was found that PCl_3 reacted with $H_2O_3PCH_2C(O)PO_3H_2 \cdot H_2O$ in di-*n*-propyl sulfone solvent to form, after hydrolysis, ethane-1-hydroxy-1,1,2-triphosphonic acid in nearly quantitative yields. Authentic $H_2O_3PCH_2C(OH)(PO_3H_2)_2$ was prepared from phosphonoacetic acid[1] and shown to be identical with the product (after hydrolysis) of $H_2O_3PCH_2C(O)PO_3H_2 + PCl_3$.

(4) V. Mark, C. H. Dungan, M. M. Crutchfield, and J. R. Van Wazer, "Topics in Phosphorus Chemistry," Vol. 5, Wiley, New York, N. Y., 1967, pp 227–457.

(5) D. J. Peterson, *J. Org. Chem.*, **31**, 950 (1966).

(6) R. H. Churi, Thesis, University of Pittsburgh, 1966.

(7) A referee has suggested that the water of hydration might actually be present as the carbonyl hydrate, $H_2O_3PCH_2C(OH)_2PO_3H_2$. The ^{31}P nmr spectrum would seem to rule this out, since such hydration would shift the contiguous phosphonate resonance some 15 ppm downfield.[9] Such a shift is not observed.

(8) G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, p 139.

(9) O. T. Quimby, J. B. Prentice, and D. A. Nicholson, *J. Org. Chem.*, **32**, 4111 (1967).

Experimental Section

Elemental analyses were carried out by the Analytical Section of these laboratories. Temperatures reported herein are uncorrected.

The phosphorus nmr spectra were measured using spinning 9-mm glass tubes with a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm. Sideband calibration was used. A Varian HR-60 spectrometer was used to obtain the proton spectra. A Bruker HX-90 pulsed Fourier transform nmr spectrometer with a Nicolet 1084 computer system was used to obtain the ^{13}C nmr spectra. Chemical shifts are reported as parts per million from an external CS_2 reference. Since the nmr spectra are adequately discussed in the text, they will not be repeated here. Infrared spectra of D_2O solutions were recorded on a Perkin-Elmer Model 421 recording spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 11 spectrometer.

Phosphonoacetic acid, chloroacetic acid, and di-*n*-propylsulfone were purchased from various chemical supply houses.

$ClCH_2C(OH)(PO_3H_2)(PO_3HNH_4)$ from $ClCH_2COOH$.—Chloroacetic acid (219 g, 1.2 mol) was heated to 62° to form a mixed liquid and crystalline slush. Phosphorus trioxide (22.1 g, 0.1 mol) was added with rapid stirring. The temperature dropped to 55° and the reaction mixture became clear. This solution was then heated to 65° and maintained there for 18 hr. The resulting condensates were hydrolyzed by adding 14.4 g of water, whereupon the solution was stirred at 65° for an additional 21 hr. The NH_4H_3 salt was precipitated from the clear solution by adding 14.1 g of ammonium acetate to the reaction solution at 60°. After 2-hr digestion the solids were removed by filtration, washed with ethyl ether, and air dried (yield 33.9 g, 66%). The solid had mp 159–160° and assayed as 100% $ClCH_2C(OH)(PO_3H_2)(PO_3HNH_4)$ by acid–base titration.

Anal. Calcd for $C_2H_{10}O_7P_2NCl$: C, 9.3; H, 3.5; P, 24.1; N, 5.4; Cl, 13.8. Found: C, 9.5; H, 3.9; P, 24.6; N, 5.5; Cl, 13.8.

Preparation of $Na_2O_3PCH_2C(O)PO_3Na_2$.—A crude sample of $ClCH_2C(OH)(PO_3H_2)_2$ (containing ~35 g of the acid) was dissolved in 450 ml of water and NaOH was added to a final pH of 10. A solid precipitated on cooling the warm solution to room temperature. The slurry was diluted with 125 ml of acetone and stirred for a short time at 25°, and the solid was removed and air dried. This solid was recrystallized from a 1:1 water–acetone mixture, yielding 49 g of hydrated $Na_2O_3PCH_2C(O)PO_3Na_2$.

A portion of this salt was passed through Dowex 50W-X8 cation exchange resin in the acid form. The aqueous eluent was concentrated on a rotary evaporator. The resulting viscous liquid crystallized on standing. This solid was washed with acetic acid and air dried. It assayed as 91.85% active $H_2O_3PCH_2C(O)PO_3H_2$, corresponding to the monohydrate. A titration curve for this acid, when plotted on the scale used in Figure 1, was essentially superimposable on curve C.

Anal. Calcd for $C_2H_6O_7P_2 \cdot H_2O$: C, 10.8; H, 3.6; P, 27.9; H_2O, 8.1; Cl, 0. Found: C, 10.8; H, 3.6; P, 28.2; H_2O, 8.1; Cl, <0.1.

Preparation of $H_2O_3PCH_2C(OH)(PO_3H_2)_2$ from $H_2O_3PCH_2C(O)PO_3H_2$.—The free acid prepared as above (4.46 g, 0.02 mol) was slurried in 18 ml of di-*n*-propyl sulfone, and PCl_3 (1.9 ml, 0.022 mol) was added at 29°. The slurry quickly resolved to two liquid phases and the temperature rose to 35°. The reaction mixture was heated to 90° over a 1.5-hr period. White solids formed during this heating period. The slurry was digested for 3 hr at 90° and then filtered. After this solid had been washed thoroughly with ethyl ether and air dried (yield 6.8 g) it was dissolved in 50 ml of water and the solution was refluxed for 2 hr. A ^{31}P nmr spectrum of this solution was superimposable on the spectrum of an aqueous solution of authentic ethane-1-hydroxy-1,1,2-triphosphonic acid (see below).

$Na_2O_3PCH_2C(OH)(PO_3HNa)(PO_3Na_2) \cdot 4H_2O$ from Phosphonoacetic Acid.—The literature method[1] for the preparation of this compound was employed with the following alteration. Purification was accomplished by titrating the aqueous solution, obtained from hydrolysis of the $H_2O_3PCH_2COOH + PCl_3$ reaction mixture, to a pH of 10.2. To this solution was added, with rapid stirring, an equal volume of acetone. The solid which separated was removed by filtration and washed with additional acetone. It was dried for 4 hr in an oven at 120°. Acid–base titration showed the resulting material to be the pentasodium salt of ethane-1-hydroxy-1,1,2-triphosphonic acid, solvated with 4 equiv of water. Proton and phosphorus nmr spectra were identical with those reported in the literature.[1]

Anal. Calcd for $C_2H_{12}O_{14}P_3Na_5$: C, 5.1; H, 2.6; P, 19.9; Na, 24.6. Found: C, 5.3; H, 2.9; P, 20.0; Na, 24.4.

Ion exchange employing Dowex 50W-X8 in the acid form produced the water solution of ethane-1-hydroxy-1,1,2-triphosphonic acid used for comparison with the product prepared above.

Kinetics of Dehydrohalogenation.—The rate of chloride release from I was followed at 25° by means of an Orion Model 94-17 solid state chloride electrode. The pH was maintained through the addition of a standard NaOH solution by a Radiometer recording pH-Stat. Reaction mixtures were made 0.1 *M* in KNO_3 to maintain the ionic strength, except during one experiment, at pH 9.0, in which the solution was made 0.1 *M* in NaCl to observe the possible effect of chloride ion on the reaction rate. For this experiment the rate was followed by the rate of consumption of standard base normalized to that of the pH 9.0 reaction run in KNO_3.

Registry No.—I, 34550-07-7; II, 36939-22-7; $ClCH_2C(OH)(PO_3H_2)(PO_3HNH_4)$, 36939-23-8; $ClCH_2COOH$, 79-11-8; $H_2O_3PCH_2C(O)PO_3H_2$, 6874-58-4; $H_2O_3PCH_2C(OH)(PO_3H_2)_2$, 21396-22-5; $Na_2O_3PCH_2C(OH)(PO_3HNa)(PO_3Na_2)$, 21396-24-7; $H_2O_3PCH_2COOH$, 4408-78-0.

Acknowledgments.—The authors wish to thank Dr. T. J. Flautt for help in interpretation of the nmr spectra.

Asymmetric Reductions with Chiral Reagents from Lithium Aluminum Hydride and (+)-(2S,3R)-4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol[1,2]

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Stereoselectivity in reductions of carbonyl compounds by a chiral reagent prepared by adding the amino alcohol (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (6) to lithium aluminum hydride in ether is reasonably high and shows remarkable reversal depending upon age of the reagent from predominantly R product to predominantly S product. Reduction of acetophenone gives either (R)-(+)- or (S)-(−)-methylphenylcarbinol in 60–70% enantiomeric purity depending upon use of the reagent either immediately after its preparation (procedure A) or upon aging overnight or refluxing for a few minutes (procedure B). This reversal in stereoselectivity with age of reagent was observed with five different carbonyl substrates. The reduction of phenyltrifluoromethyl ketone did not show this reversal phenomenon, however. Procedure A for asymmetric reduction of phenyl alkyl ketones gives the R carbinol in excess in each case. Representative enantiomeric purities (% e.e., R isomer) of the carbinols, PhCHOHR, from reduction of the ketones, PhCOR, at 0° follow: R = Me, 68% e.e.; n-Pr, 61% e.e.; i-Pr, 30% e.e.; t-Bu, 36% e.e.; CF_3, 30% e.e. This series roughly conforms to a decrease in stereoselectivity as the size of the R group increases. The reagent prepared from 6 and lithium aluminum deuteride gave upon reaction with acetophenone the corresponding deuteriated (R)-phenylmethylcarbinol-α-d, 80% e.e., and upon reaction with benzaldehyde (S)-benzyl-α-d alcohol, 40% e.e. With this chiral reducing agent we have realized a generally useful method for asymmetric synthesis of carbinols with substantial enantiomeric purities.

The reduction of an achiral carbonyl compound by a chiral reducing agent to give unequal amounts of the enantiomeric secondary carbinols has been the subject of much study.[4] Most of such studies are of theoretical interest rather than of practical value for the synthesis of optically active materials. Landor and coworkers[5] have made a detailed study of modified monosaccharide–lithium aluminum hydride complexes and Červinka and his students[6] have studied carbonyl reduction by lithium aluminum hydride–chiral alkaloid complexes. For instance, the reduction of acetophenone (4) by a reagent (3) made by mixing lithium aluminum hydride (1) and quinine (2) in a 1:1 molar ratio gave (R)-(+)-phenylmethylcarbinol (5) in 48% excess over the racemate.[6a] The stereoselectivities observed in the reduction of other substrates by this chiral reducing agent were generally less than 30%.

$$\underset{1}{LiAlH_4} + \underset{2}{\text{quinine}} \longrightarrow \underset{3}{LiAlH_3\text{–quinine}} + H_2$$

$$\underset{3}{LiAlH_3\text{–quinone}} + \underset{4}{PhCOMe} \longrightarrow \longrightarrow$$

$$HO\triangleright\underset{\displaystyle Ph}{\overset{\displaystyle Me}{C}}\triangleleft H + H\triangleright\underset{\displaystyle Ph}{\overset{\displaystyle Me}{C}}\triangleleft OH$$

74% R-(+)-5 26% S-(−)-5

A readily available chiral reagent which would achieve consistently high stereoselectivities for a wide spectrum of carbonyl compounds would constitute a valuable synthetic tool for the organic chemist. It seems likely that a superior chiral reducing agent might be designed based upon a systematic study of the structural variables of reagents of this type. We have begun such a study using the chiral amino carbinol (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol[7] of known configuration[7c] (6, R*OH)[8] for the reaction with lithium aluminum hydride in various molecular ratios to give a chiral reducing reagent represented by 7.

$$PhCH_2\overset{\displaystyle OH}{\overset{\triangledown}{C}}\text{—}\overset{\displaystyle Me}{\overset{\triangledown}{C}}CH_2NMe_2$$
$$\underset{\displaystyle Ph}{\overset{\triangle}{}}\qquad\underset{\displaystyle H}{\overset{\triangle}{}}$$

6, R*OH

$$\underset{1}{LiAlH_4} + n\underset{6}{R^*OH} \longrightarrow \underset{7}{LiAlH_{4-n}(OR^*)_n} + nH_2$$

This specific reagent was chosen because of a report[9] of reasonably high stereoselectivity using this chiral amino carbinol in the preparation of a reagent for the reduction of acetophenone and a subsequent promising preliminary study.[2] We have summarized the data we have collected in Tables I–III. Initial studies using acetophenone and a reagent prepared from lithium aluminum hydride and the chiral amino carbinol (6, R*OH, molar ratio 1.0:2.3) have shown that substantial stereoselectivities in the order of 40–75% e.e.[10] are obtained repeatedly (Table I). We have now carried out experiments designed to explore the effects of temperature, concentration, solvent, time, ratio of reactants, and

(1) We acknowledge with gratitude support of these studies by the National Science Foundation (NSF GP 27448).

(2) For a preliminary communication of a portion of this work, see S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Amer. Chem. Soc.*, **94**, 9254 (1972).

(3) On leave from Tohoku University, Sendai, Japan.

(4) This subject has been reviewed: J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1970, pp 160–218.

(5) (a) S. R. Landor and A. R. Tatchell, *J. Chem. Soc. C*, 2280 (1966); (b) S. R. Landor, B. J. Miller and A. R. Tatchell, *ibid.*, 197 (1967).

(6) (a) O. Červinka, *Collect. Czech. Chem. Commun.*, **30**, 1684, 2403 (1965). (b) O. Červinka and O. Bělavský, *ibid.*, **30**, 2487 (1965); **32**, 3987 (1967). (c) O. Červinka, V. Suchan, O. Kotýnek, and V. Dudek, *ibid.*, **30**, 2484 (1965).

(7) (a) A. Pohland and H. R. Sullivan, *J. Amer. Chem. Soc.*, **75**, 4453 (1953); (b) A. Pohland and H. R. Sullivan, *ibid.*, **77**, 3400 (1955); (c) H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963); (d) A. Pohland, L. R. Peters, and H. R. Sullivan, *ibid.*, **28**, 2483 (1963).

(8) Throughout this paper we shall use R*O– to symbolize the specific chiral alkoxy group from (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (6). R*OH is the alcohol from which the analgesic Darvon is made.

(9) See ref 4, p 205, entry 14 in Table 5-11.

(10) By % e.e. we designate the enantiomeric excess, *i.e.*, the per cent excess of one enantiomer over the racemate. This was determined either by optical rotation or by use of relative areas of suitable signals from the diastereomeric α-methoxy-α-trifluoromethylphenylacetate (MTPA) derivatives.[11]

(11) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

TABLE I

ASYMMETRIC REDUCTIONS OF ACETOPHENONE (4) BY INSOLUBLE (A)[a] AND SOLUBLE (B)[a] CHIRAL REAGENTS FROM $LiAlH_4$ AND (+)-(2S,3R)-4-DIMETHYLAMINO-3-METHYL-1,2-DIPHENYL-2-BUTANOL (R*OH)[b]

$$PhCOMe + LiAlH_n(OR^*)_{4-n} \longrightarrow \longrightarrow (+)\text{-PhCHOHMe} + (-)\text{-PhCHOHMe}$$

4 7 (R)-(+)-5 (S)-(−)-5

No.	Procedure[a]	Molar ratio[b,c] $LiAlH_4$	Molar ratio[b,c] R*OH	Molar ratio[b,c] PhCOMe	Reaction temp, °C	Extent of reduction,[d] %	Stereoselectivity[e] Configuration	Stereoselectivity[e] % e.e.
1	A	1.0	0.77	0.70	rt	Q	R	29 (31)[f]
2	A	1.0	0.76	1.39	rt	Q	R	23 (24)[f]
3	B	1.0	0.76	2.10	rt	86	R	18 (18)[f]
4	A	1.0	0.77	0.64	0	Q	R	31
5	A	1.0	1.00	0.83	0	Q	R	52
6	B	1.0	1.00	0.83	0	Q	R	47[g]
7	A	1.0	1.54	0.70	rt	Q	R	41 (40)[f]
8	A	1.0	1.53	1.39	rt	Q	R	48 (46)[f,h]
9	A	1.0	1.54	0.64	0	Q	R	65, 66[i]
10	A	1.0	2.00	0.83	0	Q	R	40, 49[j]
11	A	1.0	2.00	1.66	0	59	R	21
12	A	1.0	2.30	0.70	rt	Q	R	58 (57)[f]
13	A	1.0	2.30	0.64	0	Q	R	68 (68)[f]
14	A	1.0	2.30	0.64	−65	Q	R	75 (75)[h]
15	A	1.0	3.00	0.83	0	Q	R	26
16	A	1.0	3.00	0.83	0	Q	R	28,[i] 27[i]
17	B	1.0	2.00	0.83	rt	29	S	49
18	B	1.0	2.00	1.67	rt	15	S	45
19	B	1.0	2.30	0.64	rt	40, 43[k]	S	66, 66[k]
20	B	1.0	2.30	0.32	rt	50	S	70
21	B	1.0	2.30	0.21	rt	77	S	75
22	B	1.0	2.30	0.64	0	35	S	53
23	B	1.0	2.30	0.64	−65	9	R	5
24	D[a]	1.0	2.30	0.64	0	Q	R	29
25	B	1.0	3.00	0.83	rt	27	S	71
26	B	1.0	3.00	0.83	0	24	S	60

[a] Procedures are given in the Experimental Section. Briefly they are as follows: A, an insoluble precipitate is formed upon adding an ethereal solution of R*OH to a filtered, standardized, ethereal $LiAlH_4$ solution (the heterogeneous reagent is used immediately); B, an aged homogeneous ether solution of the reagent as prepared in A is used; C uses an aged benzene solution of the reagent; D follows procedure A except that ten times the ether solvent is used and no precipitate is formed (the reagent is used immediately). [b] R*OH symbolizes the chiral alcohol 6. [c] The actual quantities used for each reaction ranged from 0.33 to 1.5 mmol. [d] The extent of reduction is based on glc-determined ratio of methylphenylcarbinol to acetophenone in the isolated product. Q means "almost quantitative"; *i.e.*, less than 2% of ketone detected in the product. [e] Enantiomeric excess (% e.e.) is the excess of one isomer over the racemate. Unless otherwise designated this was determined by optical rotation. [f] Alternative analysis on the same sample based upon the nmr relative peak heights of the *C*-methyl doublets of the diastereomeric MTPA derivatives. [g] The initial precipitate was heated in ether for 10 min and allowed to stand overnight but did not dissolve. Acetophenone was then added. [h] Alternate analysis on the same sample based upon relative areas of the OCH_3 nmr signals of diastereomeric MTPA derivatives in the presence of 0.1 *M* $Eu(fod)_3$ nmr shift reagent. [i] Duplicate runs both analyzed by optical rotation. [j] Duplicate runs except hydride concentration adjusted to the same as that in no. 9 by reducing the amount of ether accordingly. [k] Duplicate run which was refluxed for an additional 2 hr to see if the extent of reduction could be increased. Excess hydride was present at the end of the reaction, as evidenced by liberation of hydrogen upon hydrolysis.

various substrates upon the stereoselectivity of this reduction. Pertinent observations are as follows.

(1) Of foremost interest is the previously communicated[2] observation that the sense of stereoselectivity is dependent upon the length of time that the reagent has been allowed to stand before its use for reducing the carbonyl substrate. When acetophenone was added to the reagent at 0° either 30 sec or 3 min after its preparation (by mixing **1** and **6** to form reagent **7**, $LiAlH_4$R*OH molar ratio of 1.0:2.3, procedure A), a near-quantitative yield of (*R*)-(+)-phenylmethylcarbinol [*R*-(+)-**5**] which was 68% enantiomerically pure was formed (Table I, example 13). However, when the reagent was allowed to stand overnight or was refluxed in ether for a few minutes before the same substrate was added (procedure B), then a 43% yield of the *S*-(−) enantiomer of **5**, which was 66% enantiomerically pure, was obtained (Table I, no. 19). This phenomenon is represented graphically in Figure 1.

This reversal of stereochemistry with age of the reagent is like that observed previously by Sandman, Mislow, *et al.*,[12] during the stereoselective additions of the "di-3-pinanylboron" reagent[13] to olefins.

(2) This reversal in stereoselectivity seems in part to be associated with a less soluble and more soluble form of reagent **7**. On initial preparation of this reagent, by the addition of a concentrated ether solution of amino carbinol **6** to the $LiAlH_4$ solution ($LiAlH_4$: R*OH molar ratio 1.0:2.3) there is an immediate liberation of the theoretical amount of hydrogen and formation of a precipitate which goes into solution upon

(12) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Amer. Chem. Soc.*, **90**, 4877 (1968). These authors found a freshly prepared 1:1 THF solution of (+)-α-pinene and boron hydride treated with benzonorbornadiene followed by oxidation and acetylation to give (+)-*exo*-2-benzonorbornenyl acetate with 7.4% e.e. of the 1*S*,2*R* enantiomer. However, when the reagent was warmed and held for 21 hr before the benzonorbornadiene was added, the stereoselectivity was reversed with the formation, in comparable enantiomeric purity, of the 1*R*,2*S* enantiomer. The reason for this reversal in stereoselectivity with age of the "di-3-pinanylboron" reagent is unknown and may or may not be related to the phenomenon that we observe with the chiral $LiAlH_n(OR^*)_{4-n}$ reagent.

(13) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 247 (1959); **83**, 2544 (1961).

TABLE II

ASYMMETRIC REDUCTION OF SUBSTRATES BY INSOLUBLE (A)[a] AND SOLUBLE (B)[a] $LiAlH_4$–(2*S*,3*R*)-4-DIMETHYLAMINO-3-METHYL-1,2-DIPHENYL-2-BUTANOL (R*OH 6)[b] REAGENTS. $LiAlH_4$:R*OH:SUBSTRATE RATIO 1.3:3.0:1.0

No.	Substrate	Procedure[a]	Temp, °C	Solvent[c]	Extent of reduction,[d] %	Stereoselectivity[e] Configuration	Stereoselectivity[e] % e.
1	PhCOMe	A	0	ETH	Q	*R*	68
2		B	rt	ETH	46	*S*	62
3		C	rt	THF	90	*R*	13
4		C	rt	BENZ	40	*S*	43
5		C	0	PENT	43	*S*	30
6	$PhCOCF_3$	A	0	ETH	Q	*R*	29, 30[f]
7		B	0	ETH	96	*R*	30
8		C	rt	BENZ	95	*R*	29
9	PhCO-*n*-Pr	A	0	ETH	Q	*R*	60, 62,[f] 61[g]
10		B	0	ETH	50	*S*	59[f]
11		C	rt	BENZ	41	*S*	49
12	PhCO-*i*-Pr	A	0	ETH	Q	*R*	30, 28,[f] 30[g]
13		B	0	ETH	34	*S*	20
14		C	rt	BENZ	20	*S*	48
15	PhCO-*t*-Bu	A	0	ETH	Q	*R*	36, 35[f]
16		B	0	ETH	43	*R*	28
17		C	rt	BENZ	24	*S*	9
18	MeCO-*t*-Bu	A	0	ETH	Q	*R*	16, 28,[g] 28[h]
19		B	0	ETH	42	*S*	19,[i] 21[g]
20		C	rt	BENZ		*S*	4[i]

[a] The procedures are detailed in the Experimental Section. The abbreviations are the same as outlined in the notes to Table I. [b] R*OH symbolizes the chiral alcohol 6. [c] Solvents: ETH is diethyl ether, THF is tetrahydrofuran, BENZ is benzene, and PENT is pentane. [d] Based on the carbinol–ketone ratio as determined by glc analysis; Q represents essentially quantitative yield. [e] Stereoselectivity is designated by per cent excess of an enantiomer over the racemate (% e.e.). [f] This is an alternate analysis on the same sample obtained from the nmr relative peak areas for the OCH_3 signal from the diastereomeric MTPA derivative in the presence of 0.1–0.2 *M* Eu(fod)$_3$ shift reagent. [g] Calculated on relative areas of ^{19}F nmr signals of α-CF_3 group of diastereomeric MTPA derivatives. [h] Based on relative areas of *t*-Bu nmr resonances of diastereomeric MTPA derivatives in the presence of 0.2 *M* Eu(fod)$_3$. [i] Based on the relative heights of *tert*-butyl signals of diastereomeric MTPA derivatives.

TABLE III

ASYMMETRIC REDUCTIONS OF BENZALDEHYDE AND ACETOPHENONE BY $LiAlD_4$–(2*S*,3*R*)-4-DIMETHYLAMINO-3-METHYL-1,2-DIPHENYL-2-BUTANOL (R*OH, 6) REAGENT IN ETHER SOLVENT AT 0°

$$PhCOR + LiAlD_n(OR^*)_{4-n} \longrightarrow\longrightarrow (R)\text{-}PhC^*DOHR + (S)\text{-}PhC^*DOHR$$

No.	PhCOR R	Method[a]	Molecular ratio[b] $LiAlD_4$	Molecular ratio[b] R*OH	Molecular ratio[b] PhCOR	Per cent redn[b,c] $LiAlD_4$	Per cent redn[b,c] ($LiAlH_4$)	Stereoselectivity[d] Configuration	Stereoselectivity[d] $LiAlD_4$ % e.e.	Stereoselectivity[d] $LiAlH_4$ (% e.e.)
1	H	A	1.0	2.30	0.64	Q		*S*	43, 40[f]	
2	H	B	1.0	3.00	0.83	72		*S*	19	
3	Me	A	1.0	2.30	0.64	Q	(Q)	*R*	90, 81[h]	(68)[e]
4	Me	A	1.0	2.30	0.64	Q		*R*	80[g]	
5	Me	A	1.0	1.54	0.64	Q	(Q)	*R*	78, 79[h]	(66)[e]
6	Me	A	1.0	1.54	0.64	Q		*R*	79[g]	
7	Me	B	1.0	3.00	0.83	29	(24)	*S*	73	(60)[e]

[a] See Experimental Section for details. Procedure A essentially involves the insoluble form while procedure B is the aged, soluble reagent. [b] R*OH symbolizes the chiral alcohol 6. [c] Determined by glc and based on carbinol:unreduced substrate ratios; Q represents an essentially quantitative yield. Parentheses indicate data from Table I. [d] Stereoselectivity is given as per cent excess of one enantiomer over the racemate (% e.e.) based upon optical rotation unless otherwise indicated. [e] These are the directly comparable or most closely comparable $LiAlH_n$ reductions taken from Table I. [f] Stereoselectivities determined on the same sample by use of nmr signals of benzylic protons of MTPA in the presence of 0.4 *M* Eu(fod)$_3$. [g] Duplicate experiment. [h] Stereoselectivities determined on the same sample by use of nmr signals of OCH_3 protons of MTPA ester in the presence of 0.1 *M* Eu(fod)$_3$.

swirling in about 7–8 min (2–3 min in refluxing ether). If acetophenone (4) is added to this precipitated reagent at room temperature immediately after mixing (within the first 3 min), the precipitate immediately dissolves and *R*-(+)-**5** is obtained in 58% e.e. (Table I, no. 12). Addition of **4** to a sample of this reagent which has been stirred for 8 min after mixing gave *S*-(−)-**5** in 15% e.e. At this point in time the precipitate which was formed on initial mixing had just dissolved.

(3) An added complicating factor is that, although the per cent yields of reduction product are essentially quantitative when the reagent containing the precipitate is used (procedure A), the per cent yields with the aged, soluble reagent (procedure B) fall short of the theoretical, even in the presence of 1–3 *M* excess of the hydride reagent. Unreduced carbonyl compound is recovered even though active hydride still remains in the incomplete reduction mixture, as shown by the liberation of hydrogen upon the addition of water. A clear exception to this general observation is the reduction of phenyl trifluoromethyl ketone by either the insoluble or soluble reagent which gives high per cent yields and about 30% e.e. of *R* enantiomer under all conditions tried (Table II, no. 6–8). This behavior may

be related to the well-known ease of reduction of trifluoromethyl ketones.

(4) Evidence that the reversal in stereoselectivity is not simply a difference between heterogeneous *vs.* homogeneous reactions is given by the following. When the reagent is prepared in dilute solution by adding R*OH (**6**) to an 0.05 *M* ether solution of $LiAlH_4$ (instead of to the usual 0.5 *M* $LiAlH_4$ solution), a clear solution results without the formation of a precipitate as is observed when the concentration is approximately ten times this. The immediate addition of acetophenone to this dilute homogeneous solution results in its reduction to (*R*)-(+)-phenylmethylcarbinol, 29% e.e. (Table I, no. 24). This is a lower specificity but the same sense of asymmetric reduction as observed with the precipitated complex which results when the reagent is prepared in more concentrated form.

(5) Empirical studies indicate that the highest stereoselectivities for both precipitated and soluble forms of the reagent were obtained with $LiAlH_4$:R*OH ratios from approximately 1.0:2.3 to 1.0:1.5 (68 and 66%, respectively, Table I, no. 13 and 9 at 0° for procedure A). The exact ratio for the production of reasonably high *R* stereoselectivity according to procedure A does not appear to be critical. The original rationale for using the $LiAlH_4$:R*OH ratio of 1.0:2.3 was that this represented a modest excess of $LiAlH_4$ over that required for a reagent with the empirical formula of $LiAlH(OR^*)_3$. In fact this ratio corresponds to a mixture represented by $LiAlH(OR^*)_3 \cdot 2LiAlH_2(OR^*)_2$.[14] However, with an $LiAlH_4$:R*OH ratio of 1:1, corresponding to $LiAlH_3(OR^*)$, the precipitate formed in ether does not go into solution on standing or refluxing. This 1:1 reagent affords high stereoselectivity of the *R* enantiomer, whether the freshly prepared or aged reagent is used (47 *vs.* 52% e.e., respectively, Table I, no. 6 and 5). However, addition of extra ether, which causes solution of some of this 1:1 complex, results in a reagent with reduced *R* stereoselectivity (21% e.e. *R*).

(6) The addition of an ether solution of R*OH, **6**, to $LiAlH_4$ ($LiAlH_4$:R*OH molar ratio 1.0:2.3) results in the formation of a precipitate which begins to deposit when approximately one half of the R*OH has been added. However, when the order of mixing is reversed, no precipitate is formed. Immediate use of the resulting solution, from this reverse order of mixing, for reduction of acetophenone gives the *R*-(+) enantiomer of **5**, but with low (10% e.e.) stereoselectivity in 92% yield. Longer standing of such a solution leads to a reagent which gives high *S*-(−) stereoselectivity.

(7) The stereoselectivity of the reduction by the insoluble complex was found to increase with decreasing temperature: 20°, 57% *R*; 0°, 68% *R*; −65°, 75% *R*; the percentage yield was nearly quantitative in each case (Table I, no. 12, 13, 14). The stereoselectivity of the soluble reagent seems to decrease with lower reaction temperature: 20°, 66% e.e. *S*; 0°, 53% e.e. *S*; −65°, 5% e.e. *R* (Table I, no. 19, 22, and 23).

(8) When the reagent was prepared in benzene instead of ether solution it was soluble under all conditions tried and the *S*-(−) enantiomer of **5** formed in reasonably high stereoselectivities (40–55% e.e.) in analogy with the soluble reagent in ether solution (Table II). Similarly, the reagent in pentane, using a $LiAlH_4$:R*OH ratio of 1:2.3, was soluble and afforded the *S* enantiomer of **5** (30% e.e.). Repetition in tetrahydrofuran solvent gave a homogeneous solution of the reagent which reduced acetophenone to **5** to give the *R* enantiomer with low stereoselectivity (13% e.e.), contrary to the results in benzene, pentane, and ether solution (Table II).

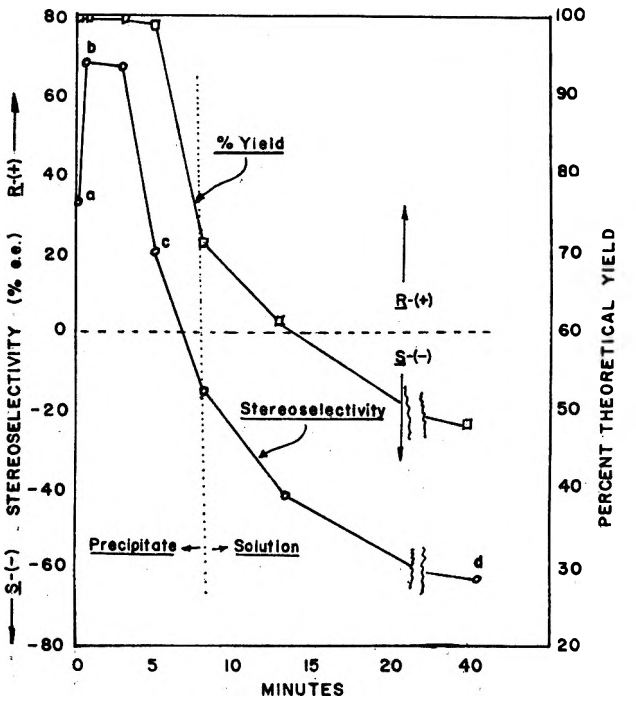


Figure 1.—Change in stereoselectivity (O—O left ordinate) and in percent yield (□—□ right ordinate) with age of reagent ($LiAlH_4$; R*OH ratio 1.0:2.3) in ether solvent at room temperature. (a) Zero time corresponds to results when acetophenone and R*OH in ether were added to $LiAlH_4$. (b) Acetophenone added to reagent 30 sec after mixing. (c) After 8 min of shaking the initial precipitate had just dissolved, at which point acetophenone was added. (d) This sample was refluxed in ether for 3 min as well as standing for 40 min before acetophenone was added.

(9) The reduction of three additional phenyl alkyl ketones (excluding phenyl trifluoromethyl ketone) showed generally decreased stereoselectivities as the size of the alkyl group increased (Table II). The aliphatic ketone, methyl *tert*-butyl ketone, showed the lowest order of stereoselectivity of these substrates. In each of these cases the heterogeneous reagent (procedure A) gave the *R* enantiomer in excess while the homogeneous reagent (procedure B) gave the *S*. However, phenyl trifluoromethyl ketone gave excess *R* enantiomer in good yield (Table II, no. 1–3) with both heterogeneous and homogeneous reagents.[15]

(10) A soluble chiral reagent prepared from sodium aluminum hydride and **6** in ether gave relative low stereoselectivities of the (*R*)-**5** enantiomer (5% e.e. with $NaAlH_4$:R*OH ratio of 1:2 and 17% e.e. with 1:3 ratio); the same reagent in benzene was soluble

(14) Throughout we shall represent the reagents as $LiAlH(OR^*)_3$, $LiAlH_2(OR^*)_2$, $LiAlH(OR^*)_2$, and $LiAl(OR^*)_4$. By these formulas we wish to designate only the ratio of the $LiAlH_4$ and R*OH used in the preparation of these reagents; we specifically do not imply that these formulas represent either the structure or state of aggregation of the reagent. These experiments were done in relatively small amounts and the exact ratios in any one experiment may easily be off by 0.1.

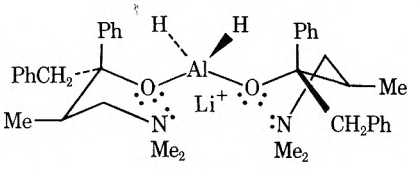
(15) It should be pointed out that because of the *R*–*S* nomenclature rules (*R*)-phenyltrifluoromethylcarbinol is configurationally related to (*S*)-phenylmethylcarbinol, where the methyl group is replaced by the trifluoromethyl group. Thus the departure from the regular pattern in the reduction of phenyl trifluoromethyl ketone by procedure A (precipitated reagent) was to give the *R* enantiomer instead of the *S*.

and gave 12% e.e. (*R*)-**5** when prepared with a 1:2.7 molar ratio of $NaAlH_4$ to R*OH. It is interesting that the soluble form of the sodium aluminum hydride reagent gives (*R*)-(+)-**5** in excess whereas the soluble form of the lithium aluminum hydride reagent gives (*S*)-(−)-**5** in excess.

(11) Several experiments were designed to obtain some information concerning the nature of the isolated precipitate. At 0°, $LiAlH_4$ and R*OH were mixed in 1.0:2.3 molar ratio and the mixture was immediately centrifuged. The supernatant layer was removed and the solid was twice washed with anhydrous ether. The resulting solid did not dissolve in ether on standing at room temperature; upon addition of acetophenone it gave (*R*)-(+)-**5** in 70% e.e. Another sample of this solid was vacuum dried and hydrolyzed to give 90–94% (duplicate runs) of the theoretical amount of hydrogen based on the formula $LiAlH_2(OR^*)_2$. Again the chiral reagent was made by mixing $LiAlH_4$ and R*OH in 1.0:2.3 molar ratio but this time the mixture was refluxed for a short time until the precipitate went into solution. It was centrifuged free of a slight amount of turbidity and the supernatant liquid was evaporated to dryness to give a white, silky solid which was completely soluble in pentane. Addition of acetophenone to this pentane solution resulted in a 43% yield of (*S*)-(−)-**5** with 30% e.e. Thus the soluble form which gives *S* stereoselectivity does not revert to the insoluble form which gives *R* stereoselectivity upon evaporation of solvent.

Discussion

We would like to be able to interpret these results from a mechanistic standpoint, *i.e.*, to postulate transition-state stereochemistries which would account for the observed configurations and generally high stereoselectivities of the products and which would explain the phenomenon of reversal in stereochemistry, depending upon the age of the reagent. We had anticipate that the stereoselectivities might be high based upon rather speculative models for this reaction involving a structure such as **8** which is held in a tight



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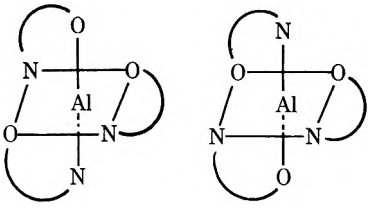
complex by coordination of the heteroatoms to the lithium cation. However, the reversal in stereoselectivity with age of the reagent was totally unexpected. This complication renders any interpretation doubly difficult.

Important parallels can be drawn between the complexities of these asymmetric reductions and asymmetric hydroborations by "di-3-pinanylborane." Attempts to rationalize the stereochemistry of asymmetric hydroborations by this chiral reagent have led to the postulation of a series of six speculative transition-state models, each one of which tried to improve on the previous model in order to accommodate some additional observation.[16] All but the last of these models were proposed before the observation on the reversal in stereoselectivity with age of this reagent.[12] None, including the last of these proposed models, attempted to account for such a reversal.

One can speculate that the state of association of the chiral reagent, for instance $[LiAlH_2(OR^*)_2]_n$, is involved in this observed reversal of stereochemistry with age of reagent. The reactivity of aluminum isopropoxide in the Meerwein–Ponndorf–Verley reduction has been studied with respect to association of the reagent. It is now established[17] that the stable form of aluminum isopropoxide in solution is the tetramer, while the active reducing species is the trimer which is in equilibrium with the tetramer. One can easily imagine that a monomer of a reagent such as **7** might have considerably different stereoselectivity from its dimer or trimer.

These uncertainties in state of aggregation of the reagent are in addition to those due to the multiple conformations that one species may assume during actual reaction with the substrate. Furthermore, in the present case, coordination number of the aluminum in solution is not known. Speculative models might be based on either a tetrahedral or octahedral aluminum geometry where coordination could be either with heteroatoms of the reagent or with solvent. If octahedral geometry is involved there is the added complication of cis *vs.* trans isomerism, **9a** *vs.* **9b**, as well as the overall chirality, *i.e.*, **9a** or **9b** *vs.* the mirror images.



9a **9b**

The chiral reducing complex resulting from reaction of $LiAlH_4$ with R*OH has the possibility of three different stoichiometries, $LiAlH_3(OR^*)$, $LiAlH_2(OR^*)_2$, or $LiAlH(OR^*)_3$, each of which could have different stereoselectivities in asymmetric reductions. The rate of reduction of such species will also differ; thus if a mixture contains more than one such species the stereoselectivity during the initial phase of the reaction should be different from that during the final stages of reduction. This complexity is compounded in that the transfer of the first active hydrogen of $LiAlH_2(OR^*)_2$ produces a new chiral reagent $LiAlH(OR^*)_2(OR'^*)$ with the reduced substrate as a ligand. This reagent should be capable of further transfer of hydrogen and should have a stereoselectivity in further reductions which would be different from that of $LiAlH_2(OR^*)_2$ or $LiAlH(OR^*)_3$. Thus the possible complexities of the reaction reported here considerably surpass those of the chiral "di-3-pinanylborane" hydroboration reaction. We are convinced that it is premature to attempt to interpret our present results in terms of transition-state models.

An initial hypothesis which we entertained was that the "*R*" reagent (*i.e.*, the reagent with *R* stereoselectivity toward acetophenone) was $LiAlH_2(OR^*)_2$ which was formed very rapidly upon mixing $LiAlH_4$ and R*OH, while the "*S*" reagent, which was formed by a slower subsequent reaction, was $LiAlH(OR^*)_3$. The

(16) The evolution of these transition state models has been reviewed in ref 4, pp 220–240.

(17) V. J. Shiner and D. Whittaker, *J. Amer. Chem. Soc.*, **85**, 2337 (1963).

change in stereoselectivity with time according to this hypothesis follows the rate of the conversion according to the following equations.

$$LiAlH_4 + R^*OH \longrightarrow LiAlH_3OR^* + H_2$$

$$LiAlH_3OR^* + R^*OH \longrightarrow LiAlH_2(OR^*)_2 + H_2$$

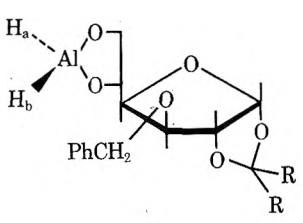
$$LiAlH_3(OR^*) + R^*OH \longrightarrow LiAlH(OR^*)_3 + H_2$$

This hypothesis is untenable, because upon adding 3 molar equiv of the alcohol (R*OH) to the $LiAlH_4$ solution 90-94% of the 3 molar equiv of hydrogen are liberated immediately, not 2 mol rapidly and a third mole much more slowly, as would be required by such a postulate.

At least two distinct reagents must be postulated, one with *R* and the other with *S* stereoselectivity with respect to acetophenone reduction; both reagents probably have the same empirical formula although not necessarily the same molecular formula. We will refer to these as the *R* and the *S* reagent. We assume that the initially formed *R* reagent is produced rapidly and that this changes more slowly into the more stable *S* reagent. This change might be an isomerization, as represented by the difference in **9a** and **9b**, or it might be a conversion from one state of aggregation into another as in the interconversion of aluminum isopropoxide trimer and tetramer.[17] However, it is not an isomerization of the skeleton of the chiral alcohol, since the R*OH is recovered unchanged in high yield from these reductions.

Superficially it might appear that the *R* reagent is the initial precipitate and that the *S* reagent is its soluble form with the reversal in stereoselectivity being a reflection of the difference between a heterogeneous *vs.* homogeneous reaction. This is readily discounted by the results obtained from a reagent prepared according to procedure A but using ten times the amount of ether solvent which gives a solution rather than a precipitate but still shows predominant *R* stereoselectivity in the reduction of acetophenone when used immediately after preparation (Table I, no. 24). Furthermore, the reagent used for the experiments reported in Figure 1 become homogeneous after 7–8 min of swirling whereas the maximum *S* stereoselectivity is not developed until longer standing.

In the studies by Landor, *et al.*,[5b] on chiral reducing agents derived from $LiAlH_4$ and monosaccharide derivatives such as **10**, it was found that one of the two available active hydrogens reacted much faster than the other to give predominant *S* stereoselectivity in the reduction of acetophenone. When 1 equiv of ethanol was added to reagent **10** the resulting new reagent **11**, which had one reactive hydrogen left, gave *R* stereoselectivity.



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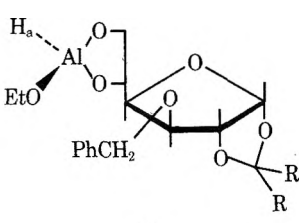

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A similar explanation in this form cannot rationalize our data, since we obtain either *R* or *S* stereoselectivity from a reagent with the same composition in which the $LiAlH_4$:R*OH ratio was unchanged, the only difference being the age of this reagent. Furthermore, we obtained this reversal in stereoselectivity with time whether the reagent had the composition $LiAlH_2(OR^*)_2$ or $LiAlH(OR^*)_3$. We have in fact carried out comparable experiments where the reagent $LiAlH_2(OR^*)_2$ was made according to procedure A and within 3 min 1 equiv of methanol (or phenol) was added in order to give a new reagent, $LiAlH(OR^*)_2(OR')$. Hydrogen was evolved upon the addition of methanol (or phenol) and the initial precipitate did *not* dissolve. Acetophenone was then added within 30 sec, with the result that (*R*)-(+)-**5** was formed in about 52% e.e (with phenol, 64% e.e.). Thus utilization of one of the two remaining available hydrogens did not result in a reversal of stereoselectivity.

However, it must be significant that *R* stereoselectivity is higher when there is sufficient $LiAlH_2(OR^*)_2$ reagent so that only one hydrogen needs to be utilized (Table I, no. 10, 40–49% e.e. *R*, quantitative yield) as compared to the experiment where both hydrogens must be used for complete reduction (Table I, no. 11, 21% e.e. *R*, 59% yield). The aged reagent with this same composition gave *S* stereoselectivity but in reduced per cent yield (Table I, no. 17 and 18, 49–45% e.e. *S*, 29–15% yield). The reduced chemical yields using the soluble reagent which gives *S* stereoselectivity is a troublesome point. It would thus seem that a large part of the active hydrogen in the soluble reagent with *S* stereoselectivity is rendered inactive toward reduction of acetophenone upon aging, perhaps by being "buried" in a relatively inaccessible position within the reagent molecule. This phenomenon is not noted with the initial insoluble reagent with *R* stereoselectivity.

Reduction of benzaldehyde by procedure A using $LiAlD_2(OR^*)_2$ instead of $LiAlH_2(OR^*)_2$ gave (*S*)-benzyl-α-*d* alcohol (40, 43% e.e., Table III, no. 1) with lower stereoselectivity than observed in the reduction of acetophenone to give (*R*)-phenylmethylcarbinol-α-*d* under comparable conditions (*ca.* 80% e.e., Table III, no. 3 and 4). These carbinols correspond in both cases to attack by deuteride on the *si* face of the respective carbonyl groups. Thus the steric course of these reductions is the same although the configurational designations of the products are opposite. A surprising observation was that the stereoselectivity was uniformly higher than the protio reagent (compare Table I, no. 9, 13, 19, and 20 and Table III, no. 3–7).

As a final point we would like to note that this asymmetric reduction system constitutes a reasonable method for obtaining either (*R*)-(+) or (*S*)-(−)-methylphenylcarbinol in approximately 70% enantiomeric purity. The same is true for the reduction of butyrophenone and to a lesser extent the other ketones tested. This is the method of choice for obtaining (*S*)-benzyl-α-*d* alcohol (40% e.e.) and presumably other α-deuterio chiral primary alcohols as well. Finally, these preliminary results point to the very real possibility of developing a superior reducing agent of the

same general type with even higher stereoselectivity.

Experimental Section

Instruments.—Optical rotations on small samples were taken on a Perkin-Elmer 141 electronic spectropolarimeter with digital read-out using 1-dm, center-filled water-jacketed cells thermostated at 20.0°; readings were ±0.002°. Rotations on larger samples were occasionally taken on a Zeiss visual polarimeter with readings to ±0.02°. Routine proton nmr determinations were made on a Varian T60 instrument; analytical determinations were made on a Varian HR-100 instrument ($CDCl_3$, solvent, TMS standard). ^{19}F determinations on MTPA diastereomeric esters[9] were made on a Varian XL-100 instrument ($CDCl_3$, solvent, trifluoroacetic acid external standard). Gas–liquid chromatographic (glc) determination were made on a Varian Aerograph at 40 ml/min, He flow rate, thermoconductivity detector, polyethylene glycol 20M, 5 ft × 0.25 in. column.

Reagents.—The (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol[7] (6 R*OH), $[\alpha]^{27}D$ +8.09° (*c* 9.63, EtOH), mp 55–57°, was obtained by regeneration from the hydrochloride[18] and was stored in a desiccator over P_2O_5. This alcohol was recovered and repeatedly reused. Ether, tetrahydrofuran (THF), and benzene were distilled over $LiAlH_4$ and stored over a Linde 4A molecular sieve. A stock lithium aluminum hydride solution in ether was passed through a glass filter under nitrogen and stored in a flask closed with a rubber septum. It was analyzed immediately prior to use. Aliquots were removed by syringe as needed.

Determination of Stereoselectivity by Optical Rotation.—The enantiomeric excess, % e.e.,[10] was obtained from the observed optical rotation and the known maximum rotations of the carbinols according to the following data by assuming a linear relationship between rotation and concentration, *i.e.*, % e.e. $100 \times [\alpha]D_{obsd}/[\alpha]D_{max}$: (*R*)-$PhCHOHCH_3$,[19] $[\alpha]^{20}D$ +43.1° (*c* 7.19, cyclopentane); (*R*)-$PhCHOHCF_3$,[20] $[\alpha]^{20}D$ −14.9° (*c* 15, benzene); (*R*)-*n*-PrCHOHPh,[21] $[\alpha]^{20}D$ +43.6° (*c* 4.18, benzene); (*R*)-*i*-PrCHOHPh[22], $[\alpha]^{20}D$ +47.7° (*c* 6.8, Et_2O); (*R*)-*t*-BuCHOHPh,[23] $[\alpha]^{20}D$ +27.4° (*c* 2.2, benzene); (*R*)-*t*-$BuCHOHCH_3$,[24] $[\alpha]^{20}D$ −3.31° (*c* 10.3, benzene); (*S*)-PhCHDOH,[25] $[\alpha]^{20}D$ +1.70° (*c* 2.2, EtOH), $[\alpha]^{20}D$ +1.52° (*c* 7.1, cyclopentane), $[\alpha]^{24}D$ +1.58° (neat). The optical rotation of methylphenylcarbinol in cyclopentane solvent was found to be significantly dependent upon the concentration of acetophenone present in solution. The following data were determined on solutions with known enantiomeric compositions of methylphenylcarbinol and known amounts of added acetophenone (the enantiomeric composition of samples made by procedure B which contained unreduced acetophenone were calculated based on these data and the known carbinol:ketone ratios determined by glc): $[\alpha]^{20}D$ +43.1° (*c* 7.19, C_5H_{10}, zero $PhCOCH_3$); $[\alpha]^{20}D$ +44.8° (*c* 7.86, $PhCHOHCH_3$, *c* 0.99, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +50.0° (*c* 6.66, $PhCHOCH_3$, *c* 5.12, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +52.0° (*c* 5.12, $PhCHOHCH_3$, *c* 5.12, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +54.0° (*c* 4.86, $PhCHOHCH_3$, *c* 7.28, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +56.5° (*c* 3.71, $PhCHOHCH_3$, *c* 8.99, $PhCOCH_3$ in C_5H_{10}); $[\alpha]^{20}D$ +58.3° (*c* 2.64, $PhCHOHCH_3$, *c* 10.60, $PhCOCH_3$ in C_5H_{10}).

Determination of Stereoselectivity by Nmr Method.—The carbinol (for instance, 0.10 mmol, 12 mg of $PhCHOHCH_3$) was treated with excess acid chloride from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA-Cl, 37 mg, 0.15 mmol) in pyridine according to the usual procedure.[11,26]

General Procedure A (Insoluble Reagent).—All experiments were carried out under a nitrogen atmosphere; transfers were made *via* syringe through rubber septums. The following is a detailed description of experiment 13, Table I. An ether solution (2.0 ml), containing the chiral amino alcohol 6 (R*OH) [1.02 g, 3.6 mmol, $[\alpha]^{28}D$ +8.09 (*c* 9.6, EtOH], was added at 0° to a magnetically stirred solution of $LiAlH_4$ (1.56 mmol, $LiAlH_4$: R*OH mole ratio 1.0:2.3) in ether (4.0 ml). A white, pasty precipitate began to form when about one half of 6 was added. The transfer was completed by rinsing the original flask and the syringe with 1.0 ml of ether. The reaction flask was shaken thoroughly at 0°; 3 min from the time of initial mixing, acetophenone, 4 (120 mg, 1.0 mmol), in 0.5 ml of ether was added dropwise to the precipitated reagent. The precipitate dissolved and gave a clear, transparent solution. The mixture stood for 12 hr and was then hydrolyzed with 1 drop of water (vigorous evolution of gas) and then excess dilute hydrochloric acid to dissolve the amino alcohol 6. The ether extracts were washed (H_2O, three times), dried ($MgSO_4$), and concentrated (water aspirator) to give a colorless oil (0.10 g, 82% yield) which contained no unreduced acetophenone as measured by glc (column temperature 170°): $[\alpha]^{20}D$ +29.3° (*c* 8.15, C_5H_{10}), 68.0% e.e. (*R*)-(+)-5. Alternate analysis by conversion to the MTPA derivative and measuring the nmr spectrum gave the same % e.e. Neutralization of the acid extract gave recovered chiral amino alcohol 6, $[\alpha]^{20}D$ +8.18° (*c* 10.2, EtOH).

In one run according to procedure A, the acetophenone was added just 30 sec after preparation of the reagent. This gave an oil containing no unreduced ketone, $[\alpha]^{21}D$ +29.8° (*c* 9.15, C_5H_{10}), corresponding to 69% e.e. of (*R*)-(+)-5 as given in Figure 1, point b. In still another experiment, 6 (3.6 mmol, 1.02 g) and 4 (1.0 mmol, 120 mg) were dissolved in ether (3.0 ml) and were added at 0° to $LiAlH_4$ (1.56 mmol, in 2.4 ml of ether). No precipitate formed. The solution yielded carbinol 5, containing no ketone, $[\alpha]^{21}D$ +14.2° (*c* 2.25, C_5H_{10}), corresponding to 33% e.e. of (*R*)-(+)-5. This is represented as the zero time, point a, in Figure 1.

Procedure B (Soluble Reagent).—Under a nitrogen atmosphere, an ether solution of amino alcohol 6 (1.02 g, 3.6 mmol in 2.0 ml of ether) was added to $LiAlH_4$ (1.56 mmol in 4.0 ml of ether, $LiAlH_4$:R*OH ratio 1.0:2.3) at room temperature. The transfer was completed by rinsing the original flask and syringe containing amino alcohol 6 with 1.0 ml of ether. The precipitate which formed initially dissolved after 2–3 min of reflux. After the solution was refluxed for 10 min and had stood for 24 hr at room temperature, acetophenone (4, 120 mg, 1.0 mmol) was added and the mixture was processed as in procedure A after standing at room temperature overnight to give 0.11 g of an oil, $[\alpha]^{20}D$ −35.4° (*c* 1.64, C_5H_{10}), which by glc analysis was 40% methylphenylcarbinol (5) and 60% acetophenone (4). Using $[\alpha]^{20}D$ +54.0° for the rotation of enantiomerically pure methylphenylcarbinol in the presence of 60% acetophenone, this corresponds to 66% e.e. as shown in example 19, Table I. A duplicate run which was refluxed for an additional 2 hr gave a 43:57 ratio of 5:4 with 66% enantiomeric purity of 5 as measured by optical rotation. Upon hydrolysis of these reaction mixtures hydrogen was evolved indicating excess unreacted reducing reagent.

Procedure C (Reduction in Benzene Solution).—Under nitrogen, 1.56 mmol of $LiAlH_4$ in ether was transferred to a 20-ml flask. The ether was removed under high vacuum and the residue of $LiAlH_4$ was treated with benzene solution (6.0 ml) containing 1.02 g (3.6 mmol) of amino alcohol 6. There was an exothermic reaction which resulted in the formation of a clear solution. Occasionally there was a small amount of a white solid that did not dissolve. After this benzene solution had stood for 1.5 hr, acetophenone (120 mg, 1.0 mmol) in benzene (0.5 ml) was added and the mixture was allowed to stand overnight. Processing as

(18) Aldrich Chemical Co., Milwaukee, Wis. We also acknowledge with gratitude a sample of the free base supplied by Dr. A. Pohland of Eli Lilly and Co.

(19) Spectrograde cyclopentane (C_5H_{10}) was used because of its ready availability in high purity and because the chiral alcohols could be freed readily of this volatile solvent. This value was determined on a sample of enantiometrically pure carbinol which had $[\alpha]^{21}D$ +43.5° (neat). R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

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(25) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966).

(26) J. A. Dale and H. S. Mosher *J. Amer. Chem. Soc.*, **95**, 512 (1973). The signals of both the *O*-methyl and *C*-methyl groups of the *R,R* diastereomer from methylphenylcarbinol appear at higher field than those of the *R,S* diastereomer. The peaks are too close together to be accurately integrated on the T-60 instrument but relative peak heights were shown to give a good approximation of the isomeric composition. The ^{19}F resonances for the α-CF_3 group at 94.1 MHz were clearly separated and readily integrated. The addition of the nmr shift reagent, $Eu(fod)_3$ (0.1 *M*), caused both the *O*-methyl and *C*-methyl resonances of the *R,R* diastereomer to be shifted to lower field more strongly than that of the *R,S* diastereomer, so that quantitative integration of the respective *O*-methyl signals was readily possible.

in procedure A gave a yellowish oil, 0.092 g, $[\alpha]^{20}D$ −22.1° (*c* 3.75, C_5H_{10}), which, as determined by glc, was a 49:51 mixture of 5:4 and thus corresponds to 43% e.e., *S* isomer.

Procedure D.—General procedure A was followed except that 1.2 mmol of $LiAlH_4$ was dissolved in 47 ml of ether maintained at 0° instead of 4 ml of ether. Under these circumstances no precipitate was formed when amino alcohol **6** (1.02 g, 3.6 mmol) was added to the solution. To this homogeneous solution was immediately added acetophenone (120 mg, 1.0 mmol) at 0°. The reaction mixture ws processed after standing overnight at room temperature to give a colorless oil (0.10 g, 82% yield), $[\alpha]^{20}D$ +12.5° (*c* 7.18, C_5H_{10}), 29% e.e., *R* isomer, which by glc analysis contained no unreduced acetophenone.

Sodium Aluminum Hydride Reductions.—To a suspension of sodium aluminum hydride (1.0 mmol) (Alfa Inorganics) in ether (5 ml, 1.0 mmol) was added chiral amino alcohol **6** (2.0 mmol in 3 ml of ether) at room temperature. After stirring overnight sodium aluminum hydride went into solution, leaving a small amount of turbidity. To this solution at room temperature was added acetophenone (1.0 mmol) and the reaction mixture was processed as usual to give an oil which was a 48:52 mixture of **5** and unreacted **4**, $[\alpha]^{20}D$ +2.73° (*c* 6.1, C_5H_{10}), corresponding to a 55% excess of the *R* enantiomer of **5**.

Repetition of this experiment using $NaAlH_4$ (1.2 mmol), amino alcohol **6** (3.6 mmol), and acetophenone (0.5 mmol), followed by processing in the usual way, gave an oil (97% **5** and 3% **4**) containing 17% e.e. of (*R*)-(+)-**5** enantiomer. A repetition of this experiment in benzene solvent gave a 99% yield of (*R*)-(+)-**5**, 12% e.e.

Commercial $NaAlH_2(OCH_2CH_2OMe)_2$ (Eastman Kodak, Vitride) in benzene solution (5.12 ml, containing 1.2 mmol) was mixed at 0° with 20 ml of a benzene solution containing amino alcohol **6** (0.34 g, 1.2 mmol). Hydrogen was evolved but there was no precipitate. Acetophenone (120 mg, in 1 ml of benzene) was added. The usual processing, after standing at room temperature overnight, gave a colorless oil which by glc was 73% carbinol **5** and 27% recovered ketone **4** with $[\alpha]^{20}D$ +0.98 ± 0.12° (*c* 1.63, cyclohexane), corresponding to 2.1 ± 0.3% e.e. of *R*-(+) isomer.

Reductions of Benzaldehyde with $LiAlD_4$–R*OH.—Amino alcohol **6** (3.6 mmol, 1.02 g in 1.1 ml of ether) was added to $LiAlD_4$ (1.56 mmol, in 5.84 ml of ether) at 0°. To the resulting reagent containing a precipitate was added benzaldehyde (1.0 mmol, 106 mg in 0.3 ml of ether) at 0° within 3 min of mixing the reagent. The precipitate did not dissolve immediately but went into solution after stirring for 25 min at 0°. The reduction mixture was processed as in procedure A after standing overnight at 0° to give an oil which showed only very small amounts of impurities by glc analysis (170°, retention time of PhCHO, 1.8 min, of PhCHDOH, 4.7 min). This was purified by preparative glc followed by distillation to give 0.07 g, $[\alpha]^{20}D$ +0.68 ± 0.02° (*c* 6.7, C_5H_{10}), which showed 0.988 ± 0.005 deuterium atoms per molecule based upon the relative areas of the benzylic and aromatic nmr proton signals. This corresponds to a stereoselectivity of 43 ± 2% of *S*-(+) enantiomer based upon the known maximum rotation, $[\alpha]^{20}D$ 1.58 ± 0.04° (*c* 7.07, C_6H_{10}), and configuration for benzyl-α-*d* alcohol.[25,27] A 22-mg sample of this product was converted to the (*R*)-MTPA derivative (55 mg). Although the nmr signals of neither the benzylic nor OCH_3 protons of the resulting diastereomers were appreciably separated at 100 MHz in $CDCl_3$ solvent, in the presence of 0.4 *M* Eu(fod)$_3$ shift reagent the benzylic signals appeared respectively at 6.35 and 6.45 ppm (100 MHz) with relative areas 70:30 corresponding to a 40 ± 2% e.e. of the *S* enantiomer.

According to procedure B (duplicating experiment 26, Table I), 212 mg of benzaldehyde was treated with a solution prepared by adding amino alcohol **6** (2.04 g, 7.2 mmol in 6 ml of ether) to $LiAlD_4$ (2.4 mmol in 8 ml of ether). After the indicated processing, an oil, 0.76 g, which was 72% benzyl alcohol and 28% benzaldehyde, was purified by glc and distillation to give benzyl-α-*d* alcohol, 0.98 ± 0.01% deuterium atoms per molecule (by nmr), $[\alpha]^{20}D$ +0.33 ± 0.04° (*c* 5.54, EtOH), corresponding to 19.5 ± 3% e.e. of the *S*-(+) enantiomer based on $[\alpha]^{20}D$ +1.70° (*c* 2, EtOH) for the pure *S* enantiomer.

Reduction of Acetophenone with $LiAlD_4$·R*OH.—At 0° according to procedure A, duplicating experiment 13, Table I but substituting $LiAlD_4$ for $LiAlH_4$ there was obtained an almost quantitative yield of 1-phenylethanol-1-*d*, $[\alpha]^{20}D$ +38.9° (*c* 6.13, C_6H_{10}), 0.99 deuterium atoms per molecule. Assuming that the rotation of the deuterio and isotopically normal compounds are the same, an assumption which could easily introduce a ±3% error, the stereoselectivity of the reaction to give the *R* enantiomer was 90%. A sample of this carbinol was converted to the MTPA derivative and the nmr spectrum was taken in the presence of 0.2 *M* Eu(fod)$_3$ shift reagent. Integration of the OCH_3 signals indicated an 81.4% excess of the *R* enantiomer. Another run using 1:1.54 molar ratio of $LiAlD_4$:**6** gave $[\alpha]^{20}D$ +34.5° (*c* 6.72, C_6H_{10}), $[\alpha]^{20}D$ +34.9° (*c* 5.94, C_5H_{10}), corresponding to 80% e.e. on the assumption that the presence of deuterium does not appreciably alter the optical rotation. Conversion of this derivative to the MTPA derivative followed by integration of the OCH_3 nmr signals in the presence of 0.2 *M* Eu(fod)$_3$ gave a value of 79.5% e.e. We discount the high rotation obtained in the initial experiment and conclude that the reaction goes with a stereoselectivity of approximately 80%.

Registry No.—**6**, 38345-66-3; lithium aluminum hydride, 16853-85-3.

(27) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher[25] have reported the maximum neat rotation of benzyl-α-*d* alcohol as $\alpha^{24}D$ +1.66 ± 0.01° (neat, *l* 1). A sample of benzyl-α-*d* alcohol from fermentation of benzaldehyde-α-*d* with 89 ± 2% deuterium had $\alpha^{24}D$ +1.43 ± 0.02° (neat, *l* 1) and $[\alpha]^{20}D$ +0.100 ± 0.001° (*c* 7.07, C_6H_{10}). On this basis $[\alpha]^{20}D$ +1.58 ± 0.04° (*c* 7, C_5H_{10}) is the maximum specific rotation in this solvent.

Thermal [2 + 2] Cycloaddition of Cyclopropylethylene with Tetracyanoethylene[1]

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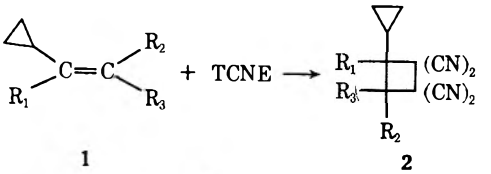
A number of ethylenes substituted by cyclopropyl group(s) (**1a–1k**) are found to undergo thermal [2 + 2] cycloaddition with tetracyanoethylene under mild conditions. Among the olefins studied, 1,1-dicyclopropylethylene (**1a**) was the most reactive while 1,2-dicyclopropylethylene (**1d** and **1e**) were the least reactive; namely, geminal cyclopropyls greatly enhanced the reactivity of ethylene. It was noted that the rate of reaction is influenced by solvent polarity; in other words, the reaction proceeds rapidly in a polar solvent: k_2 (acetonitrile)/(ethyl acetate) = 10^3. Further, the cycloaddition was found to be more than 90% stereospecific. It was surmised that the present cycloaddition should be a donor–acceptor cycloaddition of tetracyanoethylene with cyclopropylethylene, which is highly electron rich.

Tetracyanoethylene (TCNE)[2] has been known not only as a very reactive dienophile[3] but also as an activated olefin which is capable of undergoing [2 + 2] cycloaddition[4] with some conjugated olefins and with electron-rich olefins.[2,5,6] Interestingly, it reacts also with cyclopropylethylenes[7] in a [2 + 2] manner under mild conditions.[1] Recently, Effenberger and Podszun[8] and Barton and Rogido[9] also demonstrated the high reactivities of 1,1-dicyclopropylethylene and 2-cyclopropylpropene in a [2 + 2] cycloaddition with isocyanates.

Results

Structure and Reactivity of Olefins.—Various mono-, di-, and tricyclopropylethylenes (**1a–1k**) produce [2 + 2] cycloadducts in their reaction with TCNE (Table I). Among olefins, the most reactive ethylene is 1,1-dicyclopropylethylene (**1a**). The rate of reaction was so rapid that the color developed and disappeared at once, and immediate evaporation of the solvent gave the adduct **2a** in a quantitative yield. The reaction was somewhat slower with 1,1-dicyclopropylpropene (**1b**) and much slower with 1,1-dicyclopropyl-3-methyl-1-butene (**1c**). The reactivity sequence observed here,



1 **2**

a, R_1 = c-C_3H_5; R_2 = R_3 = H
b, R_1 = c-C_3H_5; R_2 = CH_3; R_3 = H
c, R_1 = c-C_3H_5; R_2 = $CH(CH_3)_2$; R_3 = H
d, R_1 = R_2 = H; R_3 = c-C_3H_5
e, R_1 = R_3 = H; R_2 = c-C_3H_5
f, R_1 = CH_3; R_2 or R_3 = c-C_3H_5; R_3 or R_2 = H
g, R_1 = R_2 = c-C_3H_5; R_3 = H
h, R_1 = R_2 = R_3 = H
i, R_1 = CH_3; R_2 = R_3 = H
j, R_1 = c-C_3H_5; R_2 = C_6H_5; R_3 = H
k, R_1 = c-C_3H_5; R_2 = R_3 = CH_3

1a > **1b** > **1c**, can be interpreted as the result of steric hindrance of the reaction caused by substitution at the 2 position.

On the other hand, *trans*- and *cis*-1,2-dicyclopropylethylene (**1d** and **1e**) exhibit the lowest reactivity. Under standard conditions (see Experimental Section), **1d** and **1e** produce blue solutions, respectively, but the color remained unchanged even after a lapse of 2 months in both cases. In a polar solvent at an elevated temperature, however, the same reaction took place, and the adducts **2d** and **2e** were isolated as crystalline products. The nmr analyses of the crude adduct fraction show that the adduct was not contaminated by its stereoisomer in both cycloadditions. Thus, it was concluded that the cycloaddition proceeds with a stereospecificity of more than 90%.[10]

Introduction of a methyl group on one of the olefinic carbons makes **1f** much more reactive than the parent **1d** or **1e**. The color faded in this case after *ca.* 5 hr under standard conditions. The third cyclopropyl group also brings about a reactivity increase, as seen in the reaction time of **1g**.

The least substituted ethylene, *i.e.*, vinylcyclopropane (**1h**), reacted fairly slowly, but the adduct **2h** was isolated in 63% yield after 28-hr reflux in methylene dichloride. Again, the substitution of C-1 hydrogen by a methyl markedly increased the reactivity of **1i**.

2,2-Dicyclopropylstyrene (**1j**), in which the substituent at the 2 position is phenyl, has a relatively low reactivity. Under standard conditions, it re-

(1) Preliminary communications: (a) S. Nishida, I. Moritani, and T. Teraji, *Chem. Commun.*, 501 (1970); (b) *ibid.*, 36 (1971).

(2) For a leading reference on the chemistry of polycyano olefins, see E. Ciganeck, W. J. Linn, and O. W. Webster in "The Chemistry of Cyano Group," Z. Rappoport, Ed., Interscience, New York, N. Y., 1970, Chapter 9.

(3) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).

(4) J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 2 (1962).

(5) (a) A. T. Blomquist and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **79**, 5316 (1957); (b) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **81**, 667 (1959); (c) J. K. Williams, *ibid.*, **81**, 4013 (1959); (d) K. Hafner and J. Schneider, *Justus Liebigs Ann. Chem.*, **624**, 37 (1959); (e) R. Criegee, *Angew. Chem., Int. Ed. Engl.*, **1**, 519 (1962); (f) C. A. Stewart, Jr., *J. Amer. Chem. Soc.*, **84**, 117 (1962); (g) C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963); (h) R. C. Cookson, J. Dance, and J. Hudec, *J. Chem. Soc.*, 5416 (1964); (i) C. A. Stewart, Jr., *J. Amer. Chem. Soc.*, **87**, 4021 (1965); (j) J. J. Eiseh and G. R. Husk, *J. Org. Chem.*, **31**, 589 (1966).

(6) (a) J. K. Williams, D. W. Willey, and B. C. McKusick, *J. Amer. Chem. Soc.*, **84**, 2210, 2216 (1962); (b) R. W. Hoffmann and H. Hauser, *Angew. Chem., Int. Ed. Engl.*, **3**, 380 (1964); (c) R. C. Cookson, B. Halton, I. D. R. Stevens, and C. T. Watts, *J. Chem. Soc. C*, 928 (1967); (d) P. D. Bartlett, *Quart. Rev., Chem. Soc.*, **24**, 473 (1970); (e) R. W. Hoffmann, U. Bressell, J. Gehlhaus, and H. Hauser, *Chem. Ber.*, **104**, 873 (1971). For leading references of related cycloadditions, see (f) S. Proscow, H. E. Simmons, and T. L. Cairns, *J. Amer. Chem. Soc.*, **88**, 5254 (1966); (g) R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **7**, 754 (1968); (h) R. Gompper, *ibid.*, **8**, 312 (1969).

(7) (a) S. Nishida, I. Moritani, E. Tsuda, and T. Teraji, *Chem. Commun.*, 781 (1969); (b) T. Teraji, I. Moritani, E. Tsuda, and S. Nishida, *J. Chem. Soc. C*, 3252 (1971).

(8) F. Effenberger and W. Podszun, *Angew. Chem., Int. Ed. Engl.*, **8**, 976 (1969).

(9) T. J. Barton and R. J. Rogido, *Chem. Commun.*, 878 (1972).

(10) Nmr spectra of **2d** and **2e** differ at several points in that the mutual contamination of the isomeric adduct can be detected by an nmr examination when more than 10% of the isomer is present in the sample.

TABLE I

CYCLOADDITION REACTIONS OF CYCLOPROPYLETHYLENE WITH TCNE

Ethylene[a]	Compd	CT_{max}, nm, in CH_2Cl_2	Reaction conditions: Solvent	Temp,[b]	Time, sec[c]	Product[h]	Mp, °C	Yield, %[d]
1,1-(c-C_3H_5)$_2$	1a	...[e]	CH_2Cl_2	rt	1–2	2a	167–168	87
1,1-(c-C_3H_5)$_2$-2-CH_3	1b	(540)[e]	CH_2Cl_2	rt	150	2b	153–155	81
1,1-(c-C_3H_5)$_2$-2-$CH(CH_3)_2$	1c	550	CH_2Cl_2	rt	25,000	2c	136–137	81
trans-1,2-(c-C_3H_5)$_2$	1d	549	CH_3NO_2	100	9,000	2d	159–160.5	11[f]
cis-1,2-(c-C_3H_5)$_2$	1e	549	CH_3NO_2	100	9,000	2e	165–167	25[f]
1,2-(c-C_3H_5)$_2$-1-CH_3[g]	1f	602	CH_2Cl_2	rt	17,000	2f	97–98.5	58
1,2,3-(c-C_3H_5)$_3$	1g	635	CH_2Cl_2	rt	900	2g	161–162.5	76
c-C_3H_5	1h	420	CH_2Cl_2	Reflux	100,000	2h	124–125	63
1-c-C_3H_5-1-CH_3	1i	448	CH_2Cl_2	rt	1,400	2i	108–109.5	35
1,1-(c-C_3H_5)$_2$-2-C_6H_5	1j	400,600	CH_3CN	rt	430,000	2j	160.5–161.5	74
1,1-(c-C_3H_5)$_2$-2,2-$(CH_3)_2$	1k	580	CH_2Cl_2	rt	140,000	2k	148–149	70

[a] c-C_3H_5 = cyclopropyl. [b] Room temperature (rt) was 20–25°; some experiments were carried out in a thermostat at 25 or 100°. [c] Time required for the completion of color change. [d] Based on the isolated and recrystallized product. [e] Color fading was so rapid that the measurement could not be made. [f] Some TCNE was recovered; yield is based on consumed TCNE. [g] A mixture of geometrical isomers. [h] Satisfactory analytical and osonometric molecular weight data were reported for all products listed in the table: Ed.

quires more than 1 month for the completion of the color change. In acetonitrile, the addition was completed after a lapse of 5 days at room temperature and the [2 +2] cycloadduct **2j** was isolated in a 74% yield.

Effect of Solvent Polarity.—The cycloaddition of **1g** with TCNE was carried out in various solvents and the time required for the completion of the color change was determined at 25°. The results are summarized in Table II. The reaction proceeds quickly in a polar solvent such as nitromethane or acetonitrile and slowly in ethyl acetate. The solvent effect observed here is very similar to those reported for the cycloaddition of *p*-methoxystyrene with TCNE.[6a,6d,11]

TABLE II

EFFECT OF SOLVENT POLARITY ON THE RATES OF CYCLOADDITION AT 25°

Solvent	1g + TCNE: Time, sec[a]	1g + TCNE: Yield of 2g, %	*p*-Methoxystyrene + TCNE: Time, sec[a,b]	*p*-Methoxystyrene + TCNE: Rel rate[c]
CH_3CN	30	80		570
CH_3NO_2	35	80	60	
$CH_3CH_2CH_2NO_2$	240	78		
CH_2Cl_2	600	66		340
$CHCl_3$	1,200	70		
$CH_3COOC_2H_5$	28,000	81	80,000	1.0
C_6H_{12}			2,600,000	0.00091

[a] Time required for the completion of color change of the solution. [b] Reference 6a. [c] Calculated from k_2 (l. mol^{-1} sec^{-1}) obtained by Wiley and Simmons, cited in ref 11a.

It will be noteworthy to mention that the products isolated in various solvents are all identical, and no 2:1 cycloadduct has been so far detected.[12] The formation of the same adduct as a single product in a different solvent was also examined in other cases. Moderately reactive **1k** gave the adduct **2k** in acetonitrile (70% yield) or in methanol (23% yield) without any other characterizable adduct. The low yield of **2k** in methanol is due to the consumption of TCNE by methanol (see Experimental Section). Indeed, the highly reactive **1a** gave **2a** in 78% yield in methanol, while the low-reactive **1j** produced **2j** only in a 9% yield. Trapping of a possible intermediate by methanol or of the 2:1 adduct has thus been unsuccessful.

Discussion

The present cycloaddition behaves like a thermal[13] [2 + 2] cycloaddition of an electron-rich olefin with a strongly electron-demanding TCNE (donor–acceptor cycloaddition). It strongly suggests that the cyclopropylethylene should be a highly electron-rich olefin like vinyl ether.[6] In fact, some representative cyclopropylethylenes have shown extraordinarily low ionization potentials as an alkene.[14] Thus, 8.08 eV was found for the adiabatic ionization potential of **1a**, 7.72 eV for **1d**, 7.70 eV for **1e**, and 7.48 eV for **1g**, respectively. *However, it was not the olefin of lowest ionization potential that shows the highest reactivity in the present cycloaddition.* For example, the most reactive **1a** possessed a rather high ionization potential, while **1g** showed a mere moderate reactivity in the cycloaddition, although its ionization potential was the lowest. Moreover, in a comparison of three dicyclopropylethylenes, the ionization potentials of 1,2-dicyclopropylethylenes (**1d** and **1e**) were considerably lower than that of 1,1 isomer **1a**, but **1d** or **1e** was far less reactive than **1a**. Apparently, the geminal cyclopropyls greatly enhance the reactivity of ethylene.[15] The important factor for the ease of the present cycloaddition, besides a high reactivity of TCNE, will thus be the strong stabilizing interaction of the cyclo-

(11) (a) E. M. Kosower, *Progr. Phys. Org. Chem.*, **3**, 81 (1965); (b) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, part 1.7.

(12) In some donor–acceptor cycloadditions, a 2:1 cycloadduct has been isolated. See (a) M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965); (b) P. Otto, L. A. Feiler, and R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **7**, 737 (1968); (c) R. Huisgen, B. A. Davis, and M. Morikawa, *ibid.*, **7**, 826 (1968). See also ref 6a.

(13) In complete dark, the reaction of **1g** with TCNE proceeded at the same rate as that under room light. Also, illumination of a blue solution of **1j** with TCNE with a 100-W tungsten lamp resulted in no change either in the reaction rate or in the course of the reaction. Therefore, the reaction is thermal.

(14) S. Nishida, I. Moritani, and T. Teraji, *Chem. Commun.*, 1114 (1972).

(15) Graf also noted in their study on the cycloaddition of *N*-chlorosulfonyl isocyanate with alkenes that the olefin possessing a structure of $R_2C{=}CH_2$ has a much higher reactivity than that of RHC=CHR: R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963); *Angew. Chem., Int. Ed. Engl.*, **7**, 172 (1968).

propyl group with an adjacent electron-deficient center[16] in the highly polarized transition state.[17] A methyl substitution at the 1 position of cyclopropylethylene also results in a reactivity increase, but its effect appears to be smaller than that caused by a successive cyclopropyl substitution (**1a**:**1i** and **1g**:**1f**). The methyl group will stabilize the polarized transition state also, but cyclopropyl accomplishes it to a much higher extent.

The substitution by an alkyl at the 2 position results in the reactivity decrease primarily because of the steric hindrance, which can be seen in a reactivity sequence of **1a** > **1b** > **1g** > **1c**. An exception for the trisubstituted ethylene was **1j**, which reacted much more slowly than either one of the trisubstituted cyclopropylethylenes. Its low reactivity may be due to self-quenching of the reaction.[18] To reach the transition state, it may be necessary for the TCNE to form a complex with the double bond to be reacted, but in **1j** the TCNE may primarily form a complex with the extended π-electron system (the styrene moiety) of **1j** and it will be far less effective for the cycloaddition.

The olefin **1k** is tetrasubstituted; thus it should have a considerably large steric hindrance. Yet the same cycloaddition proceeds rather smoothly. Again, the geminal cyclopropyls greatly enhance the reactivity of the ethylene.

Experimental Section

General.—Ir spectra were recorded on either a Hitachi EPI-S2 spectrophotometer or a Hitachi 215 grating infrared spectrophotometer. Electronic absorption spectra were taken on a Hitachi EPS-2U recording spectrophotometer. Nmr spectra were obtained with either a JEOL JNM-4H-100 or a JNM MH-60 spectrometer. Elemental analyses were performed either by the Microanalytical Laboratory, Faculty of Engineering Science, Osaka University, or by the Microanalytical Laboratory, Faculty of Pharmacy, Hokkaido University. Melting points are uncorrected.

The cycloaddition was carried out by mixing the two components in an appropriate solvent. Standard reaction conditions are set as 0.05 *M* for both reactants in methylene dichloride at room temperature. When the reaction was carried out in acetonitrile or in methanol, the concentrations of the two reactants increased up to 0.5 mol/l. The time required for the completion of the color change was determined as a measure for the reaction rate.[6a]

After the color change was completed, the product was isolated and characterized in the usual manner. In the following section, experiments of some representative ethylenes with TCNE are described.

Reaction of 1,1-Dicyclopropylethylene (1a) with TCNE. In Methylene Dichloride.—To a solution of 640 mg (5.00 mmol) of TCNE in 100 ml of methylene dichloride, 550 mg (5.10 mmol) of **1a** was added in one portion. A reddish brown color developed instantly but the solution became colorless after 1 or 2 sec. The solvent was evaporated immediately, and the residual solid, mp 164–167°, was recrystallized from the chloroform–carbon tetrachloride (1:2) mixture; 1026 mg (87%) of **2a** was obtained. Pure crystals melted at 167–168°. The high melting point and ir of the crude product were strong evidence supporting the fact that the cycloaddition was proceeding quantitatively.

In Methanol.—A solution of 642 mg (5.02 mmol) of TCNE in 8 ml of absolute methanol was made at 25°, and 541 mg (5.01 mmol) of **1a** was added to it in one portion. An orange-red color developed but it faded after *ca.* 10 sec. Solvent evaporation and recrystallization gave 917 mg (78%) of pure **2a**. A comparison run on mixture melting point and ir confirmed the identity of the two samples.

Reactions of β,β-Dicyclopropylstyrene (1j) with TCNE.—A dark violet solution (λ_{max} 376 and 545 nm) of 321 mg (2.43 mmol) of TCNE and 465 mg (2.53 mmol) of **1j** in 5 ml of acetonitrile was kept at room temperature. The absorption maximum at 545 nm decreased in intensity with the lapse of time and two new absorptions appeared at 387 and 415 nm. After 5 days, the color of the solution became yellow and no more change was observed. Therefore, the solution was concentrated under reduced pressure and the resultant residue was recrystallized from benzene. The adduct **2j** was isolated as colorless needles, 581 mg (74%). Analytically pure material melted at 160.5–161.5° dec. The yellow product, which appears to be the cause for two absorptions at 387 and 415 nm, which formed was so small in quantity that the product could not be characterized.

In methanol, under an argon stream, the same adduct **2j** was isolated in 9% yield after 9 days of reaction. When TCNE (320 mg) alone was dissolved in 5 ml of methanol, it reacted with the solvent at room temperature and the recovered TCNE after 24 hr was a mere 14 mg (4% recovery).

A blue solution (λ_{max} 400 and 600 nm) of 323 mg (2.52 mmol) of TCNE and 4662 mg (25.3 mmol) of **1j** in 100 ml of methylene dichloride was irradiated with a 100-W tungsten lamp from the bottom of the reaction flask. The mixture refluxed gently during the illumination. After 40 hr, it became light green, and it was yellow after 53.5 hr. The solution was concentrated under reduced pressure and the residue was washed with petroleum ether (bp 30–60°), mp 156–157° dec, 739 mg (94%). The ir spectrum of the present sample was superimposable on that of pure **2j** obtained before.

In a separate flask, a mixture very similar to the above was refluxed gently without illumination. The solution became light green after 35 hr and light brown after 41.5 hr.

Spectroscopic Data.—In ir spectra, all adducts exhibited the C≡N stretching vibration at 2240–2260 and cyclopropyl vibrations at 3010–3110 and 1015–1025 cm^{-1}. In the nmr (Table III), signals due to cyclobutane ring protons, methyl, isopropyl, and phenyl appeared at reasonable positions with reasonable splittings. Cyclopropyl protons appeared, in general, as two to four groups of complex multiplets with varying signal areas. The total numbers of cyclopropyl protons were, of course, those deduced from the [2 + 2] cycloadducts. In cycloadditions of tetracyclopropylethylene with TCNE and 1,1-dicyclopropyl-2,2-diphenylethylene dith TCNE,[1b] [2 + 2] cycloadducts were not produced but TCNE was cycloadded to one of the cyclopropane ring. Thus, in these adducts, additional signals due to cyclopentyl ring protons appeared at lower fields. Comparisons of these nmr spectra with those of the present adducts confirm the structure of the present products as [2 + 2] cycloadducts.

TABLE III
NMR SPECTRA OF THE ADDUCT[a]

Adduct	Nmr signals, τ
2a	7.88 (s, 2 H), 8.85–9.95 (m, 10 H)
2b	7.48 (q, 1 H, J = 7 Hz), 8.72 (d, 3 H, J = 7 Hz), 8.2–10.3 (m, 10 H)
2c	7.7 (m, 2 H), 8.92 (d, 3 H, J = 6 Hz), 9.03 (d, 3 H, J = 6 Hz), 8.4–9.7 (m, 10 H)
2d	7.6 (m, 2 H), 8.7–9.7 (m, 10 H)
2e	7.45 (m, 2 H), 8.35–9.75 (m, 10 H)
2g	7.67 (d, 1 H, J = 10 Hz), 8.2–9.9 (m, 15 H)
2h	7.1 (m, 3 H), 8.8–9.6 (m, 5 H)
2i	7.25 (s, 2 H), 8.45 (s, 3 H), 8.6–9.8 (m, 5 H)
2j	2.25 (s, 5 H), 4.20 (s, 1 H), 8.1–9.9 (m, 10 H)
2k	8.35 (s, 6 H), 8.7–9.4 (m, 10 H)

[a] In $CDCl_3$ except **2g**, which was recorded in CD_3COCD_3.

(16) C. D. Poulter and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2297 (1972), and references cited therein.

(17) R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes," Vol. 1, S. Patai, Ed., Interscience, New York, N. Y., 1964, p 787; see also ref 2, 6, 9, 11, and 12.

(18) The cycloaddition was effectively slowed down by an addition of an equimolar quantity of nonreacting aromatic hydrocarbon. Thus in the presence of various aromatics, the following time was necessary for the reaction of **1b** with TCNE under standard conditions: mesitylene, 27 min; *p*-xylene, 19 min; toluene, 11.5 min; benzene, 5.5 min; and cyclohexane, 2.5 min. Thus, the complexed TCNE with a nonreacting aromatic hydrocarbon is no more reactive, or at least far less reactive, than the free TCNE.

Registry No.—**1a**, 822-93-5; **1b**, 18738-69-7; **1c**, 38868-43-8; **1d**, 10359-44-1; **1e**, 23510-65-8; **1f**, 27847-24-1; **1g**, 23603-63-6; **1h**, 693-86-7; **1i**, 4663-22-3; **1j**, 23772-96-5; **1k**, 27720-84-9; **2a**, 26047-84-7; **2b**, 38858-55-8; **2c**, 38858-56-9; **2c**, 27926-30-3; **2e**, 27829-87-4; **2f**, 27847-26-3; **2g**, 27847-25-2; **2h**, 38858-59-2; **2i**, 27847-27-4; **2j**, 38858-61-6; **2k**, 31776-08-6; TCNE, 670-54-2.

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Secondary Deuterium Isotope Effects in the Solvolysis of Cyclobutyl and Cyclopropylcarbinyl Methanesulfonates

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Deuterated cyclobutyl methanesulfonates **1a–d** and cyclopropylcarbinyl methanesulfonates **2a–d** were prepared and their solvolysis rates were measured in 60% aqueous diglyme. With cyclobutyl methanesulfonates, a reduced α effect, an inverse β effect, and a rather large normal γ effect were observed. These results indicate a strong 1–3 interaction in the transition state. The isotope effects found in solvolysis of cyclopropylcarbinyl methanesulfonates are inconclusive with respect to a possible bridging in the transition state. A degenerate internal rearrangement of cyclopropylcarbinyl methanesulfonate was demonstrated to occur during acetolysis.

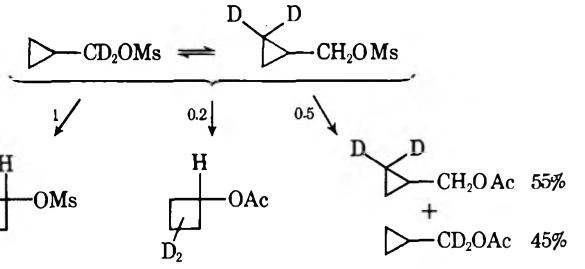
Since the early work by Bergstrom and Siegel[1] and Roberts, *et al.*,[2] solvolytic rearrangements of cyclopropylcarbinyl and cyclobutyl derivatives remained on the scene of mechanistic chemistry.[3,4] However, even after two decades the exact structure of the solvolytic intermediate(s) is still ambiguous. Recent results[4,5] clearly showed that the cyclopropylcarbinyl → cyclopropylcarbinyl, the cyclopropylcarbinyl → cyclobutyl, and the cyclopropylcarbinyl → allylcarbinyl rearrangements are highly stereospecific, the rotation of the methylene group being completely absent during rearrangements. This conclusion has been more recently confirmed by the nmr studies of stable cyclopropylcarbinyl and cyclobutyl cations generated from the corresponding alcohols in SbF_5–SO_2ClF solutions at low temperatures.[6] The nmr spectra showed three signals: two three-proton methylene doublets and a one-proton methine multiplet. Cyclobutyl and cyclopropylcarbinyl derivatives appear to solvolyze by forming in the rate-determining step one and two intimate ion pairs, respectively, which then further ionize to the corresponding equilibrating solvent-separated ion pairs.[7,8] A number of nonclassical structures for the intermediate cations could fit this scheme.

In this paper we wish to report about secondary isotope effect studies in the solvolysis reaction of cyclobutyl and cyclopropylcarbinyl methanesulfonates which lead, *inter alia*, to a reinterpretation of some earlier findings.[9]

Results

Specifically deuterated cyclobutyl methanesulfonates **1a–d** and cyclopropylcarbinyl methanesulfonates **2a–d** were prepared as described in the Experimental Section.

The acetolysis of the cyclopropylcarbinyl derivatives is known to be accompanied by an internal return to cyclobutyl isomers.[2] Therefore, a degenerate cyclopropylcarbinyl → cyclopropylcarbinyl rearrangement could also be expected. Such an internal return reaction could change the rate constant during the solvolysis of deuterated cyclopropylcarbinyl derivatives because of the label scrambling. In the present work we checked this possibility by following the acetolysis of cyclopropylcarbinyl-*1,1-d*$_2$ methanesulfonate (**2a**) in perdeuterated acetic acid at 37° using the nmr technique. The observed changes of the proton signals are shown in Figure 1. The spectra in Figure 1 clearly demonstrate the occurrence of a degenerate cyclopropylcarbinyl rearrangement reaction as well as the internal return into cyclobutyl methanesulfonate and the formation of two corresponding acetates. The relative rates obtained by integration of the final spectra are given in the scheme below.



These results are in good agreement with previous experimental evidence.[2,8]

Methanesulfonates **1a–d** and **2a–d** were solvolyzed in 60% aqueous diglyme at 40° and the reaction rates were followed by continuous titration of liberated acid by means of an automatic recording titrator. The rate constants and the corresponding kinetic isotope

(1) C. G. Bergstrom and S. Siegel, *J. Amer. Chem. Soc.*, **74**, 145 (1952).
(2) M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960), and references cited therein.
(3) Reviews: Chapters by H. G. Richey, Jr., and by K. B. Wiberg, B. A. Andes, Jr., and A. J. Ashe in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N. Y., 1971.
(4) Z. Majerski and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 665 (1971), and references cited therein.
(5) K. B. Wiberg and G. Szeimies, *J. Amer. Chem. Soc.*, **92**, 571 (1970); **90**, 4195 (1968).
(6) G. A. Olah, C. L. Jeuell, D. P. Kelly, and R. D. Porter, *J. Amer. Chem. Soc.*, **94**, 146 (1972).
(7) Z. Majerski, S. Borčić, and D. E. Sunko, *Tetrahedron*, **25**, 301 (1969).
(8) Z. Majerski, S. Borčić, and D. E. Sunko, *Chem. Commun.*, 1636 (1970).
(9) S. Borčić, M. Nikoletić, and D. E. Sunko, *J. Amer. Chem. Soc.*, **84**, 1615 (1962).

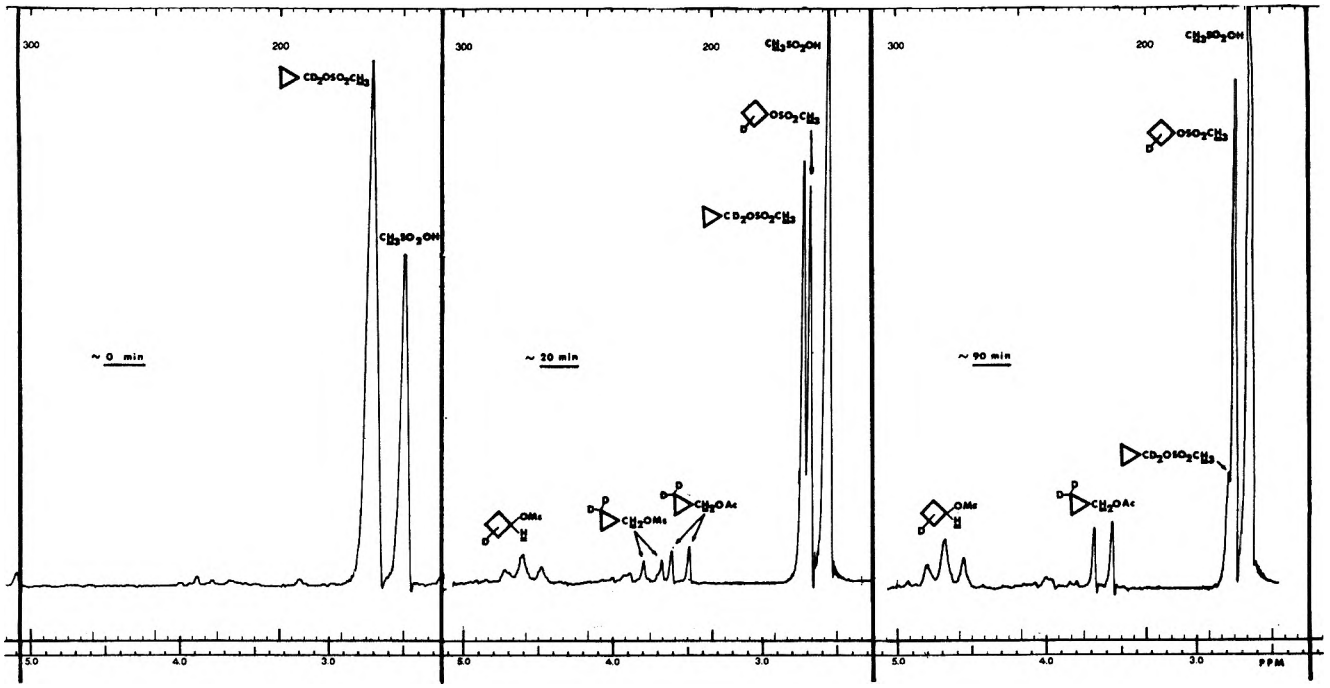


Figure 1.—The acetolysis of cyclopropylcarbinyl-*1,1-d*$_2$ methanesulfonate (**2a**) in CD_3COOD followed by nmr at 37°.

effects were calculated using a nonlinear least square program. The results are given in Table I.

The internal rearrangement of cyclopropylcarbinyl to cyclobutyl methanesulfonate under the experimental conditions used for kinetic measurements is known[7] to account for only 10% of the reaction products. Hence, it can easily be shown, on the basis of the relative rates in acetic acid as given in the scheme, that the maximum concentration of **2c** (**2a**) occurring during the solvolysis of **2a** (**2c**) is too low to produce experimentally detectable reaction rate changes.[10]

Discussion

Solvolysis of Cyclobutyl Methanesulfonates.—The α-deuterium isotope effect in the solvolysis of cyclobutyl methanesulfonate (1.10) is small compared to the maximum possible value for the solvolysis of a secondary sulfonate ester (1.22).[11] It is difficult to ascribe this reduction in magnitude of the isotope effect unequivocally to a single distinct cause. According to Shiner[11] a maximum α effect can be expected if in the reaction transition state there is no covalent bonding between the α carbon and either the leaving group or the nucleophile. In the particular case examined, nucleophilic participation by the solvent (k_s) is not probable, since the reaction products are extensively rearranged. Under the experimental conditions used in this work, it is possible that ionization (formation of the intimate ion pair) is the rate-determining step. In such a case, there would still be some covalent bonding between the reaction center and the leaving group in the transition state and the α effect should be reduced in magnitude. However, the effect is too low (by about 5%) to be ascribed to simple ionization as rate determining.[12a] On the other hand, maximum overlap calculations and ^{13}C–H coupling constants show that C–H bonding orbitals in cyclobutane have less p character ($sp^{2.65}$) than the corresponding orbitals in a tetrahedral carbon.[13] Since α-deuterium effects have been rationalized in terms of hybridization changes occurring at the reaction center, it is possible that the small α effect in the solvolysis of cyclobutyl methanesulfonate reflects this special hybridization in the ground state. Finally, neighboring group participation (k_Δ) is analogous, with respect to isotope effect, to nucleophilic partipation by the solvent (k_s). Streitwieser suggested[14] that participation could reduce the magnitude of the α effect. Available data demonstrate[15] that, indeed, the α effect is significantly reduced by participation, but only when the new bond is already rather strong in the reaction transition state. Thus, the reduced α effect measured in solvolysis of cyclobutyl methanesulfonate could also be ascribed to neighboring group participation.

Secondary β-deuterium isotope effects have been rationalized in terms of hyperconjugation and amount to $1.00 \leq k_H/k_D \leq 1.30$ per atom D, depending on the dihedral angle between the incipient empty p orbital and neighboring C–H(D) bonding orbitals.[16] The

(10) It appears from the nmr spectra that in acetolysis the maximum concentration of the rearranged cyclopropylcarbinyl methanesulfonate is reached by the time when one third of the final amount of the rearranged cyclopropylcarbinyl acetate is formed. At that time the concentration of both of these compounds is about equal. From these data and the relative rates in the scheme it can be calculated that the maximum concentration of **2a** (**2c**) in the acetolysis of **2c** (**2a**) is about 5% of the initial concentration of the starting methanesulfonate. During acetolysis, 60% of cyclopropylcarbinyl methanesulfonate internally rearranges to cyclobutyl methanesulfonate as compared with only 10% during solvolysis in 60% aqueous diglyme. It can be assumed that in the latter solvent the degenerate internal rearrangement would be also correspondingly less important.

(11) V. J. Shiner, Jr., and R. D. Fisher, *J. Amer. Chem. Soc.*, **93**, 2553 (1971), and references cited therein.

(12) Review: Chapter 2 by V. J. Shiner, Jr., in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., ACS Monograph 167, Van Nostrand-Reinhold, Princeton, N. J., 1970, (a) pp 115–118; (b) p 98; (c) p 107; (d) p 121.

(13) M. Randić and Z. B. Maksić, *Chem. Rev.*, **72**, 43 (1972).

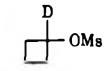
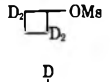
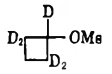
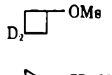
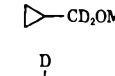
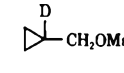
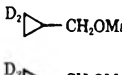
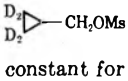
(14) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 173–175.

(15) Review: Chapter 3 by D. E. Sunko and S. Borčić in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., ACS Monograph 167, Van Nostrand-Reinhold, Princeton, N. J., 1970, and references cited therein.

(16) V. J. Shiner, Jr., and J. S. Humphrey, Jr., *J. Amer. Chem. Soc.*, **85**, 2416 (1963).

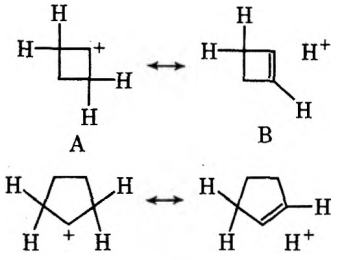
TABLE I

DEUTERIUM ISOTOPE EFFECTS IN THE SOLVOLYSIS OF THE CYCLOBUTYL (1)[a] AND CYCLOPROPYLCARBINYL (2)[b] METHANESULFONATES IN 60% AQUEOUS DIGLYME

Compd	Compd no.	Deuterium content %	Temp, °C	k_H/k_D[c]	k_H/k_D[d]
	1a	98	40	1.102 (1)	1.103 (1)
	1b	93	40	0.934 (6)	0.928 (6)
	1c	94	40	1.001 (4)	1.004 (4)
	1d	76	40	1.055 (3)	1.077 (2)
	2a	98	20	1.298 (1)	1.319 (1)
	2b	94	20	1.014 (1)	1.015 (1)
	2c	98	20	0.964 (3)	0.963 (2)
	2d	96	20	0.941 (4)	0.938 (3)

[a] Rate constant for undeuterated 1 was 2.725×10^{-4} sec^{-1}. [b] Rate constant for undeuterated 2 was 2.607×10^{-3} sec^{-1}. [c] The values of isotope effects were calculated from four to six individual rate constants for both deuterated and undeuterated compounds; the errors are given as standard errors, *e.g.*, 1.102 (1) = 1.102 ± 0.001. [d] The values corrected to 100% deuterium content.

inverse isotope effect observed in the solvolysis of **1b** is a quite unusual result[17] and requires a specific mechanistic interpretation. If the reaction transition state resembles a classical cyclobutyl cation, the unusual β effect cannot be due to conformational factors. On the basis of the increased angle strain it could be expected that the no-bond resonance structures such as B contribute less to the resonance hybrid describing the incipient cation than do the corresponding structures to the cyclopentyl cation. Thus different β-



isotope effects in these two cases could be explained by different amounts of hyperconjugative electron release from neighboring C–H(D) bonding orbitals to the electron-deficient carbon in the reaction transition state. However, this argument rests upon the assumption that the strain in cyclobutene relative to cyclobutane is higher than in cyclopentene relative to cyclopentane. In fact, there is no evidence for such an assumption. On the contrary, the difference in the heats of formation is larger for the cyclopentene–cyclopentane pair (27.0 kcal/mol) than it is for the cyclobutene–cyclobutane pair (21.1 kcal/mol).[19]

Therefore the effort to explain the inverse β effect observed with cyclobutyl-*2,2,4,4-d*$_4$ methanesulfonate in terms of a transition state resembling a classical cyclobutyl cation seems fruitless. A reasonable approach to this problem seems to be search for analogous behavior of other systems. A few years ago we suggested[20] that reduced β-deuterium isotope effect could be used as a criterion for neighboring group participation in solvolysis. It is an outstanding fact that, in solvolysis of compounds for which neighboring group participation has been demonstrated by other means, the corresponding β-deuterium effect is significantly reduced *in every single case.* This is illustrated in Table II by comparison[21-26] (when possible) with the appropriate model compound. Thus by analogy we ascribe the unusual β-deuterium isotope effect measured in the solvolysis of cyclobutyl methanesulfonate to neighboring group participation, *i.e.*, to a 1–3 bonding interaction in the rate-determining step.[27]

The observed rather large normal γ-deuterium effect is consistent with this conclusion. An analogous behavior has been observed in solvolysis of the γ-deuter-

(17) The observed rate increase can be compared with the β effect in solvolysis of cyclopentyl-*2,2,5,5-d*$_4$ brosylate (70% EtOH, 25°) where k_H/k_D equal to 1.88 was found.[18]

(18) J. O. Stoffer and J. D. Christen, *J. Amer. Chem. Soc.*, **92**, 3190 (1970).

(19) S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

(20) M. Nikoletić, S. Borčić, and D. E. Sunko, *Tetrahedron*, **23**, 649 (1967).

(21) R. Eliason, unpublished result.

(22) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *Chem. Commun.*, 1489 (1968). The value reported in this communication for the exo compound, k_H/k_D = 1.014, was shown to be too low. See also B. L. Murr and J. A. Conkling, *J. Amer. Chem. Soc.*, **92**, 3464 (1970).

(23) W. H. Saunders, Jr., S. Asperger, and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958).

(24) K. L. Servis, S. Borčić, and D. E. Sunko, *Tetrahedron*, **24**, 1247 (1968).

(25) M. Tarle, unpublished results.

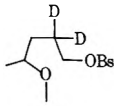
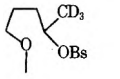
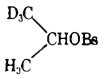
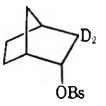
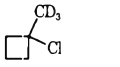
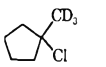
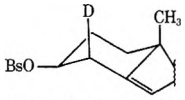
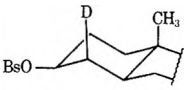
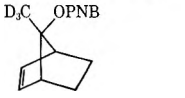
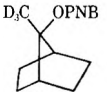
(26) M. Tomić and I. Szele, unpublished results.

(27) Recently we obtained the results[28] from theoretical calculations of the Wolfsberg–Stern[29] type. It appears that the inverse β effect is due to a low MMI factor of the Bigeleisen equation (k_H/k_D = MMI × EXC × ZPE). The ZPE factor is reduced in magnitude but is larger than unity.

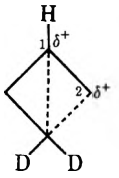
(28) B. Goričnik, Ph.D. Thesis, University of Zagreb, 1972.

(29) M. J. Stern and M. Wolfsberg, *J. Chem. Phys.*, **45**, 2618 (1966), and references cited therein.

TABLE II
SOLVOLYTIC β-DEUTERIUM ISOTOPE EFFECTS

Compd	k_H/k_D	Model compd	k_H/k_D	Ref
	0.98			15, 21
	1.09		1.19	15, 21
	1.10		1.26	15, 22
Ph_2CDCH_2OTs	1.01			23
$PhCD_2CH_2OTs$	1.00			23
	1.09		1.21	20, 24
	0.99		1.20	25, 15
	1.09		1.83	26

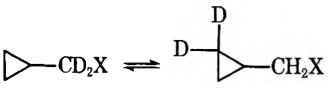
ated *exo*-2-norbornyl derivatives.[30] For compounds which do not solvolyze by anchimeric assistance, very small normal or slightly inverse γ-deuterium effects have been measured.[30] In our case, if bridging at γ carbon occurs in the rate-determining step, some changes of the γ-C–H(D) bond force constants can occur, resulting in a kinetic isotope effect. However, although an isotope effect can be expected, the direction of this effect is rather difficult to rationalize. If bridging is depicted as in the following figure[31] then it becomes apparent that the formation of the new



bond to the γ carbon is accompanied by a simultaneous breaking of another bond to the same carbon. It can be expected that the bond-breaking process will tend to increase k_H/k_D while the bond-forming process will tend to decrease this ratio. Considering the observed γ effect as analogous to α effects (with C_2 as the leaving group and C_1 as the nucleophile) it can be expected that the bond-breaking process will influence more the composite k_H/k_D value than the bond-forming process. Such a result is due to the exponential nature of the correlation between the magnitude of the α effect and the bond length attained by the bond forming/breaking process in the transition state.[15]

A similar analysis could be carried out for the situation pertaining to C_2 in the transition state. However, here the bond-breaking process is accompanied by the development of the positive charge, which (in the first approximation) is *not* the case at C_3. The electron-donating inductive effect of deuterium relative to protium will tend to make $k_H/k_D < 1.00$ and a composite, slightly inverse β-isotope effect is observed.

Solvolysis of Cyclopropylcarbinyl Methanesulfonates.—In a previous paper[9] we reported that the α-deuterium isotope effect in ethanolysis of cyclopropylcarbinyl benzenesulfonate was larger than that in acetolysis. In view of recent development in the understanding of α effects, such a result is rather surprising. Namely, the acetolysis is accompanied by a competitive internal rearrangement to cyclobutyl benzenesulfonate, while this is not the case in ethanolysis. This indicates that the formation of the intimate ion pair is probably rate determining in ethanolysis while the transformation of the intimate ion pair into external ion pair must be rate determining in acetolysis. Thus, in the transition state of acetolysis there should be no covalent bonding to the α carbon, a situation which is associated with the maximum possible α effect.[11] The transition state in ethanolysis involves probably some covalent bonding to the leaving group, and consequently the α effect should be *smaller* than in acetolysis. A possible explanation of this apparent discrepancy could be a cyclopropylcarbinyl → cyclopropylcarbinyl type of internal rearrangement competing with acetolysis which would scramble deuterium at positions 1, 3 and 4. Such a rearrangement would result in an



increasing trend in the rate constant with the per cent of completion of the reaction. This trend could have easily escaped detection by the experimental technique used in this early work.

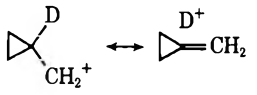
The occurrence of competitive deuterium scrambling during acetolysis of α-deuterated cyclopropylcarbinyl methanesulfonate has now indeed been demonstrated by the nmr technique as described in the Results section of this paper. Thus it appears that the k_H/k_D value for acetolysis reported previously[9] represents a composite α and γ effect and that the α effect is in fact larger.

It is difficult to estimate if the α-deuterium isotope effect of 1.32 reported in the present work is reduced in magnitude relative to the maximum possible effect. Primary alkyl derivatives normally do not solvolyze by the limiting dissociative mechanism, so that there is no good analogy for comparison. An isotope effect of 1.19 has been calculated for the change from CH_3-CHDCl to CH_2=CHD.[12b] On the other hand, it has been shown that the tightness of binding of deuterium may be nearly the same in a carbonium ion pair as in an alkene.[12d] Thus it can be estimated that a maximum k_H/k_D value for the transformation $RCD_2Cl \rightarrow RCD_2^+$ of about 1.41 could be expected. As sulfonate esters solvolyze with larger α effects than the corresponding chlorides,[12a] it could be indeed concluded that the α effect in the solvolysis of the cyclopropylcarbinyl methanesulfonate is less than the possible maximum value. This is of course, consistent with a 1–3 interaction in the transition state, but is certainly not conclusive.

(30) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *J. Amer. Chem. Soc.*, **89**, 1732 (1967).

(31) We do not pretend to represent accurately the structure of the transition state by this figure.

A very small β-isotope effect is not very informative with respect to neighboring group participation. A small β effect could here be expected for a variety of possible mechanisms. Even in the (most improbable) case that the transition state resembles a classical ion the no-bond resonance of the type



could be expected to be negligible and hence the isotope effect small.

Slightly inverse γ effects[32] can be explained without invoking bridging. Charge delocalization to C_3 and C_4 undoubtedly occurs in the rate-determining step. Thus, the inductive effect of deuterium could be responsible for the slightly increased rate of γ-deuterated compounds. Neither can the bridging be excluded because the measured k_H/k_D could be a composite effect in the way discussed previously for the solvolyses of γ- and β-deuterated cyclobutyl methanesulfonates.

In conclusion, secondary deuterium isotope effects indicate that the solvolysis of cyclobutyl methanesulfonate proceeds by way of anchimeric assistance with a strong 1–3 interaction in the transition state. In this respect, the evidence for the solvolysis of cyclopropylcarbinyl derivatives is not conclusive. In the latter case, it is quite possible that the enhanced rate is due predominantly or exclusively to vertical stabilization as discussed by Traylor.[34]

Experimental Section

Kinetic measurements were made on an automatic recording titrator (Radiometer, Copenhagen, TTT 11). Deuterium content in all compounds was determined by multiple integrations of the proton signals in the nmr spectra of appropriate intermediates in the synthetic sequence. Purity of the compounds was checked by vpc, ir, and nmr. Cyclopropylcarbinol-*1,1-d*$_2$, cyclopropylcarbinol-*2-d*$_1$, cyclopropylcarbinol-*3,3-d*$_2$, and cyclopropylcarbinol-*3,3,4,4-d*$_2$ were prepared as previously described.[9] Cyclobutanol-*2,2,4,4-d*$_4$ was obtained by repeated alkaline exchange of cyclobutanone in D_2O[2] followed by $LiAlH_4$ reduction.

1,3-Propandiol-*2,2-d*$_2$ (3).—The reduction of the deuterated dimethyl malonate with $LiAlH_4$ was done by Lambert's procedure.[35] A solution of 210 g (1.545 mol) of dimethyl malonate-d_2 (98% of deuterium) in 1000 ml of ether was added dropwise into a suspension of 86 g (2.26 mol) of $LiAlH_4$ in 1800 ml of ether under stirring. The reaction mixture was refluxed overnight, and then the solution of 7.7 g of NaOH in 160 ml of water was slowly added and the clear etheral layer was removed. The residue was washed with three 700-ml portions of boiling THF. Combined extracts were dried over anhydrous $CaSO_4$ and solvents were removed by distillation. The crude diol **3** was fractionated under vacuum, yielding 48.8 g (40.5%) of pure product, bp 120–125° (10 mm).

1,3-Dibromopropane-*2,2-d*$_2$ (4).—A 48-g (0.616 mol) portion of **3** was carefully added to stirred and cold (0°) PBr_3. Upon addition, the mixture was refluxed for 10 hr. The reaction mixture was then cooled to room temperature, 60 ml of water was added, and the product was extracted with methylene chloride. After work-up and distillation 70.1 g (55.2%) of dibromide **4**, bp 64–65° (13 mm), was obtained.

Cyclobutane-*3,3-d*$_2$-carboxylic acid (5) was prepared from 62 g (0.387 mol) of diethyl malonate and 66 g (0.32 mol) of **4** by standard procedure[36] in 62% yield. The boiling point of pure acid was 96–101° (10 mm).

Cyclobutyl-*3,3-d*$_2$-carboxamide (6).—To an equimolar mixture of **5** and triethylamine [13 g (0.1275 mol) and 12.9 g, respectively] in cold (−5°) chloroform the same (13.9 g) molar quantity of ethyl chloroformate was added, the mixture was swirled for 15 min, and then dry ammonia was passed through the mixture for an additional 15 min. After standing overnight at room temperature the reaction mixture was filtered, solvent was evaporated, and the residue was dissolved in hot benzene, filtered again, and diluted with hot *n*-hexane. Filtration after cooling to 20° gave 10.3 g (0.102 mol, 80.2%) of the amide **6**.

Cyclobutyl-*3,3-d*$_2$ Methyl Ketone (7).—Deuterated cyclobutyl carboxamide (**6**) (10.2 g) was added in small portions during 30 min into the solution of 0.436 mol of methylmagnesium iodide in dry ether. Upon refluxing overnight crushed ice was carefully added and the etheral layer was separated. The aqueous layer was acidified, saturated with NaCl, and exhaustively extracted with ether. After work-up and fractionation 3.8 g (0.038 mol) of the product **7**, bp 132–138° (759 mm), was obtained.

Cyclobutyl-*3,3-d*$_2$ Acetate (8).—A solution of 13.2 g (0.14 mol) of trifluoroperacetic acid in 40 ml of methylene chloride was added dropwise into a stirred suspension of 3.7 g (0.037 mol) of **7** and 24 g of Na_2HPO_4 in the same solvent. The reaction mixture was refluxed for 30 min, then cooled, filtered, washed with 10% aqueous Na_2CO_3 solution, and dried over $CaSO_4$. The crude product was distilled to give 2.3 g (0.0198 mol, 53.5%) of pure acetate **8**, bp 120–125° (758 mm).

Cyclobutanol-*3,3-d*$_2$ was obtained in 85.6% yield by alkaline hydrolysis of **8**. The deuterium content was 76%, determined by the nmr.

Methanesulfonates (**1a–d** and **2a–d**) of the corresponding alcohols were prepared in 65–80% yields according to the procedure published elsewhere.[7]

Registry No.—**1a**, 31053-86-8; **1b**, 31053-88-0; **1c**, 38645-08-8; **1d**, 38645-09-0; **2a**, 31053-87-9; **2b**, 38645-11-3; **2c**, 38645-12-4; **2d**, 38645-13-5; **3**, 38645-14-6; **4**, 38645-15-7; **5**, 38645-16-8; **6**, 38645-17-9; **7**, 38645-18-0; **8**, 38645-19-1; cyclobutanol-*3,3-d*$_2$, 24468-96-0; dimethyl malonate-d_2, 36647-07-1.

Acknowledgment.—This work has been supported in part by a grant from the Research Council of the Republic of Croatia.

(32) It should be mentioned that the γ effect per atom D is not significantly different for the dideuterated methanesulfonate and for the tetradeuterated analog, which is contrary to our earlier report.[9] At the time we were not fully aware of the difficulties encountered in the measurements of small isotope effects as discussed by Collins.[33]

(33) C. J. Collins, *Advan. Phys. Org. Chem.*, **2**, 63 (1964).

(34) T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton, and R. S. Brown, *J. Amer. Chem. Soc.*, **93**, 5715 (1971).

(35) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1840 (1967).

(36) G. B. Heisig and F. H. Stodola, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 213.

Reactivity of Bicyclo[4.2.2]deca-2,4,7,9-tetraene Derivatives under Conditions of Uniparticulate Electrophilic Addition. The Intramolecular Capture of Zwitterionic Bridged 1,4-Bishomotropylium (Bicyclo[4.3.1]deca-2,4,7-trienyl) Intermediates[1]

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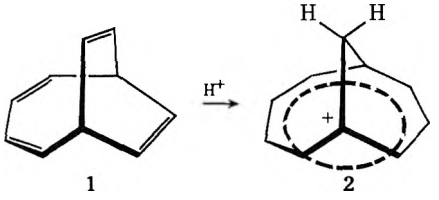
A variety of mono- and disubstituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes have been prepared and their reactivity toward chlorosulfonyl isocyanate compared to that of the parent system. In the latter case, a tricyclic lactam is obtained in which the carbon framework has undergone rearrangement to an unsaturated bicyclo[4.3.1]-decane moiety. Product formation is rationalized in terms of initial stereoselective *N*-(chlorosulfonyl) β-lactam intervention, subsequent ring opening with migration of the butadienyl bridge, and finally intramolecular cyclization to annihilate charge. The driving force for the rearrangement is attributed to 1,4-bishomotropylium cation formation. The symmetrical nature of the zwitterion in the unsubstituted example is lost upon substitution and the directional specificity of the cyclization is revealed in the derivatives. Substituents have a divergent effect on the two possible modes of closure and these results are discussed.

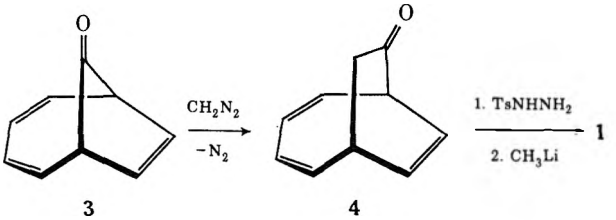
Bicyclo[4.2.2]deca-2,4,7,9-tetraene (**1**) has been discovered to rearrange to bicyclo[4.3.1]deca-2,4,7-trienyl ions when treated with electrophilic reagents. Credit for this discovery is due to Winstein[3] and Schröder,[4] who appear to have investigated independently the generation of **2** under long-life conditions below 0°.[5] Subsequently, Schröder and his coworkers have found that this same skeletal rearrangement accompanies the reaction of **1** with such biparticulate electrophiles[6] as bromine, hydrogen bromide, and mercuric acetate.[7] Current interest in such transformations has been heightened by the awareness that **2** is a bridged, 1,4-



1 **2**

bishomotropylium ion system. Recently, we reported on the generation and intramolecular capture of homo-[8] and 1,3-bishomotropylium cation intermediates[9,10] by treatment of cyclooctatetraenes and *cis*-bicyclo[6.1.0]-nonatrienes, respectively, with uniparticulate electrophilic reagents. The objectives of these studies were to establish whether such processes could function as utilitarian probes of mechanism and stereochemistry, to achieve certain synthetic goals, and to gain some basic information regarding the role of substituents on the reactivity of homoaromatic cations toward nucleophiles. Because of past successes, we have been led to investigate the related chemistry of **2** and herein report the results of this study.

Bicyclo[4.2.2]decatetraene.—Although **1** has been prepared by thermal decomposition of the sodium salt of bicyclo[6.1.0]nonatriene-9-carboxaldehyde tosylhydrazone[11] and by mercuric bromide catalyzed isomerization of bullvalene,[12] we have found it most convenient to prepare this hydrocarbon by diazomethane ring expansion of **3**[13,14] and treatment of the tosylhydrazone



3 **4**

with methyllithium.[15] When a dry methylene chloride solution of **1** was allowed to react with chlorosulfonyl isocyanate (CSI) for 6 hr at room temperature and dechlorosulfonylation was carried out with thiophenol and pyridine[16] or alkaline sodium sulfite solution,[17] tricyclic lactam **5** was obtained in 67% yield. The structure of **5** was established by a combination of spectral and chemical evidence. The compound exhibits an infrared carbonyl stretching band at 1725 cm^{-1}, a maximum at 243 nm (ε 5030) in the ultraviolet region, and the following absorptions in the nmr (100 MHz): δ 7.4 (br, 1, >NH), 5.77–6.4 (m, 5), 5.23 (ddd, J = 9.5, 3.5, and 1.8 Hz, 1), 3.74 (t with additional fine splitting, J = 5 Hz, 1), 3.44 (m, 1), 3.14 (m, 1), and 2.36 (d with additional fine splitting, J = 5 Hz, 1). Spin-decoupling experiments permitted

(1) Unsaturated Heterocyclic Systems. LXXXIX. For the previous paper in this series, see D. J. Pasto, A. F. Chen, G. Ciurdaru, and L. A. Paquette, *J. Org. Chem.*, **38**, 1015 (1973).

(2) Holder of a NATO Postdoctoral Fellowship (1970–1972) administered by the Science Research Council.

(3) M. Roberts, H. Hamberger, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 6346 (1970).

(4) G. Schröder, U. Prange, N. S. Bowman, and J. F. M. Oth, *Tetrahedron Lett.*, 3251 (1970).

(5) The remarkable stability of cation **2** is revealed by the fact that it can be heated to 80° without noticeable change in its nmr features: P. Ahlberg, D. L. Harris, M. Roberts, P. Warner, P. Seidl, M. Sakai, D. Cook, A. Diaz, J. P. Dirlam, H. Hamberger, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 7063 (1972).

(6) L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *ibid.*, **93**, 4503 (1971).

(7) G. Schröder, U. Prange, B. Putze, J. Thio, and J. F. M. Oth, *Chem. Ber.*, **104**, 3406 (1971).

(8) L. A. Paquette, J. R. Malpass, and T. J. Barton, *J. Amer. Chem. Soc.*, **91**, 4714 (1969); L. A. Paquette and T. J. Barton, *ibid.*, **89**, 5480 (1967).

(9) L. A. Paquette and M. J. Broadhurst, *ibid.*, **94**, 632 (1972); L. A. Paquette, M. J. Broadhurst, C. Lee, and J. Clardy, *ibid.*, **94**, 630 (1972).

(10) J. Clardy, L. K. Read, M. J. Broadhurst, and L. A. Paquette, *ibid.*, **94**, 2904 (1972).

(11) M. Jones, Jr., and L. T. Scott, *ibid.*, **89**, 150 (1967).

(12) H.-P. Löffler and G. Schröder, *Angew. Chem.*, **80**, 758 (1968); *Angew. Chem., Int. Ed. Eng.*, **7**, 736 (1968).

(13) L. A. Paquette, R. H. Meisinger, and R. E. Wingard, Jr., *J. Amer. Chem. Soc.*, **94**, 2155 (1972).

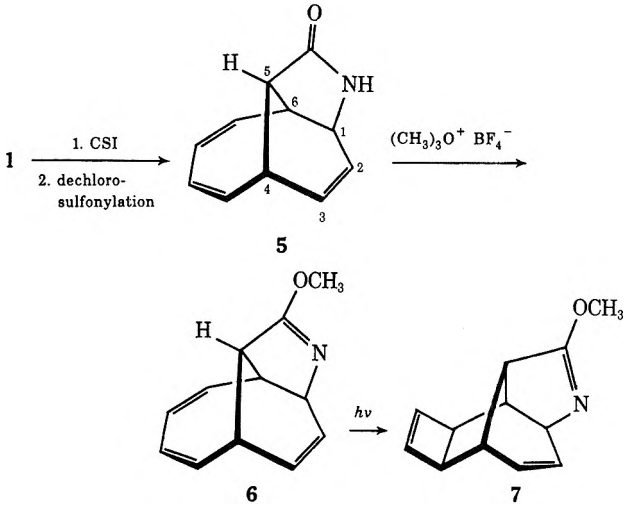
(14) (a) T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Schechter, *ibid.*, **94**, 5366 (1972); (b) K. Kurabayashi and T. Mukai, *Tetrahedron Lett.*, 1049 (1972); (c) M. Sakai, R. F. Childs, and S. Winstein, *J. Org. Chem.*, **37**, 2517 (1972).

(15) Studies carried out concurrently with those in the group of Professor H. Shechter: J. B. Press and H. Shechter, *Tetrahedron Lett.*, 2677 (1972).

(16) R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963).

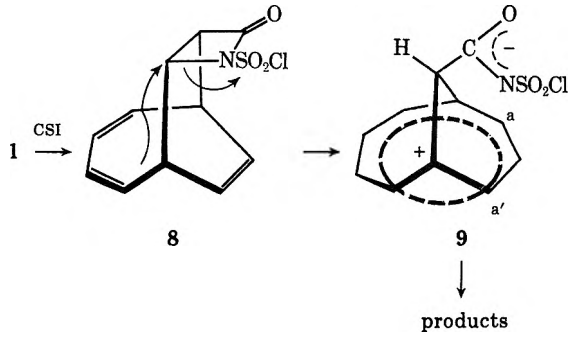
(17) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).

all proton assignments to be made and showed all coupling constants to be compatible with the assignments (see Experimental Section). Treatment of **5** with trimethyloxonium fluoroborate afforded imino ether **6**, structural assignment to which could be made with confidence on the basis of its spectra. Additionally, triplet-sensitized irradiation of **6** cleanly gave a photoproduct in which the butadiene unit had been isomerized to a cyclobutene ring (*cf.* **7**).[18]



5 **6** **7**

The formation of **5** proceeds analogously to the TCNE reaction with **1**.[19] In both cases, intervention of a zwitterionic 1,4-bishomotropylium ion intermediate (*e.g.*, **9**) appears particularly attractive, since the electrophilic moiety is quite suitably disposed in a geometric sense for ultimate cyclization to product. With particular reference to CSI, the generation of **9**



8 **9**

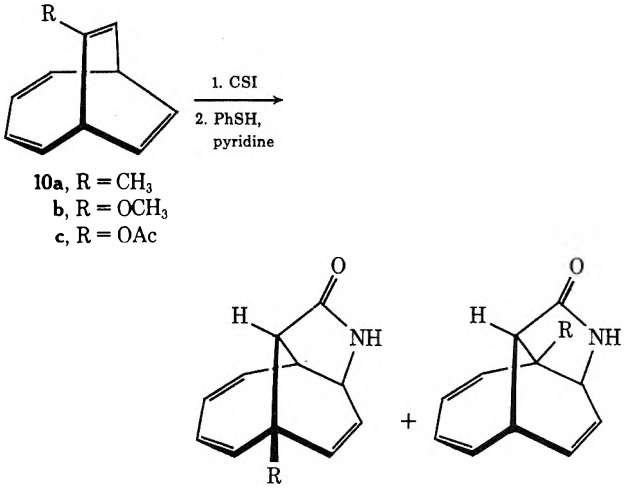
could be preceded by formation of the β-lactam derivative **8**, with subsequent ring opening and rearrangement arising owing to the driving force underlying attainment of the delocalized homoaromatic species. This proposal will subsequently be shown to have basis in fact.

Because of the innate symmetry of **9**, cyclization with charge annihilation can operate at two equivalent sites (a and a′). By making recourse to mono- or higher substitued derivatives of **1**, this symmetry consideration no longer becomes applicable. As a result, the opportunity to examine substituent effects on the direction (in particular) of C—N bond formation is readily available. Accordingly, a quantitative study of product distribution as a function of substitution was next undertaken.

Monosubstituted Bicyclo[4.2.2]decatetraenes.—Of the compounds selected for study, the 7-methyl derivative (**10a**) was synthesized by methylation of **4** and subsequent treatment of its tosylhydrazone with methyllithium; alternatively, **10a** was obtained more conveniently by diazoethane ring expansion of **3** followed by elimination from the tosylhydrazone. Preparation of methoxy tetraene **10b** was effected by O-methylation of the anion of **4** with dimethyl sulfate.[15,20] Enol acetate **10c** was readily available from the reaction of **4** with isopropenyl acetate in the presence of *p*-toluenesulfonic acid.[15]

Each of the purified tetraenes was treated with a slight excess of CSI in methylene chloride at room temperature. It was immediately clear from inspection of aliquots from the trio of reactions that two types of lactam (β and γ) were initially produced. With the passage of time, however, the carbonyl band seen at *ca.* 1825 cm^{-1} gradually disappeared; in contrast, the 1760-cm^{-1} absorption remained. In the case of **10a** and **10b**, the transient *N*-(chlorosulfonyl) β-lactam was no longer present after several hours. The β-lactam derivative arising from **10c** rearranged relatively more slowly, a finding which permitted its ultimate isolation and characterization (*vide infra*).

In each instance, two γ-lactams (**11** and **12**) were formed and their relative percentages were determined by nmr analysis of the nonhydrolyzed *N*-(chlorosulfonyl) derivatives. Control experiments showed that *N*-(chlorosulfonyl) precursors of **11** and **12** were not



10a, R = CH_3
b, R = OCH_3
c, R = OAc

11a, R = CH_3 **12a**, R = CH_3
b, R = OCH_3 **b**, R = OCH_3
c, R = OAc **c**, R = OAc

interconverted under the reaction conditions. Furthermore, the product distributions were not found to change within experimental error when the cycloadditions were allowed to proceed for varying lengths of time beyond the point at which no β-lactam could be seen. The relevant data have been collected in Table I.

The individual isomers could be distinguished readily by their nmr spectra, which, not unexpectedly, are quite similar within a given lactam series. Particular use was made of the previous spin-decoupling

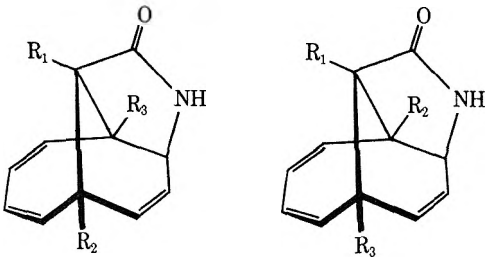
(18) Details of this particular experiment will appear elsewhere at a future date.

(19) H.-P. Löffler, T. Martini, H. Musso, and G. Schröder, *Chem. Ber.*, **103**, 2109 (1970).

(20) M. J. Goldstein, private communication. The authors thank Professor Goldstein for providing us with the experimental details in advance of publication.

TABLE I

PRODUCT DISTRIBUTIONS OBTAINED UPON CSI ADDITION TO MONO- AND DISUBSTITUTED BICYCLO[4.2.2]DECATETRAENES



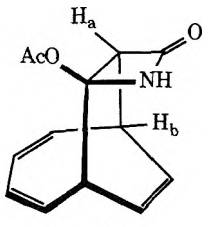
R_1	R_2	R_3	Yield, %[a]	Product distribution, %[a,b]	
H	H	CH_3	73	31.5	68.5
H	H	OCH_3	56.5	54.5	45.5
H	H	OAc	57.5	24	76
CH_3	H	OCH_3	52.5	68.5	31.5

[a] Average of several runs. [b] Analysis by repeated nmr integration of suitable peaks; estimated error, ±4%.

experiments with **5**. In this lactam, H_3 is the olefinic proton which has the most upfield chemical shift in the vinyl region; moreover, it is found in an uncomplicated region of the spectrum and is readily identified. Its appearance in **5** as a doublet of doublets of doublets is due to vicinal coupling with H_2 ($J_{2,3}$ = 9.5 Hz) and H_4 ($J_{3,4}$ = 3.5 Hz) and long-range coupling to H_5 ($J_{3,5}$ = 1.8 Hz). H_2 appears at lowest field and has like multiplicity ($J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 4.5, $J_{2,4}$ = 2.5 Hz), while H_1 is seen as a broadened triplet. The assignment of structure to lactams **11** is based on the following general spectral characteristics: H_3 appears as a doublet of doublets lacking $J_{3,4}$; H_2 is likewise only a doublet of doublets with $J_{2,4}$ absent; the H_5 absorption consists of a broad doublet ($J \simeq 5$ Hz). These observations are uniquely compatible with substitution of the R group at position 4.

In contrast, lactams **12** share the common features of multiplicities in H_2 and H_3 identical with those in **5**, appearance of H_1 as a broadened doublet, and the collapse of H_5 to a "singlet" with additional long-range coupling (Table II). Furthermore, the ultraviolet spectra of **11** and **12** differ significantly, but remain quite constant within a given set (Table III).

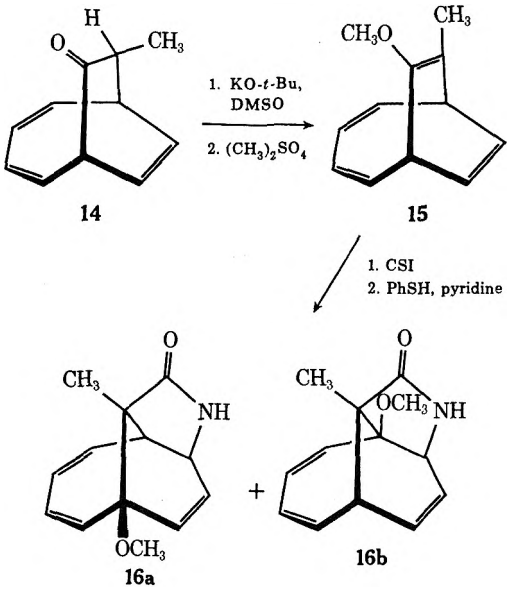
The expectation that a β-lactam could be isolated from the reaction of **10c** with CSI was realized when short reaction times (4–5 min) were employed. Under these conditions, 45.5% of **13** was obtained after cus-



13

tomary reduction with thiophenol and pyridine, together with approximately 20% of a mixture of **11c** and **12c**. From intense carbonyl absorptions at 1770 and 1730 cm^{-1}, the presence of β-lactam and acetate carbonyls could be inferred. The stereochemical relationship of the four-membered heterocyclic ring to the [4.2.2]bicyclic framework is readily ascertained by an examination of the nmr spectrum, which showed a quite narrow singlet absorption for H_a. Dihedral angle measurements made on Dreiding models revealed a relationship between H_a and H_b in **13** such that a small spin–spin interaction is expected; in contrast, a considerably larger coupling constant would seem necessary for the isomeric structure if the Karplus correlation does not break down in such systems. This is unlikely, for, in a mechanistic context, the *N*-(chlorosulfonyl) precursor to **13** can uniquely serve as the source of **11c** and **12c**. This transformation has, in fact, been realized at the experimental level.

Disubstituted Bicyclo[4.2.2]decatetraenes.—Though the results given above provide a sufficiently sharpened view into the reaction to permit several mechanistic conclusions to be drawn, it is to be noted that the substituted etheno bridge has been the site of preferential kinetic attack and that H_5 has invariably been substituted only by hydrogen. With regard to the latter point, 7-methoxy-8-methylbicyclo[4.2.2]-decatetraene (**15**) was prepared by O-methylation of



14, the recognized precursor to **10a**. In line with the relative reactivities of **10a** and **10b** and the well-established cationic stabilizing powers of methyl and methoxyl groups, initial attack by the electrophile at the methyl-bearing carbon was anticipated. This would position a methyl group at C_5. Enol ether **15** operates in this manner to produce rapidly a β-lactam (not isolated) which equally rapidly undergoes conversion to five-ring lactams. Reduction and chromatography led to the isolation (52.5% yield) of **16a** and **16b** (initially present in a 31.5:68.5 ratio). Individual identification of the two products was gained by examination of their nmr spectra (Table II), the absence of H_4 in **16a**, for example, resulting in loss of the normal coupling to H_2 and H_3.

Exposure of **17**[21] to the action of CSI under comparable conditions led to the isolation of a sole adduct, the nmr spectrum of which is consistent with struc-

(21) U. Kruerke, *Angew. Chem., Int. Ed. Engl.*, **6**, 79 (1967).

TABLE II
NMR DATA FOR THE TRICYCLIC LACTAMS
(60 MHz, CCl_4–TMS, δ VALUES)

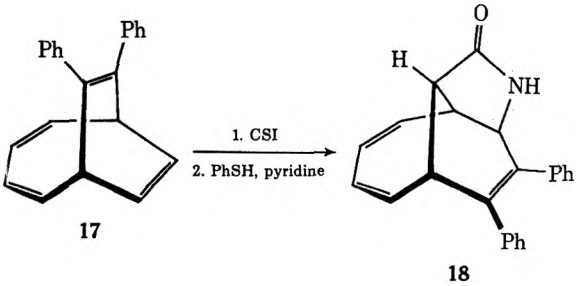
Compd	H_1	H_2	H_3	H_4	H_5	H_6	Other olefinic protons
5	3.74 (br t)[a] J = 5 Hz	6.3 (m)	5.23 (ddd) J = 9.5, 3.5, 1.8 Hz	3.44 (m)	2.36 (br d)[a] J = 5 Hz	3.14 (m)	5.77–6.1 (m)
11a	3.71 (t) J = 5 Hz	6.11 (dd) J = 9.0, 5.3 Hz	5.09 (d)[a] J = 9.0 Hz		2.22 (br d)[a] J = 5 Hz	3.17 (m)	5.45–5.9 (m) (1.38, s, $-CH_3$)
11b	3.75 (br t)[a] J = 5 Hz	6.31 (dd) J = 9.0, 5.0 Hz	5.18 (d)[a] J = 9.0 Hz		2.73 (br d)[a] J = 5 Hz	3.18 (m)	5.95 (br s) (3.53, s, $-OCH_3$)
11c	3.82 (br t)[a] J = 4.5 Hz	6.38 (dd) J = 9.2, 5.5 Hz	5.24 (d)[a] J = 9 Hz		3.3 (m)[b]	3.3 (m)[b]	5.65–6.3 (m) (2.11, s, $-COCH_3$)
12a	3.4 (m)[b]	6.3 (ddd) J = 9.0, 5.5, 2.0 Hz	5.16 (d)[a] J = 9.0 Hz	3.4 (m)[b]	2.27 (m)		5.7–6.15 (m) (1.30, s, $-CH_3$)
12b	3.55 (m)[b]	6.28 (ddd) J = 9.3, 5.8, 2.0 Hz	5.21 (d)[a] J = 9.3 Hz	3.55 (m)[b]	2.78 (m)		5.95 (m) (3.25, s, $-OCH_3$)
12c	4.32 (m)	6.30 (m)	5.30 (dd)[a] J = 9.5, 3.0 Hz	3.50 (m)	3.0 (m)		6.0 (m) (2.02, s, $-COCH_3$)
16a	3.74 (t) J = 5 Hz	6.36 (dd) J = 9.5, 5.5 Hz	5.36 (d) J = 9.5 Hz			2.78 (m)	5.98 (br s) (3.42, s, $-OCH_3$; 1.04, s, $-CH_3$)
16b	3.77 (d) J = 6.0 Hz	6.2 (ddd) J = 9.5, 6.0, 2.0 Hz	5.18 (dd)[a] J = 9.5, 3.5 Hz	3.25 (m)			6.0 (m) (3.32, s, $-OCH_3$; 1.14, s, $-CH_3$)

[a] Additional fine coupling is present. [b] Overlapping peaks.

TABLE III
ULTRAVIOLET DATA FOR THE TRICYCLIC LACTAMS
(C_2H_5OH SOLUTION)

Compd	λ_{max}	ϵ	Compd	λ_{max} (ϵ)
5	243	5030	11a	257.5 infl (3620), 248 (5310), 244 (5125)
11a	245	4680	12b	261 infl (3250), 251.5 (4980), 246 (4950)
11b	245	4200	12c	262.5 infl (3280), 251 (5400), 246 (5360)
11c	242.5	4620	16b	262 infl (3250), 253 (4910), 246.5 (4850)
16a	244	4250		

ture **18**. In particular, the lactam has only four olefinic protons (δ 5.73–6.3, m), the remaining four tetrahedrally bound hydrogens appearing at 4.22 (d, J = 4.5 Hz), 4.0 (d, J = 8 Hz), 3.45 (m), and 2.77 (m). Furthermore, the observation of the following electronic spectrum [$\lambda_{max}^{C_2H_5OH}$ 271 nm (sh, ϵ 6110), 238 (sh, 13,200), and 226 (18,200)] requires the presence of a stilbene chromophore. The lack of reactivity of the phenyl-substituted double bond in **17** is not unexpected in view of the fact that stilbene fails to react with CSI.[16]



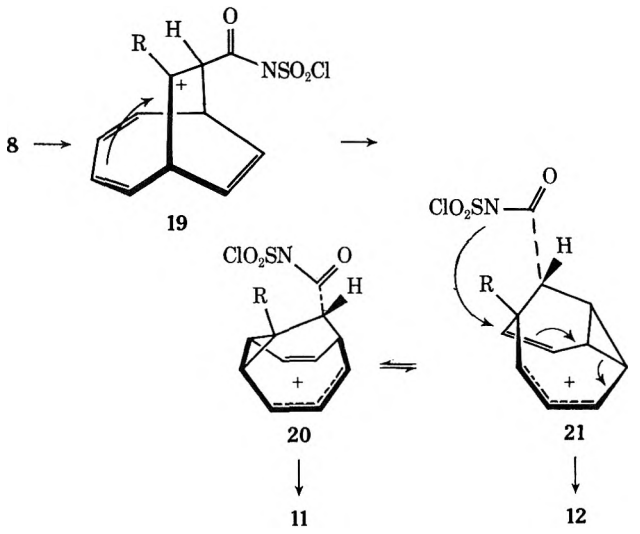
17 18

Discussion

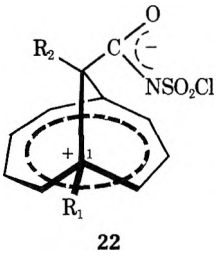
Mechanistic Considerations.—The experimental results show that the bicyclo[4.2.2]decatetraene ring system reacts with CSI to give initially a β-lactam intermediate which arises from approach of electrophile to the polyene from the direction of the etheno (rather than butadieno) bridge. Such high levels of stereoselectivity very likely arise because of steric factors and are well precedented in a number of related structural types.[14,15] Whether β-lactam formation involves a two-step ionic mechanism or a more concerted [$_\pi 2_a + {}_\pi 2_s$] process is uncertain.

The structurally rearranged nature of the γ-lactams, in combination with the fact that two isomeric products arise in the unsymmetrical examples, argue convincingly for the intervention of carbonium ion intermediates. Isomerization reactions of *N*-(chlorosulfonyl) β-lactams by cationic pathways have been reported previously on many occasions. In a formal sense, a 1,2 shift of the conjugated diene unit is involved followed by cyclization to either of two possible positions (*cf.* **8** and **9**). This bond reorganization can be viewed as the result of the rearrangement sequence outlined below. The observed product ratios now might be interpreted as reflecting the relative capability of the R group to stabilize a cyclopropane ring.

However, the accumulated evidence[3–5] obtained from protonation studies of **1** attests convincingly to the fact that cations of type **20** and **21** are less thermodynamically stable than the related homoaromatic bicyclo[4.3.1]deca-2,4,7-trienyl cations. Consequently, we have assumed that a true cyclopropane bond likewise is not present in those transient intermediates which arise from CSI addition and that the

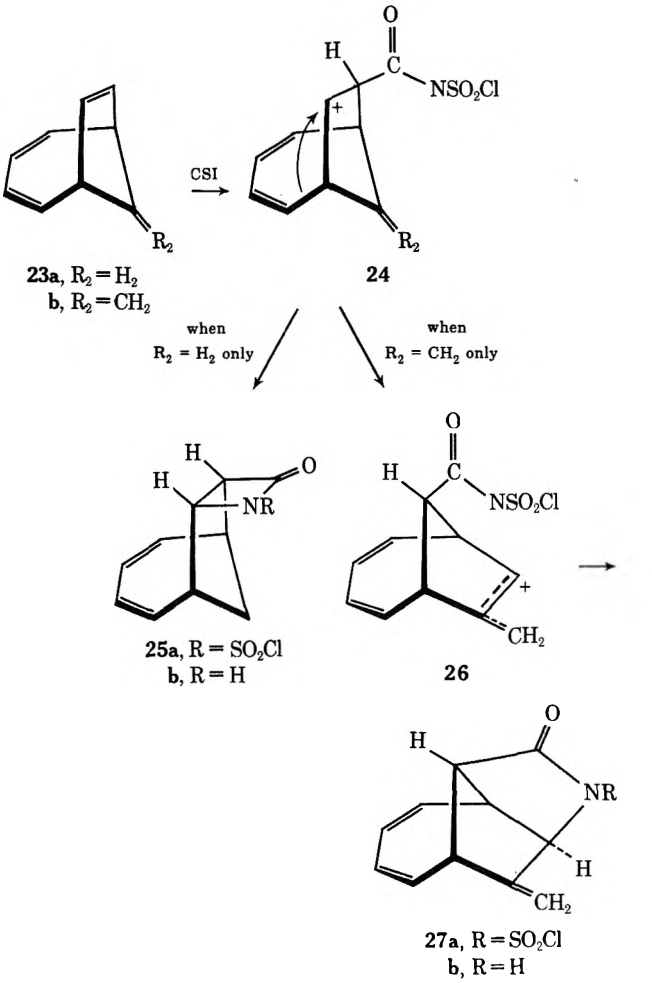


product distribution arises from differing rates of cyclization in 22.

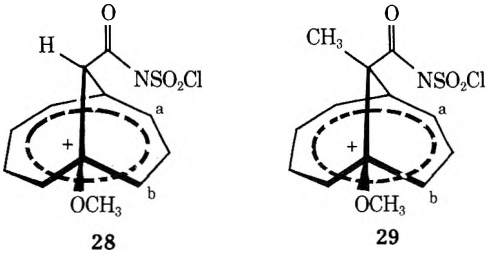


The fundamental underlying importance of charge delocalization to the successful realization of skeletal rearrangement in these systems is revealed experimentally by the contrasting behavior of structurally related hydrocarbons **23a** and **23b**. At 25°, cycloaddition of CSI to **23a** took place, giving only **25a**, dechlorosulfonylation of which led to the ready isolation of **25b** (80% yield). The exo stereochemistry of **25b** was revealed by the virtual lack of spin–spin coupling between the >CHCO– and >CHN< protons and their adjoining bridgehead counterparts, a result in keeping with the *ca.* 90° dihedral angle separating them. Comparable exclusive exo attack has been observed previously with norbornene and norbornadiene derivatives.[22,23] 9-Methylenebicyclo[4.2.1]nonatriene (**23b**) does not share with **23a** an inability to undergo bond reorganization under these conditions. Rather, **27b** is obtained as the major constituent of a reaction mixture containing a number of rearrangement products.[24]

Substituent Effects.—As established above, the positions occupied by the R substituent in lactams **11**, **12**, and **16** necessitate that the initial bonding of the isocyanate occur so as to generate the most stable bicyclo[4.2.2]trienyl cation. The β-lactams which arise from this step of the sequence could result from a "quasiconcerted" cycloadditive process, in which some charge separation develops. To arrive at the 1,4-bishomotropylium ion intermediate, substantial cationic character must become localized at that carbon



atom bearing the R group.[25] A 1,2 shift of the diene bridge subsequently gives **22** in which the lone substituent is bonded to C_1. Because of its attachment to a tetrahedral center, the substituent cannot be expected to exert any π-electron conjugative effect on the two possible modes of ring closure. Rather, the observed differences (Table I) must be attributed to inductive and field influences, steric effects, or a combination of these three factors. That steric effects may not be inconsequential in certain cases is reflected in the behavior of zwitterions **28** and **29**. In **28**, closure to

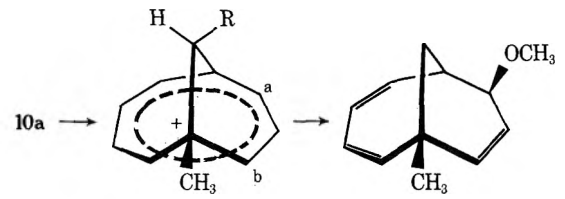


carbon a occurs to the extent of 45.5%; the additional methyl group in **29** clearly disfavors this pathway (now only 31.5%). Molecular models suggest that the methyl and methoxyl groups are in closer spatial proximity in **16a** than in **16b**.

When attention is focused uniquely on the series

(22) E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968).
(23) L. A. Paquette and T. J. Barton, unpublished observations.
(24) L. A. Paquette and M. J. Broadhurst, *J. Org. Chem.*, **38**, 1893 (1973).
(25) For convenience in discussion, the R groups under consideration are those which can stabilize positive charge. When the substituent is not carbonium ion stabilizing, the other bridge is preferentially attacked by the electrophile.[26]
(26) G. Schröder, U. Prange, and J. F. M. Oth, *Chem. Ber.*, **105**, 1854 (1972).

10a–10c, the net substituent contributions are seen to be rather divergent. The propensity of **30a** to cyclize preferably away from the methyl group has been encountered also by Schröder.[26] Subsequent to the completion of this work, he and his coworkers have described the protonation and alkaline methanol quench of **10a**. The only product isolated was **31**,



30a, R = $CONSO_2Cl$ **31**
b, R = H

but, since the yield was unfortunately only 15%, little can be said about the *overall* chemical fate of **30b** under such circumstances. Nevertheless, these data can be explained in terms of a model in which the dipolar influence of the methyl group, whether through space or σ bonds, renders the proximate site of attack less electron deficient. Consequently, C–N bond formation at the alternative more positive ring carbon (to give **11a**) is kinetically preferred.

On this basis, the more electronegative methoxyl group would be expected to transmit an electrical effect such that positive charge should be greatest in the vicinity of this substituent. This influence is opposite to that exerted by methyl. Accordingly, **12b** should dominate the product composition. At the experimental level, this lactam is formed in 54.5% relative yield.

At first sight, the acetoxyl group would appear to be an anomaly, for the results indicate it to exert an effect more similar to methyl than to methoxyl. However, if the polarization of the carbonyl group is considered and if, as now believed,[27] the propagation efficiency of a polar group resides chiefly in its field effect, then the electronegative carbonyl oxygen atom could exert an untoward influence on the $-CONSO_2Cl$ moiety.

In summary, the results collected in Table I and the necessarily tentative theoretical suggestions advanced above reveal that substituents exert phenomenologically interesting control on the directional specificity of intramolecular charge annihilation in homoaromatic bicyclo[4.3.1]deca-2,4,7-trienyl zwitterions.

Experimental Section

Melting points are corrected. Proton magnetic resonance spectra were obtained with Varian A-60A and HA-100 spectrometers and apparent coupling constants are cited. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Reaction of Bicyclo[4.2.2]deca-2,4,7,9-tetraene (1) with CSI. A. Thiophenol–Pyridine Work-Up.—A solution of 0.4 ml (4.8 mmol) of CSI in 5 ml of dry methylene chloride was added dropwise under nitrogen to 520 mg (4.0 mmol) of 1 dissolved in 10 ml of the same solvent. After 6 hr the reaction was complete (ir analysis). The solvent was evaporated and the residual pale yellow, viscous oil was dissolved in acetone and treated with thiophenol and pyridine at 0° in the usual way.[16] Chromatography on Florisil gave 461 mg (67%) of **5** as colorless crystals, mp 190.5–191°, from methylene chloride–ether, $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.08. Found: C, 76.27; H, 6.37; N, 8.09.

The following double irradiation experiments confirmed the structural assignment. Irradiation of the NH proton resulted in removal of fine coupling from H_1 which appeared as a triplet (J = 5 Hz); no other alterations were noted. Saturation slightly to lower field of the main olefinic absorption removed the major coupling (J = 9.5 Hz) from H_3 and collapsed H_1 to a doublet (J = 4 Hz). These observations suggested that both H_1 and H_3 are strongly coupled to the same olefinic region with little change elsewhere except for removal of some fine splitting from H_5 and narrowing of the multiplet due to H_4. When H_5 was saturated, H_3 appeared as a doublet of doublets (J = 9.5 and 3.5 Hz), H_6 developed triplet characteristics (J = 3.5 Hz), and H_4 lost some of its original fine coupling. The long-range coupling between H_3 and H_4 can be rationalized in terms of W coupling and has been observed for a number of structurally related compounds.[28]

Simultaneous irradiation of H_1 and H_4 resulted in collapse of the lowest field vinyl proton (H_2) to a doublet (J = 9.5 Hz) while H_3 appeared as a doublet of doublets (J = 9.5 and 1.8 Hz). Consequently, H_2 and H_3 are strongly coupled. When H_4 was saturated, H_2 was seen as a doublet of doublets ($J_{2,3}$ = 9.5, $J_{1,2}$ = 4.5 Hz) and H_3 appeared as a broadened doublet (J = 9.5 Hz). Thus, H_2 and H_4 interact long range to the extent of *ca.* 2.5 Hz. Finally, irradiation of H_6 led to the simplification of H_5 (now a broadened singlet).

B. Alkaline Sodium Sulfite Work-Up.—A solution of 1.3 g (1 mmol) of 1 and 0.9 ml (1.05 mmol) of CSI in 40 ml of methylene chloride was stirred at 25° under nitrogen for 23 hr. The solvent was evaporated and the residue was taken up in ether (20 ml). This solution was added dropwise with vigorous stirring to 30 ml of 2% sodium sulfite solution. Portions of 10% potassium hydroxide solution were added throughout the addition in order to maintain pH 7–8. Upon completion of the addition, the solution was stirred for 30 min, during which time the product began to crystallize. The total reaction mixture was extracted with methylene chloride (3 × 30 ml) and the combined extracts were dried and evaporated. A white, crystalline solid was obtained which was washed with ether and filtered. The colorless crystals so obtained (1.056 g, 61%) were identical with the sample of **5** obtained above and were of almost analytical purity, mp 187–189°.

O-Methylation of 5.—Lactam **5** (865 mg, 5.0 mmol) was dissolved in 50 ml of dry methylene chloride and treated with 1.0 g (6.6 mmol) of trimethyloxonium fluoroborate under nitrogen. The mixture was stirred at 25° for 12 hr, washed twice with saturated sodium bicarbonate solution and once with brine, dried, and evaporated. The resulting pale yellow oil (930 mg) was subjected to molecular distillation at 70° (0.3 mm) from which was obtained 821 mg (88%) of a colorless liquid which slowly crystallized on cooling to 0°: $\delta_{max}^{CDCl_3}$ 5.8–6.3 (m, 5, olefinic), 5.0 (br d, 1, H_3), 4.0 (m, 1, H_1), 2.95–3.45 (m, 2, H_4 and H_6), and 2.4 (m, 1, H_5).

The perchlorate of **7** was obtained as colorless needles, mp 193–193.5°, from methylene chloride–ether, ν_{max}^{KBr} 1660 cm^{-1}, $\lambda_{max}^{C_2H_5OH}$ 247 nm (ϵ 4725).

Anal. Calcd for $C_{12}H_{14}ClNO_5$: C, 50.09; H, 4.91; N, 4.87. Found: C, 50.02; H, 4.85; N, 4.84.

7-Methylbicyclo[4.2.2]deca-2,4,7,9-tetraene (10a).—To a solution of 5.0 g (0.038 mol) of **3** in 200 ml of methanol was added an ethereal solution of diazoethane (400 ml, prepared from 30 g of *N*-ethyl-*N*-nitrosourea) and the mixture was maintained at 0° overnight in the dark. After removal of the solvent, there remained 5.20 g of pale orange liquid, vpc analysis (5% SE-30, 130°) of which indicated the presence of **14** as the one major product.

A 530-mg sample of the crude ring-expanded ketone and 700 mg of *p*-toluenesulfonylhydrazine dissolved in 50 ml of ethanol was treated with 4 drops of concentrated hydrochloric acid and kept at 5° for 24 hr. The solution was concentrated to *ca.* 20 ml and the tosylhydrazone was allowed to crystallize during 6 days at 5°.

(27) For leading references, see (a) L. M. Stock, *J. Chem. Educ.*, **49**, 400 (1972); (b) R. Golden and L. M. Stock, *J. Amer. Chem. Soc.*, **94**, 3080 (1972); (c) C. L. Liotta, W. F. Fisher, E. L. Slightom, and C. L. Harris, *ibid.*, **94**, 2129 (1972); (d) C. L. Liotta, W. F. Fisher, G. H. Greene, Jr., and B. L. Joyner, *ibid.*, **94**, 4891 (1972); (e) C. F. Wilcox and C. Leung, *ibid.*, **90**, 336 (1968); (f) D. S. Noyce and G. A. Selter, *J. Org. Chem.*, **36**, 3458 (1971).

(28) See, for example, M. Jones, Jr., *J. Amer. Chem. Soc.*, **89**, 4236 (1967).

There was obtained 600 mg (52.5%) of colorless crystals, mp 152–154° dec, from ether–methylene chloride.

Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.84; H, 6.08; N, 8.51.

To a suspension of 3.0 g (9.1 mmol) of pure tosylhydrazone in 90 ml of dry ether was added with stirring 60 ml of methyllithium (*ca.* 1.0 *M*). The clear orange solution so obtained became cloudy and then clear red during 12 hr at room temperature. With ice cooling, water was added dropwise. The ether layer was separated, washed with saturated sodium chloride solution, dried, and evaporated. The crude orange-yellow oil (1.9 g) was chromatographed on Florisil (pentane elution) to furnish 0.87 g (66.4%) of **10a** as a clear, colorless oil. An analytical sample was prepared by vpc purification, $\delta_{TMS}^{CDCl_3}$ 5.2–6.45 (br m, 7 H, olefinic), 2.85–3.35 (br m, 2, bridgehead), and 1.78 (s with additional fine coupling, 3 H, methyl).

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.37. Found: C, 91.38; H, 8.61.

Reaction of 7-Methylbicyclo[4.2.2]deca-2,4,7,9-tetraene (10a) with CSI.—A solution of 290 mg (2.0 mmol) of **10a**[15] and 0.18 ml (2.0 mmol) of CSI in 10 ml of dry methylene chloride was stirred rapidly at 25° under nitrogen. Infrared analysis of aliquots revealed the presence of intense new carbonyl bands at 1825 and 1760 cm^{-1}; however, after 7 hr only the 1760-cm^{-1} band remained. The solvent was evaporated; nmr analysis of the residue showed the presence of two components in the ratio of 68.5:31.5. The predescribed pyridine–thiophenol work-up gave 282 mg (73%) of the lactam mixture. Crystallization from methylene chloride–ether gave the major isomer (**11a**) as colorless crystals, mp 163.5–164.5°, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: 76.98; H, 6.89; N, 7.43.

The mother liquors from several such runs were combined and chromatographed on Florisil. The minor isomer (**12a**) was eluted first with chloroform, colorless needles, mp 170.5–172.5°, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.76; H, 6.88; N, 7.59.

Reaction of 7-Methoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (10b) with CSI.—A solution of 158 mg (1.0 mmol) of **10b**[15,20] and 0.1 ml (1.4 mmol) of CSI in 10 ml of methylene chloride was stirred at 25° under nitrogen for 7 hr. The solvent was evaporated and the residue showed two methoxyl peaks (ratio 54.5:45.5) in its nmr spectrum. Processing as before gave 115 mg (56.5%) of the lactam mixture. Careful chromatography on Florisil ($CHCl_3$ elution) enabled **12b** (more rapidly moving) to be separated from **11b**. Recrystallization of the minor isomer (**11b**) from methylene chloride–ether gave colorless crystals (38 mg, 18.5%), mp 154–154.5°, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.72; H, 6.48; N, 6.85.

Lactam **12b** was likewise recrystallized from methylene chloride–ether, 50 mg (24%), colorless crystals, mp 193–194°, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.55; H, 6.57; N, 6.81.

Reaction of 7-Acetoxybicyclo[4.2.2]deca-2,4,7,9-tetraene (10c) with CSI. A. Long Reaction Time.—The enol acetate (**10c**, 270 mg, 1.5 mmol)[16] was dissolved in 15 ml of dry methylene chloride and 0.18 ml (2.0 mmol) of CSI was added in one portion with stirring under nitrogen. After 13 hr at 25°, the solvent was evaporated and nmr analysis indicated the presence of two components in a 76:24 ratio. The customary thiophenol–pyridine reduction and filtration through a short column of Florisil gave 193 mg (57.5%) of a lactam mixture. Recrystallization from methylene chloride–ether furnished a pure sample of the major product (**11c**, 128 mg, 38%) as colorless prisms, mp 193.5–194°, $\nu_{max}^{CHCl_3}$ 1735 and 1705 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.26; H, 5.61; N, 6.04.

Like purification of the minor product (**12c**) led to its isolation as colorless crystals, mp 187.5–188.5°; $\nu_{max}^{CHCl_3}$ 1735 and 1705 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.40; H, 5.67; N, 6.12.

B. Brief Reaction Period.—CSI (0.25 ml, 0.3 mmol) was added to a solution of 453 mg (0.25 mmol) of **10c** in 7 ml of methylene chloride. After stirring for 4 min, the solvent was evaporated and the residue was immediately dissolved in acetone and treated with thiophenol and pyridine at 0° in the usual way. Chromatography on Florisil and elution with pentane–chloroform (1:1) yielded 344 mg of colorless, oily β-lactam **13** which on crystallization gave 250 mg (45.5%) of colorless crystals: mp 159.5–160.5°; $\nu_{max}^{CHCl_3}$ 1770 and 1730 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 273 nm (ε 3150), 263 (5110), 253.5 (4890), and 246 (sh, 3730); $\delta_{TMS}^{CDCl_3}$ 7.3 (br s, >NH), 5.65–6.4 (m, 6, olefinic), 3.9 (m 1, bridgehead), 3.36 (s, >CHCO–), 3.16 (m, 1 bridgehead), and 2.08 (s, 3, $-COCH_3$).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.55; H, 5.75; N, 5.95.

7-Methoxy-8-methylbicyclo[4.2.2]deca-2,4,7,9-tetraene (15).—A dry 500-ml three-necked flask was fitted with a thermometer, two 10-ml addition funnels (fitted with nitrogen inlet), a mechanical stirrer, and a connection to the house vacuum *via* a stopcock. The flask was charged with 200 ml of dry dimethyl sulfoxide and 4.6 g of potassium *tert*-butoxide. The addition funnels contained 2.0 g of somewhat impure **14** and 4 ml of dimethyl sulfate. The system was degassed three times, filled with nitrogen, and cooled to 0°. The ketone was added during 30 sec and the resulting red solution was stirred for 3 min. At 0°, the dimethyl sulfate was added rapidly. The solution was stirred for 20 min at 0° and for 1.5 hr at room temperature, after which it was poured into 500 ml of 2 *M* sodium hydroxide solution. The product was extracted with pentane (10 × 100 ml) and the combined pentane extracts were washed four times with water and dried. Evaporation of the solvent gave a yellow oil (1.7 g), chromatography of which on alumina (activity I) using pentane–2% ether as eluent gave 0.83 g (38%) of **15**: ν_{max}^{neat} 1700 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 256.5 nm (ε 3360) and 248.5 (3300); $\delta_{TMS}^{CDCl_3}$ 5.5–6.54 (m, 6, olefinic), 3.50 (s, 3, $-OCH_3$), 2.92–3.5 (m, 2, bridgehead), and 1.7 (s, 3, $-CH_3$).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.09. Found: C, 82.60; H, 8.05.

Reaction of 7-Methoxy-8-methylbicyclo[4.2.2]deca-2,4,7,9-tetraene (15) with CSI.—Treatment of 340 mg (2.0 mmol) of **15** with 0.18 ml (2.0 mmol) of CSI in 20 ml of dry methylene chloride as above gave an *N*-(chlorosulfonyl) γ-lactam mixture in a ratio of 68.5:31.5. The usual chlorodesulfonylation and Florisil chromatography yielded 223 mg (52.5%) of a solid mixture of **16a** and **16b**. When the mixture was rechromatographed on Florisil (chloroform elution), separation of the two components was readily effected. The first isomer to elute was **16b**, which crystallized from methylene chloride–ether as colorless needles (143 mg, 43%), mp 189.5–190.5°, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.59; H, 6.92; N, 6.37.

From the later fractions, there was obtained 60 mg (14%) of **16a**, mp 171–172.5°, from methylene chloride–ether, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.77; H, 7.01; N, 6.47.

Reaction of 7,8-Diphenylbicyclo[4.2.2]deca-2,4,7,9-tetraene (17) with CSI.—A solution of 200 mg (0.7 mmol) of **17**[21] and 0.065 ml (0.77 mmol) of CSI in 10 ml of dry methylene chloride was stirred at room temperature for 22 hr, evaporated, and hydrolyzed with sodium sulfite solution as above. The product was extracted into methylene chloride and, after drying and evaporation, was obtained as fine, colorless needles (122 mg, 53%), mp 215.5–216.5°, from methylene chloride–ether, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89. Found: C, 84.53; H, 5.85.

Reaction of Bicyclo[4.2.1]nona-2,4,7-triene (23a) with CSI.—Hydrocarbon **23a** (470 mg, 0.4 mmol)[29] was dissolved in methylene chloride (7 ml) and treated with CSI (0.35 ml, 0.42 mmol) under nitrogen with stirring. After 14 hr, only *N*-(chlorosulfonyl) β-lactam carbonyl absorption was visible in the infrared. The solution was evaporated and the residue was treated with thiophenol and pyridine in acetone at 0°. After chromatography on Florisil (chloroform–pentane, 1:1, used for elution), 517 mg (80%) of a colorless oil was obtained which appeared homogeneous (nmr analysis). Trituration with ether–pentane at −78° and recrystallization from this solvent system gave **25b** as colorless crystals: mp 76–78°; $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 275.5 nm (ε 2950), 264.5 (5500), 255 (5600), and 248 (sh, 4240); $\delta_{TMS}^{CDCl_3}$ 7.1 (br, 1 >NH), 5.8–6.6 (m, 6, olefinic), 3.88 (d, J = 3.5 Hz, 1), 3.5 (m, 1), 2.3–3.1 (m, 3), and 1.85 (d, J = 11.5 Hz).

(29) T. J. Katz and S. Cerefice, *Tetrahedron Lett.*, 2561 (1969).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.59; H, 6.80; N, 8.74.

β-Lactam **25b** is unstable, since originally colorless crystals become yellow and partly insoluble over a period of a few days. In the noncrystalline state, polymerization is particularly rapid.

Registry No.—**1**, 15677-13-1; **3**, 34733-74-9; **5**, 38910-79-1; **7**, 38910-80-4; **7** perchlorate, 38910-81-5; **10a**, 37494-24-9; **10b**, 36629-02-4; **10c**, 36629-05-7; **11a**, 38910-85-9; **11b**, 38910-86-0; **11c**, 38910-87-1; **12a**, 38910-88-2; **12b**, 38910-89-3; **12c**, 38910-90-6; **13**, 38910-91-7; **14**, 38910-92-8; **14** tosylhydrazone, 38974-04-8; **15**, 38910-93-9; **16a**, 38910-94-0; **16b**, 38898-33-8; **17**, 14690-42-7; **18**, 38898-35-0; **23a**, 38898-36-1; **25b**, 38898-37-2; CSI, 1189-71-5.

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Uniparticulate Electrophilic Addition as a Probe of Possible Bicycloaromatic and Antibicycloaromatic Carbonium Ion Character. Reactions of Chlorosulfonyl Isocyanate with Exocyclic Methylene Precursors to Such Cations[1]

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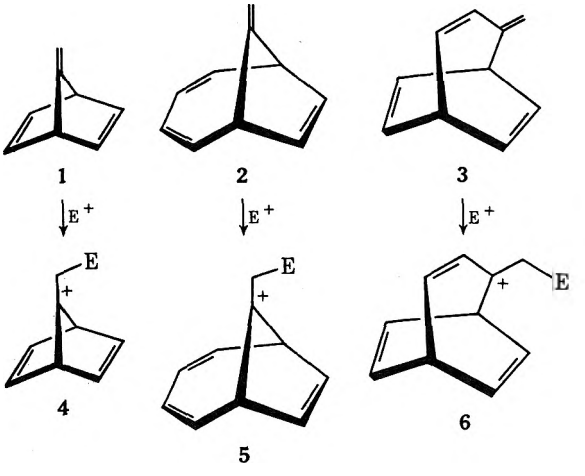
Synthesis of the methylene polyolefins 9-methylenebarbaralane (**10**), 2-methylenebicyclo[3.2.2]nona-3,6,8-triene (**3**), 9-methylenebicyclo[4.2.1]nona-2,4,7-triene (**2**), and their benzologs, as well as 7-methylenenorbornadiene (**1**) and 7-methylenequadricyclane (**8**), has been achieved and the reactions of these hydrocarbons with chlorosulfonyl isocyanate studied. The systems examined were those which upon attack at the methylene group would lead to the generation of possible bicycloaromatic (*e.g.*, **4**) or antibicycloaromatic (*e.g.*, **5**, **6**) zwitterionic intermediates. Possible mechanistic pathways leading to the products are proposed and conclusions relating to stabilization and destabilization of the relevant cations are drawn.

The concept of bicycloaromaticity, initially formalized in 1967,[3] relates to possible extensive charge delocalization in tricyclic ions containing three π bridges in a longicyclic topology.[4] Of interest because it extends the phenomenon of homoaromaticity[5] to a third dimension, this theory has received an ever increasing amount of attention since its introduction. To this time, the several relevant cations which have been studied have been generated either solvolytically (short-life conditions)[6] or by protonation in superacidic media at low temperatures (long-life conditions).[7] Access to anions has been gained by the action of sodium–potassium alloy on a suitable methoxyl precursor[6g,8] and by deprotonation.[9] In this paper, we present yet another way to assess the possible bicyclo- or antibicycloaromatic character of cationic species which relies upon the generation and capture of these elusive intermediates with the uniparticulate electrophile[10] chlorosulfonyl isocyanate (CSI).

In earlier work, the necessity of a suitable reference system for evaluation of the level of bicycloaromatic character in each individual ion under study has presented certain problems. Originally, Goldstein and Odell[6a] resorted to a compound possessing the same number of trigonal carbon atoms and π electrons. More recently, Grutzner and Winstein[6h] selected a homoaromatic reference system in which interaction operates between two bridges isolated from the third. The ideal situation is, of course, one in which the identical geometry is available to both the standard and potentially bicycloaromatic entity.

In view of the practicality of synthesizing alicyclics **1–3** and related exocyclic methylene hydrocarbons, we have entertained the possibility of employing each of these hydrocarbons as its own standard of reference. Were electrophilic attack to occur at the exocyclic



(1) Unsaturated Heterocyclic Systems. XC. Preceding contribution in this series: L. A. Paquette and M. J. Broadhurst, *J. Org. Chem.*, **38**, 1886 (1973).

(2) Holder of a NATO Postdoctoral Fellowship (1970–1972) administered by the Science Research Council.

(3) M. J. Goldstein, *J. Amer. Chem. Soc.*, **89**, 6357 (1967).

(4) M. J. Goldstein and R. Hoffmann, *ibid.*, **93**, 6193 (1971).

(5) S. Winstein, *Chem. Soc., Spec. Publ.*, **No. 21**, 5 (1967).

(6) (a) M. J. Goldstein and B. G. Odell, *J. Amer. Chem. Soc.*, **89**, 6356 (1967); (b) A. S. Kende and T. L. Bogard, *Tetrahedron Lett.*, 3383 (1967); (c) J. C. Barborak, J. Daub, D. M. Follweiler, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 7760 (1969); (d) J. C. Barborak and P. v. R. Schleyer, *ibid.*, **92**, 3184 (1970); (e) J. B. Grutzner and S. Winstein, *ibid.*, **92**, 3186 (1970); (f) D. Cook, A. Diaz, J. P. Dirlam, D. L. Harris, M. Sakai, S. Winstein, J. C. Barborak, and P. v. R. Schleyer, *Tetrahedron Lett.*, 1405 (1971); (g) J. S. Blair, J. Clark, and G. V. Meehan, *ibid.*, 3097 (1972); (h) J. B. Grutzner and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2200 (1972).

(7) (a) P. Ahlberg, D. L. Harris, and S. Winstein, *ibid.*, **92**, 2146 (1970); (b) P. Ahlberg, J. B. Grutzner, D. L. Harris, and S. Winstein, *ibid.*, **92**, 3478 (1970); (c) P. Ahlberg, D. L. Harris, and S. Winstein, *ibid.*, **92**, 4454 (1970); (d) P. Ahlberg, D. L. Harris, M. Roberts, P. Warner, P. Seidl, M. Sakai, D. Cook, A. Diaz, J. P. Dirlam, H. Hameberger, and S. Winstein, *ibid.*, **94**, 7063 (1972).

(8) J. B. Grutzner and S. Winstein, *ibid.*, **90**, 6562 (1968).

(9) S. W. Staley and D. W. Reichard, *ibid.*, **91**, 3998 (1969).

(10) L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *ibid.*, **93**, 4503 (1971).

methylene center in each case, one bicycloaromatic (**4**) and two antibicycloaromatic cations (**5** and **6**) would be formed.[3] In the latter examples, the resulting long-range destabilization of the carbonium ion center could serve to substantially reduce the kinetic preference for electrophilic bonding to the $=CH_2$ group with the result that attack at a different olefinic site could become dominant.[11] Alternatively, **5** and **6** could exhibit a high propensity (relative to **4**) for structural rearrangement. Seemingly, if bicycloaromaticity does provide a source of stabilization to certain three-dimensional π-electronic arrays but not to others, then widely differing chemical reactivity toward uniparticulate electrophiles would be expected for **1**–**3** and related molecules.

Preparation of the Methylene Derivatives.—Synthetic entry to **1** was gained by Wittig reaction of quadricyclanone (**7**) with methylenetriphenylphosphorane and subsequent valence isomerization of the resulting methylenequadricyclane (**8**) with $[Rh(NOR)Cl]_2$.[12] The structural assignment to **1** follows from the directed synthesis and spectral evidence. Of particular interest was the finding that **1** exhibits a methylene proton signal at δ 3.63, approximately 0.9 ppm to higher field than that found in the other compounds studied herein. The excessive shielding of these two protons points to strong polarization of the exocyclic double bond in **1** with the negative terminus of the dipole oriented away from the bicyclic framework. The importance of ground-state contributions from structure **9** is revealed by the substantial dipole moment of the hydrocarbon (0.71 D) and its ^{13}C nmr and photoelectron spectra.[12]

The methylene hydrocarbons **2** and **3**, as well as 9-methylenebarbaralane (**10**) and methylenehomosemibullvalene (**11**), were synthesized by treatment of the derived ketones under Wittig conditions with methylenetriphenylphosphorane. The possibility was considered that benzo derivatives of certain of these polyenes might provide added mechanistic information. Goldschmidt and Kende, while studying the photochemical interrelationships of a number of polyolefinic hydrocarbons, have previously described the the preparation of **12**–**14**.[13] In contrast, because ketone **19** had been previously isolated only in low yield from benzyne addition to tropone,[14] an improved synthesis of this molecule was sought. The present scheme depends on the dienophilic character of the etheno bridge in bicyclo[4.2.1]nona-2,4,7-trien-9-one (**15**)[15,16] and subsequent adjustment of the

(11) In this regard, CSI does not differ from the common biparticulate electrophilic reagents which exhibit a kinetic preference for attack at a terminal methylene group in the presence of otherwise disubstituted double bonds: R. Graf, *Angew. Chem., Int. Ed. Engl.*, **7**, 172 (1968).

(12) Subsequent to the completion of this work, we learned of a similar synthesis of **1** in Professor R. W. Hoffmann's laboratory: R. W. Hoffmann, R. Schuttler, W. Schafer, and A. Schweig, *Angew. Chem.*, **84**, 533 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 512 (1972).

(13) Z. Goldschmidt and A. S. Kende, *Tetrahedron Lett.*, 4625 (1971).

(14) T. Miwa, M. Kato, and T. Tamano, *ibid.*, 1761 (1969); H. Tanida and T. Irie, *J. Org. Chem.*, **36**, 2777 (1971).

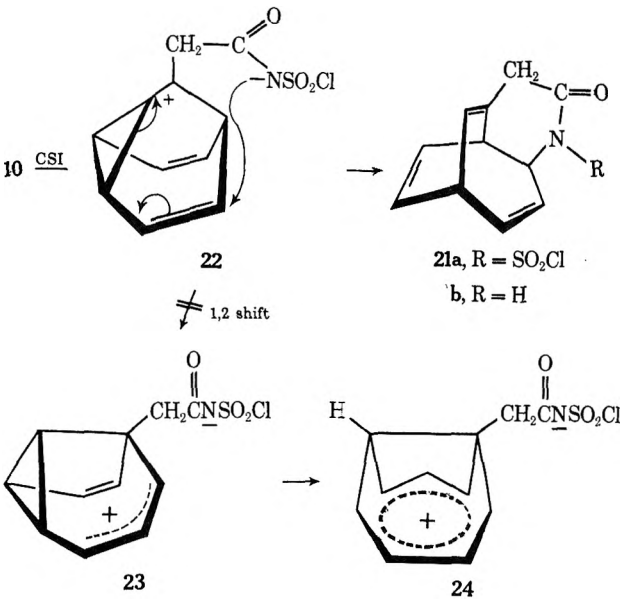
(15) L. A. Paquette, R. H. Meisinger, and R. E. Wingard, Jr., *J. Amer. Chem. Soc.*, **94**, 2155 (1972).

(16) T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Shechter, *ibid.*, **94**, 5366 (1972); K. Kurabayashi and T. Mukai, *Tetrahedron Lett.*, 1049 (1972); M. Sakai, R. F. Childs, and S. Winstein, *J. Org. Chem.*, **37**, 2517 (1972).

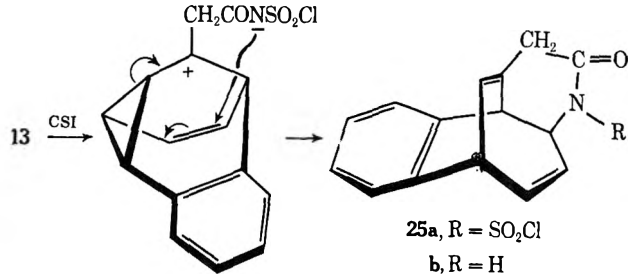
oxidation level by such controlled means which would aromatize a new six-membered ring fused to that position without engendering loss of carbon monoxide. To this end, reaction of **15** at 120–130° with an excess of α-pyrone (**16**) in xylene solution containing hydroquinone afforded, after purification by chromatography, a 34% yield of the desired adduct (**17**). A sharp-melting material was isolated, but it was not possible to determine from the available nmr data which isomer (**17a** or **17b**) was in hand. Thermal decarboxylation of **17** at 230° (0.3 mm) resulted in the formation of **18** in 80% yield. Surprisingly, ketone **18** proved to be somewhat resistant to dehydrogenation. Only when solutions of **18** in benzene containing relatively large quantities of 10% palladium on carbon were heated at reflux for 24 hr was a reasonable (54%) yield of **19** obtained. Treatment of **19** as before with methylenetriphenylphosphorane led readily to **20**.

Chlorosulfonyl Isocyanate Additions. 9-Methylenebarbaralane and Its Benzolog.—Reaction of **10** with CSI in dry methylene chloride solution at 25° for 2.5 hr and subsequent dechlorosulfonylation with alkaline sodium sulfite[17] resulted in the formation of lactam **21b**. Its infrared carbonyl absorption (1660 cm^{-1}) is typical of a δ-lactam. The absence of ultraviolet absorption apart from end absorption attests to the lack of extended conjugation. The nmr spectrum shows five olefinic protons as a series of three unevenly weighted multiplets at δ 6.8 (area 1), 6.18 (area 3), and 5.0 (area 1), an allylically disposed >CHN< hydrogen at 3.6 (m), a sharp methylene singlet (2 H) at 3.3, and a broad methine multiplet (2 H) centered at 3.2. These data signify in particular that (a) electrophilic attack has occurred at the methylene carbon in **10** with ultimate attachment of the $-CH_2CO-$ functionality to a trigonal carbon (note downfield position of the methylene singlet); (b) structural rearrangement accompanied by opening of the cyclopropane ring did operate (note lack of cyclopropyl protons); and (c) closure of the intermediate zwitterion occurred with C–N bond formation at an allylic center to produce a six-ring lactam. Double-resonance studies, which are detailed in the Experimental Section, confirmed the structural assignment to **21**.

A reasonable mechanism for the formation of **21a** involves initial generation of zwitterion **22**, followed by direct trapping of this barbaralyl cation according to the indicated series of electron shifts. Interestingly, **22** has given no evidence for rearrangement *via* **23** to **24**, despite the bishomoaromatic nature of this species.[18] This is in contrast to the 9-methylbarbaralyl cation, which under long-life conditions rearranges at −116° exclusively to the methyl 1,4-bishomotropylium ion corresponding to **24**.[7a,18] We attribute this difference to the rapid intramolecular capture of **22** which, because it is simply an exothermic bond-forming charge annihilation process, can compete favorably with the apparently more energetically demanding 1,2 carbon shift required for passage to **24**.



When benzo derivative **13** was similarly treated with CSI, a lactam of comparable structure (**25b**)

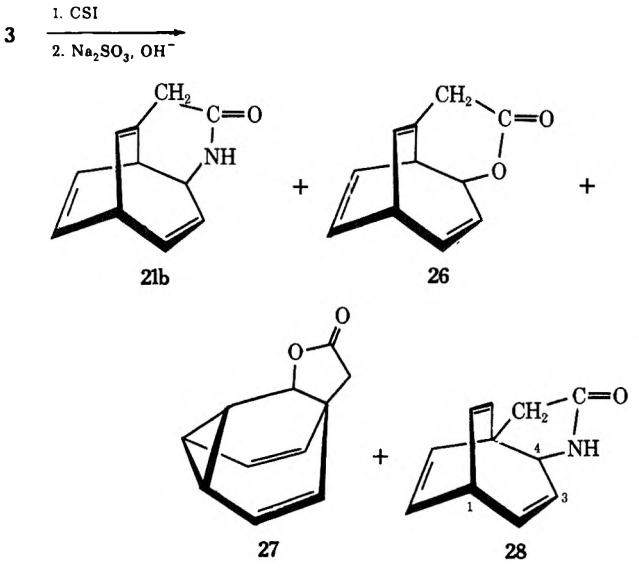


was isolated. Since one of the double bonds in **22** remains essentially isolated from the requisite electronic shifts, the formation of **25** was not unexpected.[6g] Structure **25b** was assigned chiefly on the basis of the following nmr observations. In addition to the four aromatic protons seen as a multiplet centered at δ 7.2, two olefinic proton absorptions were evident at 6.1–6.5 (m, area 2) and 4.85–5.2 (m, area 1). The bridgehead protons were deshielded relative to those in **21b** and appeared at 3.75 superimposed upon the >CHN< hydrogen. The chemical shift of the methylene group (3.35) was again in accord with expectations based upon its allylic nature.

2-Methylenebicyclo[3.2.2]nona-3,6,8-triene and Its Benzolog.—CSI addition to **3** was carried out under conditions which matched those used for **10** and **13**. A number of products, all resulting from initial electrophilic attack at the methylene group, was formed. Direct crystallization of the reaction mixture permitted isolation of the major product (52%), which was identified as lactam **21b**. Subsequent column chromatography served to separate a two-component lactone mixture from residual **21b** and a second lactam. Preparative-scale vpc permitted isolation of **26** (2%) and a second lactone tentatively characterized as **27** (4%). The first of these substances exhibited an intense carbonyl stretching frequency at 1780 cm^{-1} and showed resonances in the nmr at δ 3.18–7.05 (m, 4), 5.75 (d with fine splitting, J = 8 Hz, 1), 5.3 (dd, J = 10.5 and 2.5 Hz, 1), 4.5 (m, 1), 3.45 (m, 1), and 2.83 (narrow AB pattern, 2). Of particular significance are the chemical shifts of the methylene (2.83) and >CHO–

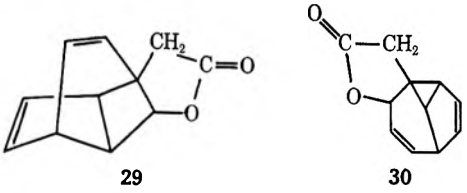
(17) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).

(18) (a) S. Yonida, S. Winstein, and Z. Yoshida, *Bull. Chem. Soc. Jap.*, **45**, 2510 (1972); (b) R. Hoffmann, W.-D. Stohrer, and M. J. Goldstein, *ibid.*, **45**, 2513 (1972); (c) R. E. Leone and P. v. R. Schleyer, *Angew. Chem., Int. Ed. Engl.*, **9**, 860 (1970).



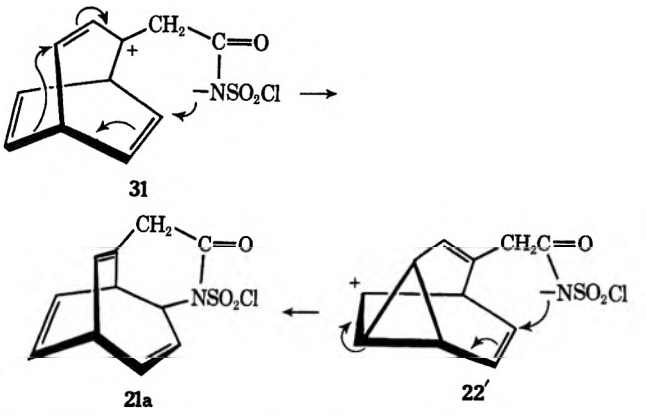
protons, which reveal their nonallylic and allylic features, respectively, the presence of six olefinic hydrogens, and the unique triply allylic nature of the *lone* methine proton. Spin-decoupling studies confirmed the spatial orientation of the various protons (see Experimental Section).

The second lactone (ν_{max} 1780 cm^{-1}) has proven more difficult to characterize unambiguously. The presence in **27** of an additional ring is revealed by the appearance in the nmr of only four olefinic protons at δ 5.45–6.05 (m, 3), and 5.12 (d, 1). The upfield positions of the >CHO– (3.9) and methylene protons (2.57) seemingly attests to their attachment to nonallylic tetrahedral carbon. Insufficient material precluded examination of the possible fluxional nature of **27**. Accordingly, we point out that other structural formulations such as **29** and **30** cannot be excluded on the basis of the available data.

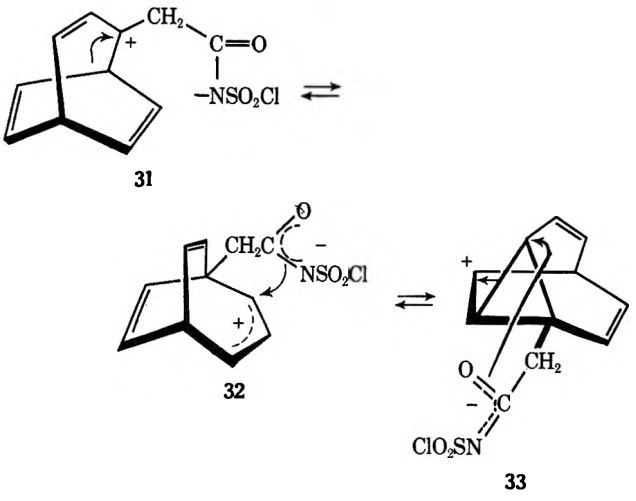


The minor lactam (**28**) was characterized by an nmr spectrum exceedingly similar to that of **26**, thus showing that these products were of comparable structure.

The formation of **21b** formally requires the 1,2 shift of a vinyl bridge. Although this reaction course can be depicted by means of the electronic reorganization shown in zwitterion **31**, it is perhaps more reasonable in the light of ancillary data to formulate the genesis of **21a** on the basis of barbaralyl cation **22′**. For example, Winstein,[7c,d] Schleyer,[6c,d] and Goldstein[6a] have provided evidence that suitable precursors of the destabilized $3^{+}2^{0}2^{0}$ cation lead instead to generation of the barbaralyl cation. Also, the nearly exclusive production of **21a** from 9-methylenebarbaralane, which must necessarily involve **22**, serves to support additionally the likely involvement of **22′** in the present situation.

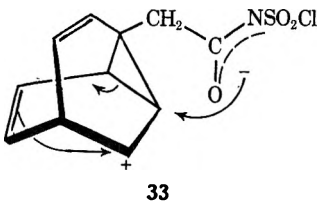


The isolation of lesser amounts of **26** and **28** serves to reveal, however, the less marked capability of the bicyclo[3.2.2]nona-3,6,8-trien-2-yl cation for degenerate rearrangement.[6d,6e,18] Whether **31** transmutes



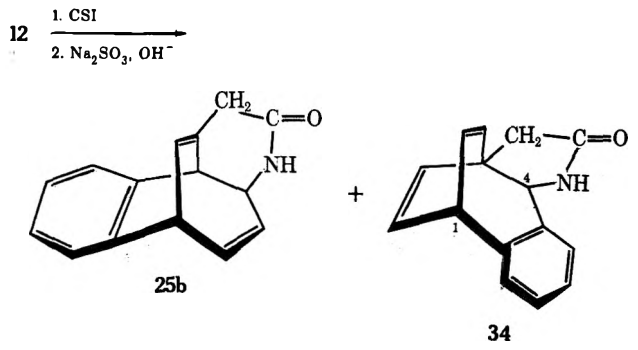
to **32** through a 1,2-vinyl shift mechanism (as illustrated), the equivalent homoallylic barbaralyl cation (**33**), or a combination of these processes is not known (see Discussion). Once access is gained to **33**, C–N and C–O bond formation can now operate to furnish **28** and **26**, respectively.

It can be immediately seen that alternative intramolecular bonding in **33** adapts itself nicely to the

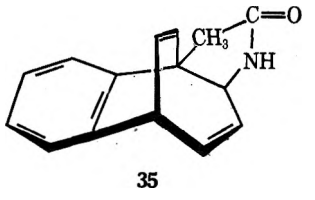


ultimate formation of **27**. In this connection, it is noteworthy that traces of a lactam corresponding in structure to **27** were also encountered in the very minor fractions obtained from the chromatographic separation.

When treated similarly with CSI, the benzo analog **12** was found to give rise to **25b** (68%) and **34** (2.4%). Lactone formation was not observed. The identity of **34** is apparent on the basis of its physical and spec-

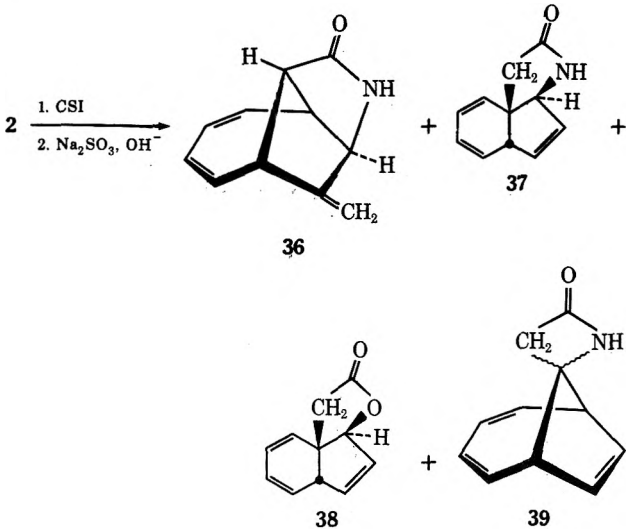


tral properties, which match those recorded above for this lactam. The assignment of structure to **34** was supported by comparison of its nmr spectrum with that of **28**. In particular, alternative formulation **35**

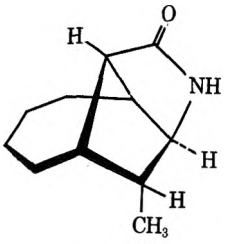


which would result from 1,2-benzo migration can be convincingly ruled out on the following grounds. Firstly, the high-field olefinic doublet of doublets due to H_3 in **28** is absent in **34**. Secondly, H_4 in **34** appears as a relatively sharp singlet, indicating lack of sizable spin–spin interaction with adjacent protons; H_4 is a higher order multiplet in **28** and appears at significantly higher field in the latter spectrum. Lastly, H_1 in **34** is seen to experience a 0.6-ppm downfield shift relative to **28** as a result of its benzylic environment. The results with **12** are most economically explained in terms of an intermediate benzobicyclo[3.2.2]nonatrienyl zwitterion[19] and its subsequent rearrangement *via* 1,2-benzo migration.

9-Methylenebicyclo[4.2.1]nona-2,4,7-triene and Its Benzolog.—When **2** was treated with CSI in analogous fashion, a complex mixture of products resulted. The four major components of this mixture have been isolated in a pure state, but those substances present in trace quantities have not been characterized. The principal cycloadduct was obtained in 26% isolated yield and assigned structure **36**. The absorption



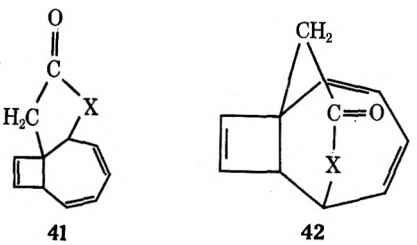
maximum at 1705 cm^{-1} in chloroform was appropriate for a γ-lactam, as was the ultraviolet maximum in ethanol at 254 nm for the conjugated diene moiety. In the nmr spectrum, there were the expected absorptions for the olefinic protons of the diene (δ 5.5–6.45, m, 4) and exocyclic methylene groups (5.15, d, J = 2.5 Hz, 2) in addition to the allylic >CHN< proton (4.25, m, 1), doubly allylic (3.38, m, 1) and allylic bridgehead hydrogen (2.88, m, 1), and α-carbonyl proton (2.33, br s, 1) peaks. Double-resonance studies supported these assignments. Confirmatory evidence for the presence of the exocyclic methylene functionality was obtained by catalytic hydrogenation of **36** to the hexahydro lactam **40**, the nmr spectrum



of which now revealed the presence of a sharp doublet at δ 0.98 (J = 7 Hz) typical for a methyl group attached to a saturated carbon atom and coupled to a lone methine hydrogen.

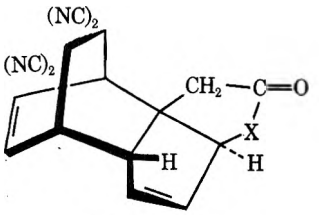
β-Lactam **39** (1%) was readily identified as a product of CSI addition to the terminal methylene group of **2** without structural reorganization of the [4.2.1]-bicyclic skeleton. This colorless solid showed the expected 1760 cm^{-1} carbonyl stretching frequency and an ultraviolet spectrum characteristic of bicyclo[4.2.1]nona-2,4,7-trienes. Additional support for the assignment comes from comparison of the nmr of **39** with that of hydrocarbon **2**. The observed chemical shift of the methylene protons (δ 3.77) does not, however, allow an unequivocal decision to be made between the two possible stereoisomers of this β-lactam.

The ultraviolet spectra of **37** and **38** are consistent with a conjugated diene system in a six-membered ring and inconsistent with isomeric 1,3-cycloheptadiene structures such as **41** and **42**, particularly owing



to the twisted diene chromophore structurally enforced in the latter pair of molecules. Spin-decoupling experiments were of little confirmatory value in these cases. In confirmation of the structural assignments, however, **37** and **38** underwent ready [4 + 2] cycloaddition to TCNE at room temperature to give adducts **43a** and **43b**, respectively. Of particular relevance was the finding that the chemical shifts of the proton α to the heteroatom in **43a** and **43b** remained essentially unchanged from their positions in the spectra of the parent compounds. This observation

(19) J. S. Blair, J. Clark, and G. V. Meehan, *Tetrahedron Lett.*, 3097 (1972).

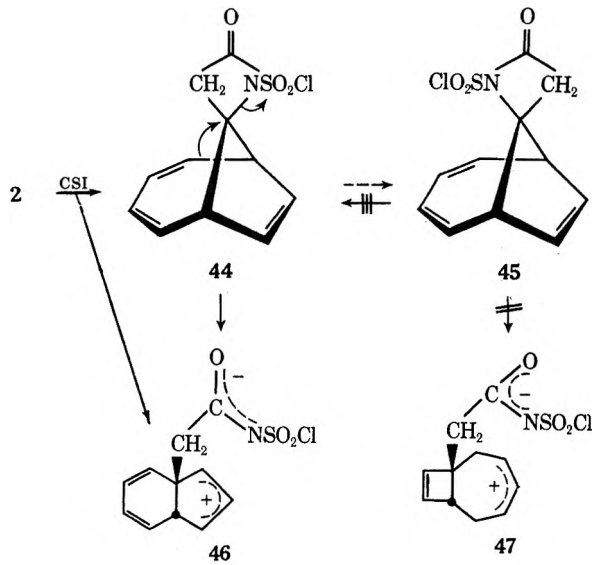


43a, X = NH
b, X = O

signifies that no gross structural reorganization has occurred in the vicinity of the particular carbon atom in question and is in keeping with **37** and **38** and not **41** and **42**.

A mechanistic rationalization of the formation of **37**, **38**, and **39** involves the assumption that **2** is first attacked by CSI at the exocyclic double bond from the less sterically hindered direction[16] to give **44**. Monitoring of the progress of the reaction by ir spectroscopy did provide evidence of *N*-(chlorosulfonyl) β-lactam intervention. Interestingly, however, there invariably remained a weak carbonyl absorption due to this functionality which no longer decayed with time. We reason that this band corresponds to the precursor to **39**. The questions arise as to why any β-lactam remains at all and why only a single isomer was isolated. A possible explanation is that **45** is formed in the reaction. Whether this adduct arises from ring opening of **44** and closure from the opposite direction or from direct [2 + 2] condensation is not known. It does appear, however, that **45** is not reconvertible to **44**.[20]

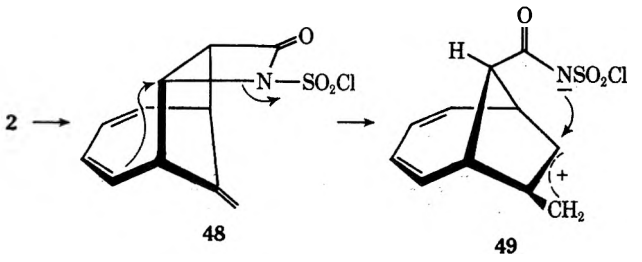
What there is to say about the mechanism of conversion of **44** to **37** and **38** is based in part upon the earlier observations of Kende and Bogard,[6b] who observed that treatment of 9-phenylbicyclo[4.2.1]-nona-2,4,7-trien-9-ol with 2 equiv of thionyl chloride and 1 equiv of pyridine gave a high yield of 1-chloro-9-phenyl-*cis*-8,9-dihydroindene. Thus, C–N bond heterolysis in **44** and essentially synchronous 1,2-diene migration from the rear side direction could lead to **46**. Alternatively, **46** could arise by bond reorganization in the electrophilic process proper. A similar driving



(20) Implicit in this conclusion is the requirement that **39** be related configurationally to **45**. This is consistent with the spectral data.

force does not appear to underlie the conversion of **45** to **47**, where a 1,2-vinyl shift is necessary. However, this possibility cannot be entirely excluded, since it remains possible that **47** could cyclize exclusively by bonding of nitrogen to the proximate trigonal cyclobutene carbon with electronic readjustment to regenerate the [4.2.1] bicyclic unit.[18]

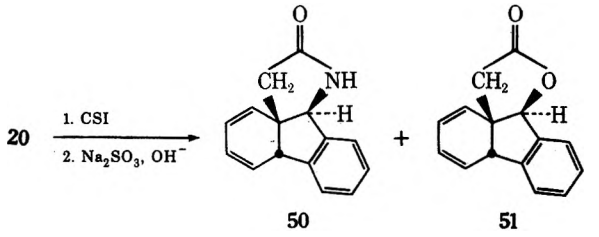
Competitive attack by the CSI reagent at the etheno bridge in **2** is revealed by the isolation of **36**. Indeed, it appears that **2** may resemble to an extent the closely related bicyclo[4.2.2]deca-2,4,7,9-tetraene system[1] and lead *via* **48** to zwitterion **49**. Stereoselective ap-



48 **49**

proach from the exo direction is required, followed by preferential 1,2-migration of the butadiene bridge. Charge annihilation in **49** understandably is regioselective because of strain considerations.

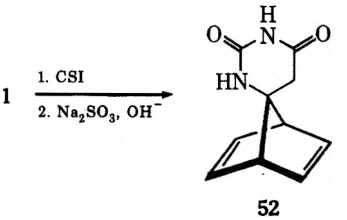
Benzo derivative **20** also undergoes the interesting conversion to lactam **50** (51.5%) and lactone **51**



50 **51**

(~10%) resulting from exclusive initial bonding to its terminal methylene group. Examination of the nmr spectra of both products discloses an unmistakable similarity with those of **37** and **38**. The ultraviolet spectra of these compounds likewise show significant common features.

7-Methylenenorbornadiene and 7-Methylenequadricyclane.—When **1** was allowed to react with CSI at room temperature, there resulted rapid consumption of the reagents. Aqueous sodium bisulfite treatment followed after 10 min and the highly insoluble uracil derivative **52** was obtained in good yield. The nmr, ir,

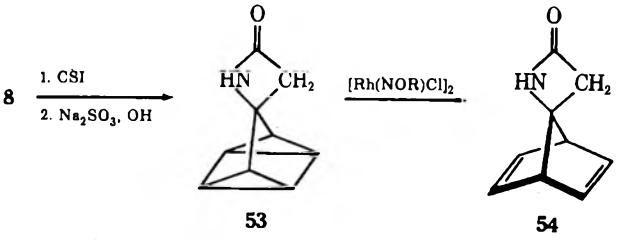


52

and mass spectra, as well as the low solubility in organic solvents and high melting point, befit this structure well.

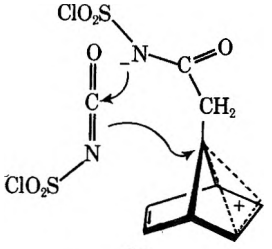
The β-lactam originally expected from this reaction (**54**) was then prepared by treatment of **8** with CSI and subsequent isomerization of the novel β-lactam **53**

with Rh(I). In contrast to the behavior of **8** toward the rhodium catalyst, **53** reacted rapidly and exothermically in $CDCl_3$ to afford **54**. Not unexpectedly, the spectral and physical properties of **54** differ markedly from those of **52**.



53 54

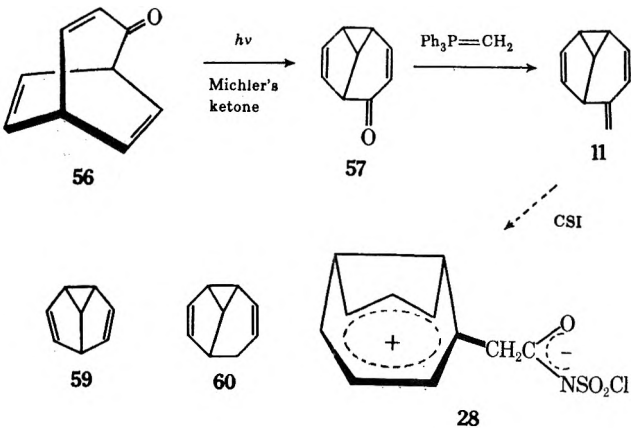
The unique nature of **52** appears to be a consequence of an inordinately long lifetime for the stabilized zwitterionic intermediate **55**,[21] such that sufficient



55

time is available for reaction with a seond molecule of CSI.[22] Alternatively, it can be argued that cyclization to the β-lactam is particularly slow in this instance because of strain factors. However, the ready formation of **53** does not lend support to the latter proposal.

5-Methylenetricyclo[6.1.0.0^{4,9}]nona-2,6-diene and Related Compounds.—Although not of direct relevance to the bicycloaromaticity question, the reaction of CSI with **11** and **14** was studied to determine if exocyclic methylene derivatives of this general structure could serve as synthetically useful precursors to zwitterionic 1,4-bishomotropylium ions such as **58**.[23] Triene **11** was most readily accessible from triplet-sensitized photoisomerization[24,25] of **56**[6a] and subsequent reaction of homosemibullvalenone **57** with methylenetriphenylphosphorane. When **11** and **14** were allowed to react with CSI, rapid formation of insoluble yellow polymeric substances were observed. No characterizable lactam or lactone products could be isolated. The causative factors underlying the ill-defined nature of these processes are not known. However, it is worthy of note that similar results have been obtained with the somewhat related divinylcyclopropanes semibullvalene (**59**) and homosemibullvalene (**60**).[26]



56 57 11 59 60 28

Discussion

The fact that lactam **21b** is the product of CSI addition to 9-methylenebarbaralane (**10**) is in consort with the assumption that this reaction is proceeding through barbaralyl cation **22**. In view of the stabilized nature of the $3^+3^-1^+$ construct inherent in **22**,[4] high preference for attack by the uniparticulate electrophile at the methylene carbon should be exhibited, and such is observed. Our inability to isolate β-lactam product which would result from direct collapse of **22** is perhaps a consequence of kinetic control, which would presumably lead to more rapid six-center cyclization. Transient formation of β-lactam products in all of the described reactions must, however, be considered to be a possible initial event.[27]

The experimental results show that exclusive attack at the methylene carbon of 2-methylenebicyclo[3.2.2]-nona-3,6,8-triene (**3**) also occurs. However, the absence of unrearranged products in the mixture, **21b** and **26–28**, introduces the possibility that [3.2.2] zwitterion **31** may never be truly formed during the addition. In actuality, the seemingly overwhelming preference for initial bonding to the methylene carbon of **3** might be construed to mean either that the [3.2.2] cation is not really destabilized so that its intervention can compete favorably with the several other possibilities or that this positional selectivity is the result of direct passage to the barbaralyl system, the stabilization in which is reflected in the transition state. An unequivocal answer to this dichotomy is not presently available. However, it is clear from the relative yields of products that a preference for the intermediacy of **22** does exist. No obvious guideline is available to assess why the intervention of isomeric skeletal modification **33** is not fully competitive.

The less discriminatory reactivity of **2** toward CSI has been discussed above in mechanistic terms. Electrophilic attack at the etheno bridge is followed by structural bond reorganization to a [3.2.1] bicyclic framework in a manner reminiscent of the behavior of bicyclo[4.2.2]decatetraenes.[1] Interestingly, attack at the methylene center also occurs, this reaction mode operating exclusively in **20** where benzo fusion denies access to the first process. In this instance, consideration must be accorded to the stereoselectivity of CSI attack. Analysis of the product data reveals

(21) (a) R. K. Lustgarten, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 6350 (1967); (b) M. Brookhart, R. K. Lustgarten, and S. Winstein, *ibid.*, **89**, 6352, 6354 (1967); (c) R. K. Lustgarten, M. Brookhart, and S. Winstein, *ibid.*, **90**, 7364 (1968).

(22) Analogous behavior of CSI, albeit, under quite different circumstances, has been encountered previously: E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968); E. J. Moriconi and Y. Shimakawa, *ibid.*, **37**, 196 (1972).

(23) M. Sakai, D. L. Harris, and S. Winstein, *ibid.*, **37**, 2631 (1972).

(24) A. S. Kende and Z. Goldschmidt, *Tetrahedron Lett.*, 783 (1970).

(25) The singlet excited state behavior of such ketones has been examined: (a) O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *J. Amer. Chem. Soc.*, **91**, 6856 (1969); (b) A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *ibid.*, **91**, 6858 (1969).

(26) M. Sakai, D. L. Harris, and S. Winstein, *J. Chem. Soc., Chem. Commun.*, 861 (1972).

(27) J. R. Malpass and N. J. Tweddle, *ibid.*, 1244, 1247 (1972); T. J. Barton and R. J. Rogido, *Tetrahedron Lett.*, 3901 (1972).

that approximately 1% of unrearranged adduct in the form of **39** is isolable. Lactam **37** and lactone **38**, on the other hand, denote the transient formation of dihydroindenyl zwitterion **46**. It is not possible at this time to distinguish between the direct intervention of **46** or its genesis as a result of a 1,2-butadienyl shift in **44**. Transient *N*-(chlorosulfonyl) β-lactam formation is observed, but the number of reaction pathways which give rise to this functionality is unknown. Since CSI additions have been claimed to be "quasiconcerted" in certain cases, it is not unreasonable that the formation of **44** could operate without build-up of excessive cationic character at C_9. Notwithstanding, the incursion of competitive electrophilic addition elsewhere in the molecule serves to provide convincing evidence that the bicyclo[4.2.1]-nona-2,4,7-trien-9-yl cation is not particularly stabilized.

The high reactivity of 7-methylenequadricyclane (**8**) toward CSI agrees well with the remarkably rapid solvolytic behavior of 7-nortricyclyl chloride and tosylate.[28,29] The absence of structural rearrangement in **53** also compares favorably with the earlier results of Story and Fahrenholtz,[30] who demonstrated that sodium borohydride reduction of nortricyclyl brosylate is capable of almost completely trapping the derived cation prior to isomerization.

The rapidity with which 7-methylenenorbornadiene (**1**) reacts with CSI can be attributed to the highly polarized ground state of this hydrocarbon and the exceptional stability of the 7-norbornadienyl cation.[31] The extent of interaction between the two vinyl bridges and the cationic center cannot be derived from the CSI reaction. However, the previous demonstration by Winstein[21a] of the unsymmetrical nature of this carbonium ion[32] is probably applicable here with little modification. Exclusive formation of uracil **52** phenomenologically distinguishes zwitterion **55** from the other dipolar species evaluated herein. Apart from the question of whether the stability of the 7-norbornadienyl cation has its origin in homaromatic or bicycloaromatic interaction,[6g,31] it must once again be concluded that it represents a particularly fascinating example of long-range longicyclic carbonium ion stabilization.

Experimental Section

Nmr spectra were obtained with Varian A-60A and HA-100 instruments; ir spectra with a Perkin-Elmer Infracord; mass spectra with the AEI-MS9. The elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

7-Methylenequadricyclane (8).—To a stirred suspension of methyltriphenylphosphonium bromide (16.8 g, 0.047 mol) in dry ether (125 ml) under a nitrogen atmosphere was added *n*-butyllithium (24 ml of 2 *M* solution in hexane). The mixture was stirred for 1 hr at room temperature and then a solution of quadricyclanone (**7**, 5.0 g, 0.047 mol)[33] in ether (25 ml) was added over a period of 5 min. A thick, white precipitate formed immediately. The reaction mixture was stirred and heated under reflux for 4 hr, cooled, and poured into ice water (200 ml). The ether layer was separated and the aqueous layer was extracted twice with pentane (50 ml). The combined organic extracts were washed five times with water, dried, and carefully evaporated through a short (1 cm) Vigreux column. The residue was distilled under reduced pressure to give 2.0 g (40%) of **8** as a colorless oil, bp 80–85° (25 mm). An analytical sample was obtained by preparative vpc isolation (5 ft × 0.25 in. column packed with 20% SE-30 at 55°): $\delta_{TMS}^{CDCl_3}$ 5.08 (s, 2, methylenes), 1.85 (d, J = 3.5 Hz, 2), and 1.52 (t, J = 3.5 Hz, 2).

Anal. Calcd for C_8H_8: C, 91.25; H, 8.75. Found: C, 91.38; H, 8.85.

7-Methylenenorbornadiene (1).—To a solution of 1.0 g of **8** in 15 ml of carbon tetrachloride was added 90 mg of $[Rh(NOR)Cl]_2$ and the mixture was refluxed under nitrogen for 20 min. At this point, vpc analysis indicated that no starting material remained. The solvent was carefully evaporated and the residue was distilled to furnish 850 mg (85%) of **1** as a colorless liquid, bp 70° (40 mm). An analytical sample was obtained by preparative-scale vpc isolation as above: $\lambda_{max}^{cyclohexane}$ 242 nm (ε 200); $\delta_{TMS}^{CDCl_3}$ 6.8 (t, J = 2.5 Hz, 4, olefinic), 3.84 (m, 2, methine), and 3.63 (s, 2, methylene).

Anal. Calcd for C_8H_8: C, 91.25; H, 8.75. Found: C, 91.42; H, 8.81.

9-Methylenebicyclo[4.2.1]nona-2,4,7-triene (2).—This hydrocarbon was prepared from the corresponding ketone[15,16] by a method identical with that utilized above. From 9.6 g of the ketone, there was isolated 3.6 g (38%) of **2** as a colorless liquid: bp 40–42° (0.5 mm); $\delta_{TMS}^{CDCl_3}$ 5.7–6.4 (m, 4, diene protons), 5.4 (s, 2, ethano protons), 4.79 (s, 2, methylene), 3.44 (broadened d, J = 6.5 Hz, 2, methine); $\lambda_{max}^{cyclohexane}$ 270 nm (ε 3400) and 261 nm (3400) with shoulders at 280 (2150) and 254 (2850).

Anal. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: 92.39; H, 7.73.

2-Methylenebicyclo[3.2.2]nona-3,6,8-triene (3).—Reaction of 2.01 g of bicyclo[3.2.2]nona-3,6,8-trien-2-one[6a] with an equimolar amount of methylenetriphenylphosphorane in the predescribed manner furnished 1.35 g (68%) of **3** as a colorless liquid: bp 70° (5 mm); $\lambda_{max}^{cyclohexane}$ 255 nm (sh, ε 5500) and 232 (9050); $\delta_{TMS}^{CDCl_3}$ 5.90–6.75 (m, 5, olefinic), 5.48 (d with fine splitting, J = 10 Hz), 5.05 (s with fine splitting, 1, methylene proton), 4.7 (s with fine splitting, 1, methylene proton), and 3.20–3.87 (m, 2, methines).

Anal. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 91.98; H, 7.92.

9-Methylenetricyclo[3.3.1.0^{2,8}]nona-3,6-diene (9-Methylenebarbaralane, 10).—Treatment of 9.1 g of barbaralone[15,16,34] with an equimolar quantity of methylenetriphenylphosphorane as described above afforded 5.7 g (63.5%) of **10** as a colorless liquid: bp 71–73° (5 mm); $\delta_{TMS}^{CDCl_3}$ 5.65 (m, 2, olefinic), 4.7 (s, 2, methylene protons), 4.12 (m, 4), and 2.82 (m, 2).

Anal. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 92.13; H, 7.76.

Reaction of Bicyclo[4.2.1]nona-2,4,7-trien-9-one (15) with α-Pyrone (16).—A solution of 18.6 g (0.14 mol) of **15**,[15,16] 20 g (0.21 mol) of α-pyrone,[35] and 100 mg of hydroquinone in 30 ml of xylene was heated at 120–130° under nitrogen for 20 hr. After cooling, the product was chromatographed on Florisil. Elution with chloroform afforded 11.06 g (34%) of **17** as colorless needles, mp 204–205° dec, from methylene chloride–ether: $\nu_{max}^{CHCl_3}$ 1765 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 310 nm (ε 400), 274 (3000), 264 (3580), and 258 (sh, 2830); $\delta_{TMS}^{CDCl_3}$ 6.5 (m, 2, olefinic), 5.85 (m, 4, diene protons), 5.26 (m, >CHO–), 3.72 (m, 1, methine), 3.25 (br m, 2, methine), and 2.6 (m, 2, methine).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.46; H, 5.17.

Decarboxylation of 17.—A 1.5-g sample of **17** was heated to 230° in a small, short path distillation column under 0.3 mm pressure. Carbon dioxide evolution was observed and a distillate which solidified in the cold portion of the apparatus was obtained. Upon completion of the gas evolution, the product was washed out with ether. Evaporation of the solvent yielded 830 mg (70%) of **18** as colorless crystals: mp 74–77° (sublimation at 80° (0.5 mm) raised the melting point to 81–83°); $\nu_{max}^{CHCl_3}$ 1745

(28) H. G. Richey, Jr., and N. C. Buckley, *J. Amer. Chem. Soc.*, **85**, 3057 (1963).

(29) P. R. Story and S. R. Fahrenholtz, *ibid.*, **86**, 527 (1964).

(30) P. R. Story and S. R. Fahrenholtz, *ibid.*, **88**, 374 (1966).

(31) S. Yoneda, Z. Yoshida, and S. Winstein, *Tetrahedron*, **28**, 2395 (1972).

(32) S. Winstein and C. Ordronnean, *J. Amer. Chem. Soc.*, **82**, 2084 (1960); P. R. Story and M. Saunders, *ibid.*, **84**, 4876 (1962).

(33) R. K. Lustgarten, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2347 (1972).

(34) W. von E. Doering, B. M. Ferrier, E. D. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967).

(35) H. E. Zimmerman, G. L. Grunewald, and R. M. Paufler, *Org. Syn.*, **46**, 101 (1966).

cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 310 nm (sh, ϵ 930), 258 (6500), and 240 (5150); $\delta_{TMS}^{CHCl_3}$ 5.4–5.9 (m, 8, olefinic), 3.45 (m, 2, methine), and 2.65 (m, 2, >CHCO–).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.59. Found: C, 84.71; H, 6.56.

7,8-Benzobicyclo[4.2.1]nona-2,4,7-trien-9-one (19).—A solution of 1.2 g of **18** in 20 ml of benzene containing 2.0 g of 10% palladium on charcoal was heated at reflux for 24 hr. The catalyst was separated by filtration, the solvent was evaporated, and the pale yellow oil was chromatographed on Florisil. Elution with benzene–pentane (1:1) furnished 650 mg (54%) of **19** as colorless crystals, mp 80–82° (lit.[14] mp 82–82.5°).

9-Methylene-7,8-benzobicyclo[4.2.1]nona-2,4,7-triene (20).—Ketone **19** (800 mg) was treated with 1 equiv of methylenetriphenylphosphorane as described earlier. After the usual work-up, the crude reaction mixture was chromatographed on Florisil. Elution with pentane gave 450 mg (56%) of **20** as a colorless oil which slowly crystallized on cooling to 0°: $\lambda_{max}^{cyclohexane}$ 284 nm (ϵ 2920), 273 (4700), 262 (4400), 254 (3260), and 242 (sh, 2960); $\delta_{TMS}^{CDCl_3}$ 7.15 (s, 4, aromatic), 6.0–6.4 (m, 2, olefinic), 5.5–5.85 (m, 2, olefinic), 4.98 (s, 2, methylene), and 4.1 (d, J = 7.5 Hz, 2, methine).

Anal. Calcd for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.46; H, 6.75.

Reaction of 10 with CSI.—To a magnetically stirred solution of 4.55 g (35.5 mmol) of **10** in 50 ml of dry dichloromethane was added under nitrogen 3.1 ml (37 mmol) of CSI dissolved in 20 ml of the same solvent over a period of 20 min. The solution was stirred at room temperature for 2.5 hr and the solvent was evaporated. The residue was dissolved in 40 ml of ether containing 10 ml of acetone and this solution was added dropwise to a rapidly stirred suspension of sodium sulfite (30 g) in 80 ml of water. The pH of the aqueous layer was kept at *ca.* 8–9 by the addition of 20% aqueous potassium hydroxide solution as required. After the addition was complete, stirring was continued for a further 45 min and the product was then extracted into methylene chloride (6 × 50 ml). The combined organic layers were dried and evaporated to give a colorless, crystalline product which was triturated with ether, filtered, and dried (4.7 g, 77.5%). Recrystallization from dichloromethane gave pure **21b**: mp 207.5–208.5°; $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ end absorption only; $\delta_{TMS}^{CDCl_3}$ 7.4 (br, 1, >NH), 6.8 (m, 1, olefinic), 6.18 (m, 3, olefinic), 5.0 (m, 1, >CHN<), 3.3 (s, 2, methylene), and 3.2 (m, 2, methine).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.08. Found: C, 76.13; H, 6.40; N, 7.96.

When the >NH proton was saturated, the absorption at δ 3.6 collapsed to a triplet with no other observable changes. Double irradiation of the δ 3.6 multiplet resulted in the appearance of the high-field olefinic proton (dd, J = 10.5 and 2.0 Hz); clearly, this proton must be the adjoining vinyl hydrogen, the small coupling constant arising from allylic coupling to the bridgehead proton. This last conclusion was supported by the finding that spin decoupling of the δ 3.2 multiplet caused simplification of this olefinic proton (dd, J = 10.5 and 4 Hz). Expectedly, additional simplification of all the remaining olefinic signals was also seen.

Evaporation of the mother liquors resulting from the cycloaddition yielded an oily residue that was chromatographed on Florisil. Elution with chloroform gave a crystalline lactam fraction (400 mg, 6.5%), the nmr spectrum of which indicated it to consist mainly of **21b**. However, a small amount of a second component was also present. Attempts to obtain a pure sample of this very minor component were not successful.

Reaction of 13 with CSI.—Treatment of 470 mg (2.6 mmol) of **13**[13] with 360 mg of CSI in 10 ml of methylene chloride (25°, 40 min) and subsequent dechlorosulfonylation as above afforded 370 mg (64%) of **25b** as colorless crystals, mp 224–224.5°, from methylene chloride–ether: $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 265 nm (ϵ 150); $\delta_{TMS}^{CDCl_3}$ 7.2 (m, 4, aromatic), 6.1–6.5 (m, 2, olefinic), 4.85–5.2 (m, 1, olefinic), 3.75 (m, 3, methine), and 3.35 (m, 2, $-CH_2CO-$).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.43; H, 5.87; N, 6.23.

Reaction of 3 with CSI.—From 1.2 g (9.25 mmol) of **3** and 0.84 ml (9.5 mmol) of CSI in 40 ml of dichloromethane (25°, 2 hr) and subsequent hydrolysis with alkaline sodium sulfite solution, there resulted a slightly sticky, colorless solid, trituration of which with ether gave 810 mg (50.5%) of **21b** identical in all respects with the lactam isolated above.

Evaporation of the filtrate yielded *ca.* 1 g of a pale yellow, oily residue which was chromatographed on Florisil. Pentane–chloroform (4:1) eluted a colorless oil which crystallized from ether at −78° to give 120 mg (7.5%) of colorless crystals, mp 67–76°. The nmr spectrum clearly indicated a mixture of two components and the ir spectrum suggested that these were lactones (ν_{max} 1780 cm^{-1}). These were separated by preparative scale vpc (5 ft × 0.25 in. column packed with 5% SE-30, 130°).

The major component has been tentatively assigned structure **27**: $\nu_{max}^{CHCl_3}$ 1780 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ shoulder on end absorption, 222 nm (ϵ 3600); $\delta_{TMS}^{CDCl_3}$ 5.45–6.05 (m, 3, olefinic), 5.12 (d, 1, olefinic), 3.9 (br s, 1 >CHO–), 2.7 (m, 3, methine), and 2.57 (s, 2, methylene); mass spectrum, 174.0682 (calcd for $C_{11}H_{10}O_2$, 174.0681).

The minor component was identified as lactone **26**: $\nu_{max}^{CHCl_3}$ 1780 cm^{-1}; uv showed only end absorption; $\delta_{TMS}^{CDCl_3}$ 6.18–7.05 (m, 4, olefinic), 5.75 (d with fine splitting, J = 8 Hz, 1, olefinic), 5.3 (dd, J = 10.5 and 2.5 Hz, 1, olefinic), 4.5 (m, 1, >CHO–), 3.45 (m, 1, methine), and 2.83 (s, 2, methylene) [the latter absorption was shown to be a distorted AB system (J = 16 Hz) at 100 MHz]; mass spectrum, 174.0678 (calcd for $C_{11}H_{10}O_2$, 174.0681).

Continued elution of the chomatography column with chloroform gave a solid mixture of three lactams (nmr analysis) weighing 105 mg (6.5%). Rechromatography of this mixture on Florisil using pentane–chloroform (1:1) as eluent gave 52 mg (3.2%) of pure lactam **28** as the first compound from the column: colorless crystals; mp 145–147°; $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; uv showed only end absorption; $\delta_{TMS}^{CDCl_3}$ 6.0–6.96 (m, 5, olefinic and >NH), 5.73 (d with fine splitting, J = 8 Hz, 1, olefinic), 5.1 (dd, J = 10.5 and 2.5 Hz, 1, olefinic), 3.92 (m, 1, >CHN<), 3.25 (m, 1, methine), and 2.61 (distorted AB pattern, J = 15 Hz, 2, methylene).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.08. Found: C, 76.01; H, 6.40; N, 8.14.

Continued elution of the column with chloroform yielded an additional 45 mg (2.8%) of **21b**. Only traces of the third lactam were eluted and these were insufficient for characterization.

Reaction of 12 with CSI.—The cycloaddition was carried out essentially as described above with 7.3 g (40.5 mmol) of **12**.[13] After the usual work-up and solvent removal, trituration of the solid residue with ether gave 5.63 g (62.5%) of **25b**, mp 224–224.5°, identical in all its spectral properties with the lactam isolated above.

Chromatography of the noncrystalline residue on Florisil using pentane–chloroform (1:1) as eluent led to the isolation of **34** (220 mg, 2.4%) as fine, colorless needles, mp 204.5–205.5°, from methylene chloride–ether: $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 268 nm (ϵ 300); $\delta_{TMS}^{CDCl_3}$ 8.0 (br, 1, >NH), 7.18 (m, 4, aromatic), 6.23–7.0 (m, 3, olefinic), 5.8 (d, J = 8 Hz, 1, olefinic), 4.54 (s, 1, >CHN<), 3.86 (m, 1, methine), and 2.73 (part of distorted AB pattern, J = 16 Hz, 2, methylene).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.32; H, 5.81; N, 6.27.

After the appearance of **34**, an additional 503 mg (5.5%) of **25b** was obtained upon continued elution.

Reaction of 2 with CSI.—A 5.5-g (43 mmol) sample of **2** was treated with 3.7 ml (44 mmol) of CSI in 60 ml of methylene chloride as outlined above. After dechlorosulfonylation and solvent removal, a sticky white solid was obtained which on trituration with ether afforded 2.23 g (30.5%) of white solid. Nmr analysis of this material showed it to be a mixture of **36** and **37** in a ratio of *ca.* 3:1. These lactams were readily separated by chromatography on Florisil, lactam **36** eluting with chloroform–pentane (1:1) and **37** eluting with chloroform.

36 was a colorless solid: mp 168.5–169.5°; $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 254 nm (ϵ 4950); $\delta_{TMS}^{CDCl_3}$ 7.3 (br, 1, >NH), 5.5–6.45 (m, 4, diene protons), 5.15 (d, J = 2.5 Hz, 1, exocyclic methylene), 4.85 (d, J = 2.0 Hz, 1, exocyclic methylene), 4.25 (m, 1, >CHN<), 3.38 (m, 1, doubly allylic methine), 2.88 (m, 1, methine), and 2.33 (br s, 1, >CHCO–).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 640; N, 8.08. Found: C, 75.99; H, 6.35; N, 7.99.

37 was a colorless solid: mp 120–122°; $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 276 nm (sh, ϵ 2250), 267 (3990), 259 (3930), and 250 (sh, 2900); $\delta_{TMS}^{CDCl_3}$ 7.4 (br, 1, >NH), 5.45–6.02 (m, 6, olefinic), 4.4 (m, 1, >CHN<), 3.48 (m, 1, methine), and 2.41 (distorted AB pattern, J_{AB} = 17 Hz, 2, methylene).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.08. Found: C, 76.21; H, 6.38; N, 8.08.

Evaporation of the above filtrate gave a pale yellow, viscous residue which was chromatographed on Florisil. Elution with pentane–chloroform (4:1) gave 433 mg (5.9%) of lactone **38** as colorless crystals, mp 54.5–55.5°, from pentane–ether: $\nu_{max}^{CHCl_3}$ 1770 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 276 nm (sh, ϵ 1965), 269 (3795), 256 (3795), and 248 (sh, 2887); $\delta_{TMS}^{CDCl_3}$ 5.47–6.15 (m, 6, olefinic), 5.2 (m, 1, >CHO–), 3.5 (m, 1, methine), and 2.6 (distorted AB pattern, J_{AB} = 18 Hz, 2, methylene).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.06; H, 5.80.

Continued elution of the column with pentane–chloroform (1:1) gave 77 mg (1%) of β-lactam **38** as colorless crystals: mp 158–159°; $\nu_{max}^{CHCl_3}$ 1760 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 285 nm (ϵ 1350), 271 (sh, 2380), and 265 (2450); $\delta_{TMS}^{CDCl_3}$ 6.4 (br, 1, >NH), 5.95 (m, 4, diene protons), 5.42 (d, J = 1 Hz, 2, olefinic), 4.1 (m, 2, methine), and 3.77 (d, J = 1.5 Hz, methylene).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.08. Found: C, 75.97; H, 6.41; N, 8.03.

Further elution yielded fractions rich in lactam **36** contaminated with small amounts of unidentified products. Crystallization yielded an additional 320 mg (4.4%) of pure **36**. Attempts to obtain pure samples of the minor components were not successful because of a lack of material and their apparent ready polymerization.

Finally, elution with chloroform afforded a further 410 mg (5.6%) of **37** after crystallization from methylene chloride–ether.

Hydrogenation of 36.—A solution of 200 mg of **36** in 25 ml of ethyl acetate containing 100 mg of 10% palladium on charcoal was hydrogenated at 25 psig and 25° in a Parr apparatus for 25 hr. The catalyst was removed by filtration and the filtrate was evaporated to give 178 mg of **40** as a colorless solid, mp 138.5–141.5°, $\delta_{TMS}^{CDCl_3}$ 1.03 (d, J = 6.5 Hz, 3, methyl).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.47; H, 9.39; N, 7.76.

TCNE Addition to Lactam 37.—A solution of 60 mg of **37** and 56 mg of TCNE in 1.5 ml of dry tetrahydrofuran was left to stand at room temperature for 24 hr. The colorless, crystalline product that formed (96 mg, 92%) was separated by filtration and recrystallized from acetone–ether. The resulting white crystals darken above 270° and decompose with melting at 290–300°: ν_{max}^{Nujol} 1695 cm^{-1}; $\delta_{TMS}^{acetone\text{-}d_6}$ 7.25 (br, 1, >NH), 6.55–7.15 (m, 2, olefinic), 5.9 (s, 2, olefinic), 4.55 (m, 2, >CHN< and and one methine proton), 4.1 (m, 1, methine), 3.48 (m, 1, methine), 3.4 and 2.56 (centers of AB doublets, J = 18 Hz, 2, methylene).

Anal. Calcd for $C_{17}H_{11}N_5O$: C, 67.77; H, 3.68; N, 23.24. Found: C, 67.55; H, 3.70; N, 23.20.

TCNE Addition to Lactone 38.—Reaction of 154 mg of **38** and 160 mg of TCNE in tetrahydrofuran as above gave 223 mg (84%) of adduct **43b** as colorless crystals, mp >270° dec, from acetone–ether: ν_{max}^{Nujol} 1760 cm^{-1}; $\delta_{TMS}^{acetone\text{-}d_6}$ 6.5–7.1 (m, 2, olefinic), 5.9–6.25 (m, 2, olefinic), 5.3 (m, 1, >CHO–), 4.55 (d with fine splitting, 1, methine), 4.15 (t of d, J = 6.0 and 1.5 Hz, 1, methine), 3.61 (m, 1, methine), 3.66 and 2.92 (centers of AB doublets, J = 19 Hz, 2, methylene).

Anal. Calcd for $C_{17}H_{10}N_4O_2$: C, 67.51; H, 3.33; N, 18.54. Found: C, 67.55; H, 3.35; N, 18.55.

Reaction of 20 with CSI.—Treatment of 150 mg (8.45 mmol) of **20** with 0.08 ml (9.5 mmol) of CSI in 7 ml of methylene chloride (25°, 14 hr), subsequent hydrolysis with sulfite ion, and chromatography on Florisil gave (pentane elution) 13 mg of a colorless oil identified as lactone **51**: $\nu_{max}^{CHCl_3}$ 1780 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.28 (s, 4, aromatic), 5.65–6.0 (m, 4, olefinic), 5.5 (s, 1, >CHO–), 3.87 (m, 1, methine), and 2.62 (s, 2, methylene).

Continued elution of the column with pentane–chloroform (1:1) furnished 96 mg (51.5%) of **50** as colorless crystals, mp 180–182°, from chloroform–ether: $\nu_{max}^{CHCl_3}$ 1685 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.7 (br s, 1, >NH), 7.2 (s, 4, aromatic), 5.55–6.0 (m, 4, olefinic), 4.72 (s, 1, >CHN<), 3.84 (m, 1, methine), and 2.42 (s, 2, methylene).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.90; H, 5.81; N, 6.28.

Reaction of 1 with CSI.—To a solution of 104 mg (1 mmol) of **1** in 7 ml of dry methylene chloride was added under nitrogen 0.084 ml (1 mmol) of CSI. After stirring for 10 min, the solvent was evaporated and the residue was hydrolyzed in the usual manner. The product was extracted into methylene chloride and this solution was dried and evaporated to give 50 mg (52%) of white, crystalline product: mp 234–235° dec; $\nu_{max}^{CHCl_3}$ 1700 cm^{-1} (sh at 1725 cm^{-1}); $\delta_{TMS}^{DMSO\text{-}d_6}$ 7.48 (br s, 1, >NH), 6.63 (t, J = 2 Hz, 4, olefinic), 3.38 (m, 2, methine), and 2.77 (s, 2, methylene); mass spectrum, 190.0744 (calcd m/e 190.0742).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.91; H, 5.33; N, 14.64.

Reaction of 8 with CSI.—Treatment of 400 mg (3.8 mmol) of **8** with 0.33 ml (4 mmol) of CSI in 10 ml of methylene chloride for 15 min at 25° led to the ready isolation of 300 mg (53%) of **53** after dechlorosulfonylation as colorless crystals, mp 96.5–97°, from ether–pentane: $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.4 (br, 1, >NH), 3.2 (d, J = 1.5 Hz, 2, methylene), 1.77 (m, 4, cyclopropyl), and 1.29 (m, 2, cyclopropyl).

Anal. Calcd for C_9H_9NO: C, 73.41; H, 6.16. Found: C, 73.16; H, 6.25.

Rearrangement of 53.—To a solution of 30 mg of **53** dissolved in 0.4 ml of $CDCl_3$ in an nmr tube was added three crystals of $[Rh(NOR)Cl]_2$. The initially orange-brown solution rapidly became warm and then changed in color to a pale yellow. A small amount of yellow, insoluble precipitate formed also. The nmr spectrum of the reaction mixture showed complete conversion to **54**. The solution was filtered and evaporated to give a quantitative yield of colorless crystals, mp 123–125°, from ether–pentane: $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.9 (br, 1, >NH), 6.6 (m, 4, olefinic), 3.48 (m, 2, methine), and 2.53 (d, J = 1.5 Hz, 2, methylene).

Anal. Calcd for C_9H_9NO: C, 73.41; H, 6.16; N, 9.56. Found: C, 73.19; H, 6.22; N, 9.61.

Tricyclo[6.1.0.0^{4,9}]nona-2,6-dien-5-one (57).—A solution of 400 mg of **56**[6a] and 200 mg of Michler's ketone in 400 ml of benzene maintained under a constant nitrogen atmosphere was irradiated with a 450-W Hanovia lamp source through Pyrex for 20 min. The solvent was evaporated and the residue was extracted with pentane–ether (1:1). The combined organic layers were washed with dilute hydrochloric acid and distilled water, dried, and evaporated to give 344 mg of **57** as a colorless oil contaminated with approximately 5% of starting material. This material was utilized without further purification in the next step.

5-Methylenetricyclo[6.1.0.0^{4,9}]nona-2,6-diene (11).—To a solution of methylenetriphenylphosphorane in 50 ml of ether prepared from 1.8 g of methyltriphenylphosphonium bromide and 2.1 ml of 2 M n-butyllithium solution in hexane was added 560 mg of somewhat impure **57**. The mixture was heated at reflux for 4 hr and worked up in the customary manner. Vacuum transfer afforded 210 mg of colorless oil, vpc analysis of which indicated it to be chiefly **11**. Purification was achieved by preparative scale vpc isolation from a 0.25 in. × 5 ft column packed with 5% SE-30 on Chromosorb W at 60°: $\delta_{max}^{CDCl_3}$ 5.22–6.42 (m, 4, olefinic), 4.67–4.92 (m, 2, methylene), 3.50–3.73 (m, 1, methine), and 1.36–2.46 (m, 3, cyclopropyl).

Anal. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 92.23; H, 7.66.

Registry No.—**1**, 37846-63-2; **2**, 38898-39-4; **3**, 38898-40-7; **7**, 1072-92-0; **8**, 38898-42-9; **10**, 37816-60-7; **11**, 38898-44-1; **12**, 34886-92-5; **13**, 34886-93-6; **15**, 34733-74-9; **16**, 504-31-4; **17**, 38898-48-5; **18**, 38898-26-9; **19**, 22824-77-7; **20**, 38898-50-9; **21b**, 38898-51-0; **25b**, 38974-07-1; **26**, 38898-52-1; **27**, 38898-53-2; **28**, 38898-54-3; **29**, 38898-55-4; **36**, 38898-56-5; **37**, 38898-27-0; **38**, 38898-28-1; **39**, 38898-57-6; **40**, 38898-29-2; **43a**, 38898-30-5; **43b**, 38974-08-2; **50**, 38898-31-6; **51**, 38898-32-7; **52**, 38898-58-7; **53**, 38898-59-8; **54**, 38898-60-1; **56**, 17684-75-2; **57**, 38898-62-3; bicyclo[4.2.1]nona-2,4,7-trien-9-one, 34733-74-9; bicyclo[3.2.2]nona-3,6,8-trien-2-one, 17684-75-2; barbaralone, 6006-24-2; CSI, 1189-71-5; TCNE, 670-54-2; Michler's ketone, 90-94-8.

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Aluminum Chloride Catalyzed Reactions of Certain Benzyltetralins. Synthesis of *cis*- and *trans*-1-Benzyl-2-methyltetralin[1]

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The $AlCl_3$-induced rearrangements of 1-benzyltetralin (**5**) to 1,5-diphenylpentane (**12**) and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**13**), of 1-benzyl-3-methyltetralin (**6**) to 2-methyl-1,5-diphenylpentane (**14**) and 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**15**), and of 1-benzyl-1-methyltetralin (**7**) to compounds **6**, **14**, and **15** were examined in detail. Diastereoisomers of **6** were synthesized and subjected to similar treatment. Cis–trans interconversion of the diastereoisomers proceeded faster than the formation of products **14** and **15**. The formation of the products is discussed in light of the production of the carbonium ion intermediates formed by the simultaneous protonation of the benzene ring and hydride abstraction from the alicyclic ring. Treatment of 1-benzyl-3,3-dimethyltetralin (**8**) and 1-benzyl-4,4-dimethyltetralin (**9**) with $AlCl_3$ resulted in the production of 1,8-dimethyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**28**), the formation of which required a 1,2 shift of a methide ion.

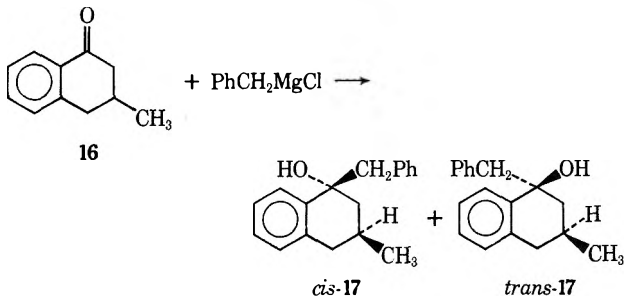
Our interest in the cyclialkylations and bicyclialkylations of diphenylalkyl chlorides with Friedel–Crafts catalysts has resulted in the reports that 1-chloro-3,4-diphenylbutane (**1**) cyclized to give almost exclusively 2-phenyltetralin (**4**),[2] and that 1-chloro-4,5-diphenylpentane (**2**) cyclized to give mainly 1-benzyltetralin (**5**),[3] while the diastereomeric 1-chloro-2-methyl-4,5-diphenylpentanes (**3**) gave mainly 1-benzyl-3-methyltetralin (**6**), together with some 1-benzyl-3,3-dimethylindan (**10**) and 1,1-dimethyl-3-phenyltetralin (**11**).[3,4] From these observations, we concluded (i) that six-membered ring (tetralin) formation was preferred over five-membered ring (indan) formation (the latter was observed only when the carbonium ion intermediate so formed possessed some degree of stability, or when indan formation became the only possible reaction path[5]), and (ii) that seven-membered ring (benzosuberane) formation was not observed under the reaction conditions.[6]

From 1-chloro-4,5-diphenylpentane (**2**), there were also isolated 1,5-diphenylpentane (**12**) and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**13**), and from 1-chloro-2-methyl-4,5-diphenylpentane (**3**), the corresponding compounds 2-methyl-1,5-diphenylpentane (**14**) and 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**15**) were obtained.[3] We demonstrated that these compounds came directly from the rearrangement of the initially formed 1-benzyltetralins **5** and **6**.[3] The ring-cleaved compounds **12** and **14** must come from benzene ring protonation followed by dephenylation, while the bicyclized compounds **13** and **15** are formed *via* hydride ion abstraction from the alicyclic ring followed by cyclialkylation. It is interesting to note that, although examples of molecules having the potential for both of these two diverse types of reactions are rare, we have found a system which possesses such properties. It is therefore worthwhile to study the system in some detail in order to define the scope of these reactions, and to gain a deeper insight into the nature of the mechanistic pathways.

We are also aware that the formation of two diastereomeric pairs of 1-benzyl-3-methyltetralins (**6**) was possible from the cyclization of 1-chloro-2-methyl-4,5-diphenylpentane (**3**), and that behavioral differences of these diastereomers could be manifested under the reaction conditions. Realizing that isolation of these diastereomeric compounds from the reaction mixture could be very difficult, we undertook to synthesize them separately and to subject each of them to similar reaction conditions in order to compare their behavior.

Results and Discussion

Our original plan to secure *cis*-**6** and *trans*-**6** was first to isolate the diastereomeric alcohols *cis*-**7** and *trans*-**17** from the reaction



cis-**17** *trans*-**17**

and then, after having established the configuration of each, to reduce the individual alcohols stereoselectively. However, although we were able to obtain these stereoisomeric alcohols in pure form by repeated column chromatography, the assignment of the configuration posed each a big uncertainty that we discontinued this plan in favor of Scheme I.

The successful synthesis of *cis*-1-benzyl-3-methyltetralin (*cis*-**6**) and the trans isomer (*trans*-**6**) was accomplished according to the flow diagram depicted in Scheme I.

The Stobbe condensation of benzaldehyde with diethyl succinate, giving phenylitaconic acid (**18**),[7] the

(1) (a) Part XXIX of the series "New Friedel-Crafts Chemistry." Part XXVIII: A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **38**, 1388 (1973). (b) Generous support of this research, including a postdoctoral fellowship for K.-H. B. by the Robert A. Welch Foundation, is gratefully acknowledged.

(2) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 89 (1966), and references cited therein.

(3) R. M. Roberts, G. P. Anderson, Jr., A. A. Khalaf and C.-E. Low, *J. Org. Chem.*, **36**, 3342 (1971).

(4) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, in press; *cf.* ref 1a.

(5) See, for example, A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).

(6) A similar conclusion was reached in other systems; see (a) L. R. C. Barclay, R. A. Ginn, and C. E. Milligan, *Can. J. Chem.*, **42**, 579 (1964); (b) L. R. C. Barclay in H. A. Olah, Ed., "Friedel-Crafts and Related Reactions," Vol. II, Interscience, New York, N. Y., 1964, p 932.

(7) E. C. Horning and G. N. Walker, *J. Amer. Chem. Soc.*, **74**, 5147 (1952).

catalytic reduction[8] of it to give phenylsuccinic acid (19), conversion to phenylsuccinic anhydride (20),[9] and cyclization of it to give 3-carboxy-1-tetralone (21)[7] are literature procedures. Reaction of 3-carboxyl-1-tetralone (21) with 2 molar equiv of benzylmagnesium chloride gave 1-benzyl-1-hydroxy-1,2,3,4-tetrahydro-3-naphthoic acid γ-lactone (22)[10] and 1-benzyl-1-hydroxy-3,4-dihydro-3-naphthoic acid (23). Obviously, the lactone 22 can only be formed *via* an intermediate having the hydroxyl and the carboxyl functions cis to each other. When this lactone was reduced by treatment with $LiAlH_4$ to give 1-benzyl-1-hydroxy-3-hydroxymethyltetralin (24), we were then able to assign the hydroxyl group at C_1 and the hydroxymethyl group at C_3 to be cis to each other.[11] Subsequent catalytic hydrogenolysis with Raney nickel in ethanol gave *trans*-1-benzyl-3-hydroxymethyltetralin (*trans*-25), in which retention of configuration[12] was observed. Similarly, catalytic hydrogenolysis with Pd/C in ethanol gave the cis isomer (*cis*-25) in which the configuration at C_1 was inverted.[12a,13] Tosylation of the hydroxyl group and reduction in the last step did not affect the stereochemistry at C_3.[14]

Reactions of Benzyltetralins with Aluminum Chloride.—The results of the treatment of 1-benzyltetralin (5) in CS_2 with $AlCl_3$ at room temperature with or without hydrogen chloride as promoter are listed in Table I. 2,3:6,7-Dibenzobicyclo[3.3.1]nona-2,6-diene (13) was formed more rapidly than 1,5-diphenylpentane (12). Of the numerous low-boiling products, which constituted only a minor portion (<5% of the product), the main one was found to be 1-methyltetralin (26). Table II depicts the results of rearrangement of 1-benzyl-3-methyltetralin (6, 80% cis, 20% trans) under the same conditions. It can be seen that corresponding products were formed and that 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (15) was produced at a faster rate than 2-methyl-1,5-diphenylpentane (14). The major low-boiling product (<5% of the product) was identified as 1,1-dimethyltetralin (27). In this reaction, an additional feature emerged, namely, *cis*-6 was rapidly converted to *trans*-6, and this isomerization appeared to proceed faster than the product-forming reaction during the initial stages of the reaction.

TABLE I

REACTION OF 1-BENZYLTETRALIN (5) WITH ALUMINUM CHLORIDE[a]

		Reaction mixture composition, %[b]			
Conditions	Time, hr	Unchanged 5	12	13	26
CS_2	1.0	91	2	7	Trace, increased
	3.0	80	7	13	
	8.0	45	21	34	
	25.0	18	25	57	
	56.0	10	18	72	
CS_2,	0.5	80	6	14	Trace, increased
	1.5	37	23	40	
HCl gas[c]	4.0	15	27	58	
	8.5	8	14	78	

[a] Reactant ratios, 5:$AlCl_3$:CS_2 = 5 mmol:2.5 mmol:10 ml. [b] Glpc analysis: 5 ft × 0.125 in. (o.d.) SE-30 silicone gum rubber (5%) column operated at 220° with N_2 carrier gas at 5 psi. [c] HCl gas was passed gently into the reactants during the first 3 min.

TABLE II

REACTION OF 1-BENZYL-3-METHYLTETRALIN (6) WITH ALUMINUM CHLORIDE[a]

		Reaction mixture composition, %[b]				
Conditions	Time, hr	*cis*-6	*trans*-6	14	15	27
CS_2	0.0	80	20			
	1.0	56	36	3	5	Trace, increased
	3.0	36	43	8	13	
	8.0	15	28	21	36	
	25.0	6	10	30	54	
	56.0	6	8	19	67	
CS_2,	0.0	80	20			
	0.5	47	33	9	11	Trace, increased
HCl gas[c]	1.5	13	23	27	37	
	6.0	5	6	38	51	
	8.0	4	6	34	56	

[a] Reactant ratios, 6:$AlCl_3$:CS_2 = 5 mmol:2.5 mmol:10 ml. [b] Glpc analysis: 10 ft × 0.125 in. (o.d.) Bentone-34 (5%) and SE-52 silicone gum rubber (5%) column operated at 210° with N_2 carrier gas at 60 psi. [c] Gentle passage of HCl gas for the first 3 min.

On treating pure *cis*-6 and *trans*-6 separately with $AlCl_3$ under comparable conditions, other interesting results became apparent. As is revealed in Table III,

TABLE III

REACTION OF *cis*- AND *trans*-1-BENZYL-3-METHYLTETRALIN (6) WITH ALUMINUM CHLORIDE[a]

		Reaction mixture composition, %[b]			
Isomer	Time, hr	*cis*-6	*trans*-6	14	15
cis-6	2.0	73	20	Trace	7
	4.0	65	25	2	8
	15.5	42	36	6	16
	22.0	33	39	7	21
	32.0	23	40	7	26
trans-6	2.0	12	83	Trace	5
	4.0	18	70	6	6
	11.0	20	58	6	16
	20.0	15	40	16	30
	69.0	4	8	23	65

[a] Reactant ratios, same as in Table II. [b] Glpc analysis, same as in Table II.

(8) (a) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Amer. Chem. Soc.*, **77**, 1764 (1955); (b) R. H. Baker and W. W. Jenkins, *ibid.*, **68**, 2102 (1946).

(9) W. F. Beech and N. Legg, *J. Chem. Soc.*, 1887 (1949).

(10) This illustrates a long-known case in which a keto group reacts faster with the Grignard reagent than the carbomethoxy or carboxyl group, resulting in the direct formation of a γ-lactone if the parent compound is a γ-ketocarboxylic acid or its ester. For further examples, see C.-E. Low, Ph.D. Dissertation, The University of Texas at Austin, Austin, Texas, 1970.

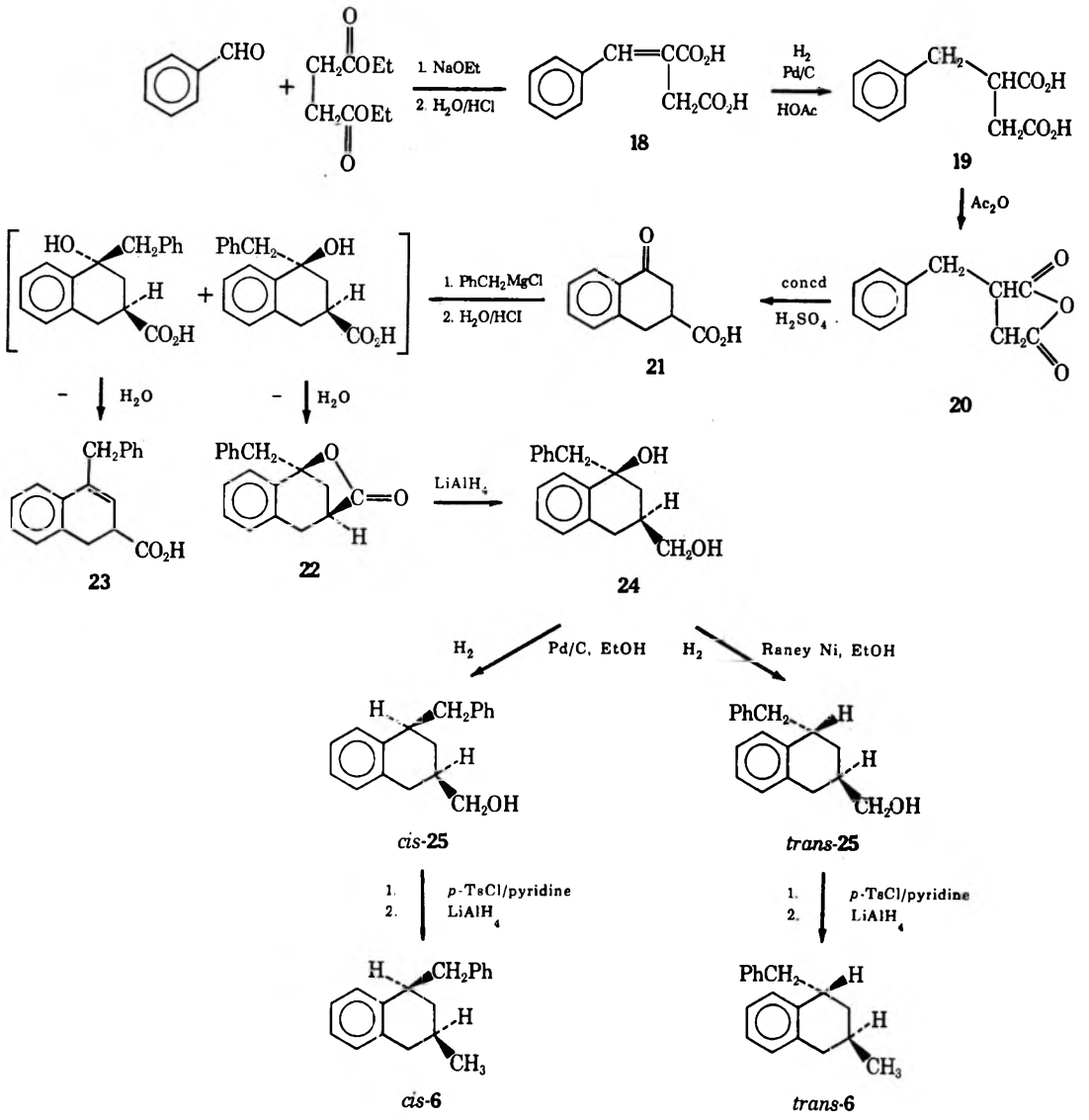
(11) (a) H. L. Goering and C. Serres, Jr., *J. Amer. Chem. Soc.*, **74**, 5908 (1952); (b) R. Grewe and E. Nolte, *Justus Liebigs Ann. Chem.*, **575**, 1 (1951); (c) N. L. Drake and E. H. Price, *J. Amer. Chem. Soc.*, **73**, 201 (1951); (d) W. G. Brown in R. Adams, "Organic Reactions," Vol. V, Wiley, New York, N. Y., 1951, p 469; (e) G. S. Davy, *et al.*, *J. Chem. Soc.*, 2696, 2702 (1951); (f) G. S. Davy, *et al.*, *Chem. Ind. (London)*, 732 (1950); 233 (1951).

(12) (a) S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind. (London)*, 1354 (1963); (b) J. C. Sheehan and R. E. Chandler, *J. Amer. Chem. Soc.*, **83**, 4795 (1961); (c) C. L. Arcus, *et al.*, *J. Chem. Soc.*, 34 (1955), 1195 (1960), 660 (1961), 1213 (1963); (d) D. Y. Curtin and S. Schmukler, *J. Amer. Chem. Soc.*, **77**, 1105 (1955); (e) D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954); (f) W. A. Bonner, J. A. Zderic, and G. A. Casaletto, *ibid.*, **74**, 5086 (1952).

(13) D. Lipkin and T. D. Stewart, *J. Amer. Chem. Soc.*, **61**, 3295 (1939); V. Prelog and H. Sherrer, *Helv. Chim. Acta*, **42**, 2227 (1959).

(14) D. S. Noyce and D. B. Denny, *J. Amer. Chem. Soc.*, **72**, 5743 (1960); D. J. Cram, *ibid.*, **52**, 2149 (1952).

SCHEME I



cis-**6** reacted faster than *trans*-**6**, in isomerization and in forming the ring-opened product **14** and the bicyclized product **15**. During the initial stages of reaction, the cis–trans interconversion went faster than conversion of either isomer to the products. Although the products cannot definitely be ascribed to the individual isomers, a close examination of Table III suggests that the bicyclized product **15** is produced more readily from *cis*-**6** than from *trans*-**6**. These differences may be rationalized by the proposal that hydride abstraction at C_3 is retarded somewhat in the case of *trans*-**6** by the benzyl group. Since the C_3 hydrogen and the benzyl group are on the same side of the tetralin ring, the approach of the catalyst to this hydrogen will be sterically hindered by the bulky benzyl group, especially as the catalyst can complex with the benzene ring.[15] On the other hand, *cis*-**6** not only does not suffer from this steric retardation of hydride abstraction, but may possibly profit from anchimeric assistance by the benzene ring in the removal of the C_3 hydride ion when both the methyl and the benzyl groups are situated in axial positions in a half-chair conformation of the tetralin ring.[16]

It was observed that the proportion of the bicyclized products **13** and **15** increased throughout the course of the reactions (Tables I–III). This is probably due to the fact that these compounds do not undergo significant rearrangement to any of the other compounds observed under the same or even more vigorous conditions, as was proved in the case of **15** by separate treatment. However, the proportion of the ring-opened products **12** and **14** was observed to pass through a maximum and then decrease (Tables I and II). An examination of the separate reaction of **14** with $AlCl_3$ seemed in order. The results as listed in Table IV indicate that this compound was converted to *cis*-**6** and *trans*-**6** or **7**[18] and to 1-methyl-2,3:6,7-dibenzo-

(15) In Friedel–Crafts alkylation reactions, complex formation between the catalyst and the aromatic substrate has been regarded as a necessary step in the substitution reactions. See, for example, G. A. Olah and M. W. Meyer, in G. A. Olah, Ed., "Friedel–Crafts and Related Reactions," Vol. I, Interscience, New York, N. Y., 1963, p 710 ff.

(16) If the reaction proceeds *via* this conformation, then formation of the bicyclized product **15** by the anchimeric assistance of the benzylic phenyl ring (A_r6) without proceeding through the carbonium ion intermediate (*vide infra*) may take place, although steric retardation of hydride abstraction alone is sufficient to account for the observed small difference in reaction rates. Anchimeric assistance of the benzene ring to facilitate cyclization is probably rather important in the cyclialkylation of the diphenylalkyl chlorides **1**, **2**, and **3** reported earlier,[2,3] and there is analogy with some solvolytic studies.[17]

(17) R. Heck and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 314 (1957).

(18) *cis*-**6** was resolved from *trans*-**6** and **7** by the chromatographic technique, but *trans*-**6** and **7** were not resolved.

TABLE IV

REACTION OF 2-METHYL-1,5-DIPHENYLPENTANE (14) WITH ALUMINUM CHLORIDE[a]

Time, hr	Reaction mixture composition, %[b] Unchanged 14	Tetralin derivatives[c]	15	27
6.0	93	4	3	Trace
10.0	91	5	4	

[a] Reactant ratios, 14:$AlCl_3$:CS_2 = 5 mmol:2.5 mmol:10 ml. [b] Glpc analysis: same column and conditions as in Table II. [c] Total amount of compounds *cis*-6 and *trans*-6 or 7.

bicyclo[3.3.1]nona-2,6-diene (**15**), but only at a very slow rate. The formation of a tetralin from **14** represents the first example of cyclialkylation of a *diphenylalkane* by $AlCl_3$, to our knowledge.[19] Because of the experimental difficulty in distinguishing between *trans*-**6** and **7**, it is not certain whether **7** was actually produced from **14**; however, it would be expected that the tertiary hydrogen in **14** would be more easily abstracted than the secondary hydrogen, and the cation produced by abstraction of the tertiary hydrogen is the one that would cyclize directly to **7**. It is to be noted that **15** would result from bicyclization of both **6** and **7**.

Because of the uncertainty as to whether **7** was actually produced from **14**, **7** was synthesized separately and treated with $AlCl_3$ under the conditions used with **14**. The results are tabulated in Table V. As depicted in Table V, compounds **6**, **14**, **15**, and **27** were all observed to be produced. The rate of conversion of the starting material **7** to the products was considerably faster than that of the isomeric compound **6**. It is especially noticeable that compound **14** produced at a remarkably faster rate. This was to be expected, as the phenyl–C_1 bond would sever readily, since the C_1 position was tetrasubstituted.[20]

TABLE V

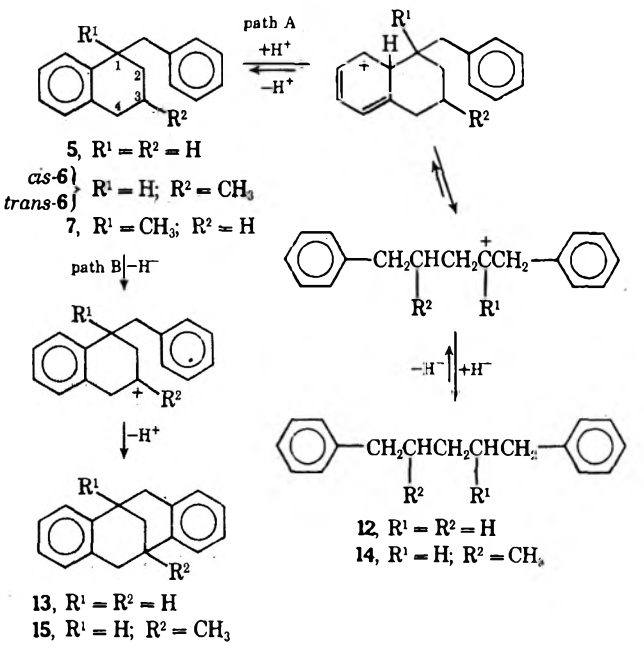
REACTION OF 1-BENZYL-1-METHYLTETRALIN (7) WITH ALUMINUM CHLORIDE[a]

Time, hr	Reaction mixture composition, %[b] Unchanged 7 or 6[c]	14	15	27
1.0	86	5	9	Trace, increased
3.0	51	20	29	
6.0	39	27	44	
10.0	15	32	53	

[a] Reactant ratios, 7:$AlCl_3$:CS_2 = 5 mmol:2.5 mmol:10 ml. [b] Glpc analysis: same column and conditions as in Table II. [c] Combined composition of compounds **7**, *cis*-**6**, and/or *trans*-**6**.

The major products from the reactions of the 1-benzyltetralins **5**, **6**, and **7** can be accounted for by the mechanistic pathways mentioned before. The ring-cleaved products **12** and **14** are formed *via* initial protonation of the tetralin benzene ring, followed by cleavage of the phenyl–C_1 bond (path A, Scheme II),

SCHEME II



while the bicyclization products **13** and **15** are formed by initial hydride ion abstraction from the alicyclic ring, followed by cyclialkylation of the benzyl ring (path B, Scheme II).

Consideration of the stoichiometry of path B ($-H^-$, $-H^+$) and path A ($+H^+$, $+H^-$) of Scheme II would seem to indicate that bicyclialkylation products (**13** or **15**) and ring-cleaved products (**12** or **14**) should be produced in equal amounts. This was not observed, however, probably because of the disappearance of some of the products by means of secondary reactions. It is interesting to note that the ratio of ring-cleaved product (**14**) to bicyclialkylation product (**15**) from compound **7** is about the same as the ratio of the corresponding products from compound **6**, although a higher proportion of ring-cleaved product from **7** might be expected because of the tetrasubstitution at the C_1 carbon, which should facilitate the cleavage by stabilizing the carbonium ion.

The formation of the bicyclialkylation products **13** and **15** could conceivably be initiated by abstraction of a hydride ion at any of the four positions in the alicyclic ring of the tetralins **5** and **6**, followed by intramolecular hydride shifts to place the positive charge at C_3. However, in the case of compound **7**, the fact that there is no hydrogen at C_1 rules out the possibility that initial hydride abstraction at C_1 is required for bicyclialkylation.

It was surprising to find that the rates of disappearance of the starting compounds **5** and **6** and the rates of formation of products in both cases were similar (Tables I and II). Although it might be expected that the reactions by path A to form **12** and **14** would be similar, since the methyl group at C_3 should have little effect on the cleavage at C_1, this methyl group would be expected to facilitate hydride abstraction at C_3. The lack of effect may be explained in two ways. The rate-controlling step in the reaction of both **5** and **6** may be abstraction of the benzylic hydride ion at C_4, followed by a (faster) 1,2 shift of the C_3 hydride ion. Alternatively, it may be that $AlCl_3$ is such a powerful catalyst that it levels off the intrinsic difference in the activation

(19) Cyclialkylations of phenylalkyl chlorides,[2] diphenylalkyl chlorides,[3,4] and phenylalkanols[5] have been reported in previous papers, but this is the first case in which the reactive intermediate in the cyclialkylation is produced by hydride abstraction from a hydrocarbon (except, of course, in the *bicyclialkylations* reported here, in which the hydrocarbon is a tetralin).

(20) R. M. Roberts, E. K. Baylis, and G. J. Fonken, *J. Amer. Chem. Soc.*, **85**, 3454 (1968).

energy for the abstraction of the secondary and tertiary hydrogens at C_3.

At first, it was thought that, by assessing the rearrangement of 1-benzyl-3,3-dimethyltetralin (**8**) and 1-benzyl-4,4-dimethyltetralin (**9**), it would be possible to decide the preference of hydride abstraction at position 3 or 4. The results of such reactions are grouped in Table VI. Compound **8** reacted very reluctantly.

TABLE VI

BICYCLIALKYLATION OF 1-BENZYL-3,3-DIMETHYLTETRALIN (8) AND 1-BENZYL-4,4-DIMETHYLTETRALIN (9)[a]

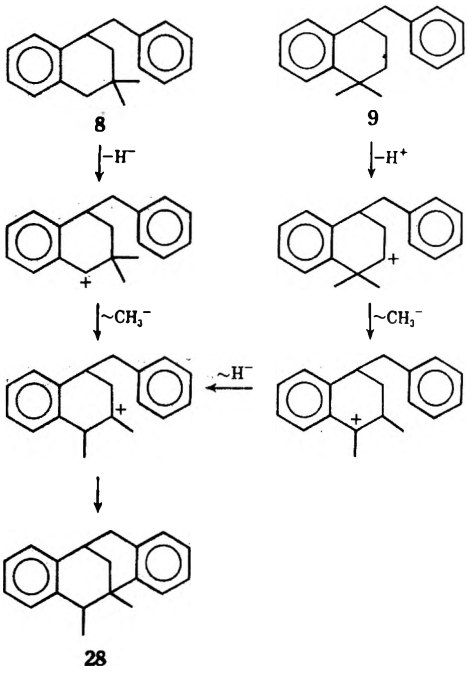
Hydrocarbon	Conditions	Time, hr	Reaction mixture composition, %[b,c] Unchanged starting material	28
8	CS_2	24.0	97	Trace
		56.0	85	7
8[d]	CS_2	8.0	91	2
		30.0	56	30
8	CS_2,	4.0	95	Trace
	HCl gas[e]	6.0	90	2
		48.0	30	24
9	CS_2	2.0	60[f]	4
		5.0	44[f]	9
		18.0	21[f]	30
		29.0	9	48

[a] Reactant ratios, hydrocarbon:$AlCl_3$:CS_2 = 5 mmol:2.5 mmol:10 ml unless noted otherwise. [b] Glpc analysis: same column and conditions as in Table II. [c] The remaining products were not identified. [d] Reactant ratios, 8:$AlCl_3$:CS_2 = 5 mmol: 5 mmol:10 ml. [e] Gentle passage of HCl gas during the first 3 min. [f] The starting compound 9 and one of the unidentified products were not resolved.

The expected bicyclization product, 1,8-dimethyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**28**), was not observed until after 24 hr under the normal reaction conditions. Under more severe conditions, compound **28** was formed more readily, but undesirable polymeric side products were formed even more rapidly. Compound **9**, on the other hand, reacted very rapidly to give after 2 hr at least six major products by glpc analysis. Although no attempt was made to identify each of them, one can speculate that they were largely ring-opened as well as bicyclized products. One of them, compound **28**, was isolated by column chromatography at the end of the reaction (29 hr), and was found to have physical and spectroscopic properties that were identical with those of the compound obtained by cyclodehydration of 4-benzyl-2,2-dimethyl-1-tetralol.[21]

The difference in behavior of compounds **8** and **9** in forming compound **28** poses a rather puzzling situation, because, although both require a 1,2-methide shift, compound **9** requires further a 1,2-hydride shift, in order to produce the carbonium ion that can bicyclize to compound **28**; yet it reacts more readily (Scheme III). Since 1,2-hydride shifts normally take place very rapidly, the difference would appear to lie in the preference of the initial hydride ion abstraction. However, the hydride abstracted from **8** is a secondary benzylic hydrogen, whereas the hydride abstracted from **9** is an ordinary secondary hydrogen, which would not be expected to be abstracted as readily, on the basis of the energy of the resultant carbonium ion. The only plausible explanation remaining would seem to be a steric factor in which the methylene hydrogens in **9** are more open to attack by catalyst than those in **8**, which are between the *gem*-dimethyl groups and the benzene ring.

SCHEME III



Experimental Section[22]

1-Benzyltetralin (**5**), 1,5-diphenylpentane (**12**), 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**13**), and 2-methyl-1,5-diphenylpentane (**14**) were prepared as previously reported.[3] 1-Methyltetralin (**26**) was prepared by a known procedure.[5a] 1-Benzyl-1-methyltetralin (**7**), 1-benzyl-4,4-dimethyltetralin (**9**), 1,1-dimethyltetralin (**27**), and 1,8-dimethyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**28**) were synthesized by methods described separately.[21]

1-Benzyl-3,3-dimethyltetralin (8).—4-Benzyl-2,2-dimethyl-1-tetralone,[23] bp 161–164° (0.25 mm), dissolved in glacial acetic acid containing a small amount of 70% $HClO_4$ and 5% Pd/C, was subjected to hydrogenation in a Parr apparatus at an initial pressure of 60 psi. After the required amount of hydrogen had been taken up, the product mixture was worked up in the usual way, yielding a very viscous oil: bp 114–116° (0.2 mm); $n^{23}D$ 1.5618; ir compatible with assigned structure; nmr (60 MHz, CCl_4) δ 0.82 (s, 3, methyl), 0.98 (s, 3, methyl), 1.05–1.55 (m, 2, methylene), 2.23–2.67 and 2.94–3.46 (overlapping ABX and AB patterns, 5, benzylic), and 6.87–7.45 ppm (m, s at 7.10, 9, aromatic); mass spectrum *m/e* (rel intensity) 250 (2), 159 (100), 91 (12).

Anal. Calcd for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 90.97; H, 8.90.

3-Methyl-1-tetralone (16) was synthesized according to a literature procedure.[24] The Grignard reaction of this compound with benzylmagnesium chloride[25] gave 1-benzyl-3-methyl-1-tetralol (**17**) as a slightly greenish, viscous oil: bp 128° (0.02 mm); $n^{23}D$ 1.5814; nmr (60 MHz, CCl_4) δ 0.86 (d, 3, J = 6.0 Hz, methyl), 1.15–3.05 (m, 5, alicyclic), 2.45 (apparent s, 1,

(21) C.-E. Low and R. M. Roberts, *J. Org. Chem.*, **38**, 1909 (1973).

(22) All temperatures are uncorrected. Ir spectra were recorded on a Beckman IR-5A instrument; nmr spectra were taken with a Varian A-60 or a Varian HA-100 instrument, using TMS as internal standard; mass spectra were taken with a CEC 21–49 instrument operated at 70 eV.

(23) R. M. Roberts and C.-E. Low, paper in preparation.

(24) F. Weygand and K. Schröder, *Ber.*, **74**, 1844 (1941).

(25) F. E. Zimmermann, F. H. Owens, and P. R. Fellmann, *J. Org. Chem.*, **25**, 1808 (1960).

hydroxy, exchangeable with D_2O), 2.82 (s, 2, benzylic), and 6.86–7.50 ppm (m, 9, aromatic); ir ν_{max}^{film} 3560, 3450 cm^{-1}.

1-Benzyl-3-methyl-1-tetralol (17, mixed isomers) was subjected to hydrogenolysis in glacial acetic acid containing a small amount of perchloric acid, using 5% Pd/C at an initial hydrogen pressure of 60 psi. 1-Benzyl-3-methyltetralin (**6**) was obtained in quantitative yield as a viscous oil: bp 115–116° (0.2 mm); $n^{23}D$ 1.5694; nmr (60 MHz, CCl_4) δ 0.92 and 0.98 (two doublets in 4:1 ratio, 3 H total, J = 6.8 Hz, methyl), 1.25–3.45 (m, 8, alicyclic and benzylic), and 6.90–7.30 ppm (m with sharp peak at 7.12, 9, aromatic). The ratio of doublets at 0.92 and 0.98 ppm indicated an 80:20 ratio of *cis*-**6**:*trans*-**6** (see nmr of authentic *cis*-**6** and *trans*-**6** below). This product was used as starting material in the reaction, yielding the results presented in Table II.

The individual diastereoisomeric alcohols, *cis*-**17** and *trans*-**17**, were separated by repeated column chromatography using a 110 × 3 cm column filled with silica gel (E. Merck, type G, pH 7) with benzene as eluent, the unwanted fractions being discarded. The trans isomer was eluted first. The separated oily isomers exhibited the following spectroscopic properties: *cis*-**17**, nmr (60 MHz, CCl_4) δ 0.95 (d, 3, J = 6 Hz, methyl), 1.90 (s, 1, hydroxy), 1.10–2.75 (m, 5, alicyclic), 3.05 (AB pattern, 2, J = 13 Hz, exocyclic benzylic), and 6.80–7.60 ppm (m, 9, aromatic); ir ν_{OH}^{film} 3600 (sh), 3500 cm^{-1}; *trans*-**17**, nmr (60 MHz, CCl_4) δ 1.00 (d, 3, J = 6.0 Hz, methyl), 1.50 (s, 1, hydroxy), 1.1–3.1 (m, 7, alicyclic and benzylic), and 6.80–7.60 ppm (m, 9, aromatic); ir ν_{max}^{film} 3600 (sh), 3500 cm^{-1}. Although the spectra of the two isomers were quite similar, dissimilarities were noted at 1274, 1015, 995, and 926 cm^{-1} and in the region 775–665 cm^{-1}. The tlc chromatograms of the two isomers also showed slightly different R_f values.

Separate samples of *cis*-**17** and *trans*-**17** were subjected to hydrogenolysis as described above. The products were identical in their spectroscopic properties and chromatographic behavior with authentic *cis*-**6** and *trans*-**6**, respectively, prepared as described below according to Scheme I.

Phenylitaconic acid (18),[7] mp 183–186°, benzylsuccinic acid (**19**),[7] mp 155–159°, benzylsuccinic anhydride (**20**),[8] mp 95–97°, and 3-carboxy-1-tetralone (**21**),[7] mp 144–146°, were obtained following the literature procedures.

Grignard Reactions of 3-Carboxy-1-tetralone (21) with 2 Molar Equiv of Benzylmagnesium Chloride.—To a suspension of 19.0 g (0.10 mol) of finely powdered 3-carboxy-1-tetralone (**21**) in 250 ml of dry ether, a solution of benzylmagnesium chloride prepared from 27.9 g (0.22 mol) of magnesium turnings was added at room temperature. The reaction was allowed to proceed for 2 hr and was then poured on ice–HCl (5%), whereupon a crystalline mass was obtained. Fractional crystallization from ethanol gave 10.6 g (40%) of 1-benzyl-1-hydroxy-1,2,3,4-tetrahydro-3-naphthoic acid γ-lactone (**22**): mp 180–182.5°; nmr (60 MHz, $CDCl_3$) δ 1.8–2.4 (m, 2, methylene), 2.7–4.1 (m, 6, benzylic), and 7.0–7.6 ppm (m, 9, aromatic); ir $\nu_{C=O}$ 1780 cm^{-1} (5-ring lactone), no OH; mass spectrum M^+ 264.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.82; H, 6.06. Found: C, 81.80; H, 5.99.

The mother liquors were evaporated and the residue was recrystallized from benzene–cyclohexane, yielding 4.75 g (18%) of 1-benzyl-3-carboxy-3,4-dihydronaphthalene (**23**): mp 130–132°; nmr (60 MHz, $CDCl_3$) δ 2.8–3.6 (m, 3, endocyclic benzylic and C_3 methinyl), 3.82 [s (broad), 2, exocyclic benzylic], 5.92 [d (broad), 1, J = 3 Hz, olefinic], 6.9–7.5 (m, 9, aromatic), and 9.75 ppm [s (very broad), 1, carboxylic].

1-Benzyl-1-hydroxy-3-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (24).—To a suspension of 3.70 g (0.014 mol) of lactone **22** in 50 ml of THF, 400 mg (0.01 mol) of $LiAlH_4$ was added. The mixture was heated to reflux for 12 hr and then poured into 200 ml of 10% aqueous HCl solution. The crystals thus obtained were collected and recrystallized from ethanol, yielding 3.23 g (86%) of **24**, mp 201–203°. Both **22** and **24** were very sparingly soluble in THF. The best technique for this reduction was to add lactone **22** *via* a Soxhlet extractor to a suspension of $LiAlH_4$ in THF. Compound **24** was too insoluble in common solvents to enable the taking of its nmr spectrum: ir ν_{OH} 3350 cm^{-1} (strong), no C=O; mass spectrum 250 (M^+ − 18) (loss of water).[26]

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.60; H, 7.46. Found: C, 80.43; H, 7.53.

***trans*-1-Benzyl-3-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (*trans*-25).**—A suspension of 795 mg (0.003 mol) of compound **24** in boiling ethanol together with approximately 10 g of freshly prepared Raney nickel was shaken for 24 hr. The catalyst was filtered off, the ethanol was evaporated, and the solid residue was recrystallized twice from petroleum ether (bp 30–60°), giving 650 mg (84%) of *trans*-**25**: mp 79°; nmr (100 MHz, CCl_4) δ 1.0–3.2 (m, 7, alicyclic and methylenic), 3.40 (d, 2, J = 6.0 Hz, benzylic), 6.8–7.3 ppm (m, 9, aromatic); ir ν_{OH} 3250, 3325 cm^{-1} (sh); mass spectrum M^+ 252.

Anal. Calcd for $C_{18}H_{20}O$: C, 85.71; H, 7.93. Found: C, 85.93; H, 7.95.

***cis*-1-Benzyl-3-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (*cis*-25).**—A 950-mg (0.0035 mol) sample of **24** was hydrogenated catalytically with Pd/C in ethanol under a pressure of 25 psi for 12 hr. After removal of the catalyst and evaporation of the solvent, the solid residue was recrystallized from petroleum ether to give 490 mg (55%) of *cis*-**25**: mp 76°; nmr (100 MHz, $CDCl_3$) δ 0.8–3.6 (m, 11, alicyclic, benzylic, methylenic, and hydroxylic) and 7.0–7.6 ppm (m, 9, aromatic); ir ν_{OH} 3350 cm^{-1}; mass spectrum M^+ 252. A mixture of *cis*-**25** and *trans*-**25** began melting at *ca.* 56°.

Anal. Calcd for $C_{18}H_{20}O$: C, 85.71; H, 7.93. Found: C, 85.49; H, 8.14.

***trans*-1-Benzyl-3-methyltetralin (*trans*-6).**—To 250 mg (0.001 mol) of *trans*-**25** in 30 ml of dry pyridine was added at 0° 275 mg (0.0015 mol) of *p*-TsCl in 10 ml of dry pyridine. The mixture was allowed to warm slowly to room temperature and was stirred overnight (*ca.* 14 hr). The reaction mixture was then poured into water, whereupon the tosylate was obtained as an oil that did not crystallize. It was taken up in ether and dried thoroughly with $MgSO_4$. Then 40 mg (0.001 mol) of $LiAlH_4$ was added to the ethereal solution and the mixture was refluxed for 2 hr, poured into 10% HCl solution, and extracted with ether. The resulting hydrocarbon, *trans*-**6** (65% yield), was identical in properties with the product obtained from catalytic hydrogenolysis of *trans*-**17** (*vide supra*): nmr (100 MHz, CCl_4) δ 1.02 (d, J = 7.0 Hz, 3, methyl), 1.10–3.20 (four sets of multiplets, 8, aliphatic), and 6.90–7.50 ppm (m, 9, aromatic); nmr (pyridine) δ 0.91 (d, J = 7.0 Hz, 3, methyl), 1.00–3.40 ppm (four sets of multiplets, 8, aliphatic).

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.29; H, 8.61.

***cis*-1-Benzyl-3-methyltetralin (*cis*-6).**—This compound was obtained in like manner from *cis*-**25** in 58% yield. Its properties were identical with those of the product obtained by catalytic hydrogenolysis of *cis*-**17** (*vide supra*): nmr (100 MHz, CCl_4) δ 0.97 (d, J = 7 Hz, 3, methyl), 1.10–3.50 (four sets of m, 8, aliphatic), and 6.90–7.50 ppm (m, 9, aromatic); nmr (pyridine) δ 0.83 (d, J = 7.0 Hz, 3, methyl) and 1.00–4.00 ppm (four sets of m, 8, aliphatic).

These pure isomers were used as starting materials in the experiments described in Table III.

Reactions of the Arylalkyl Hydrocarbons with $AlCl_3$.—In a small flask was placed 5 mmol of the hydrocarbon dissolved in 10 ml of CS_2, and then 2.5 mmol of $AlCl_3$ was added to the magnetically stirred solution at room temperature. At various time intervals, approximately 0.5 ml of the reaction mixture was withdrawn with a pipet and decomposed at once in a small vial containing about 1.5 ml of cold water. The organic layer was taken up in ether, which was concentrated, and the residual liquid was analyzed by glpc. The identification of the products was accomplished by comparing their chromatographic behavior with those of the authentic samples in the following columns: (1) 6 ft × 0.25 in., SE-30 silicone gum rubber (30%) operated at 220° with helium carrier gas at 40 psi; (2) 6 ft × 0.25 in., Cyanosilicone (30%) operated at 160° with helium carrier gas at 35 psi; (3) 6 ft × 0.125 in., DEGA (15%) operated at 220° with nitrogen carrier gas at 40 psi; and (4) 10 ft × 0.125 in., Bentone-34 (5%) and SE-52 silicone gum rubber (5%) operated at 210° with nitrogen carrier gas at 60 psi.

With HCl-gas promotion, a three-necked flask equipped with a reflux condenser carrying a $CaCl_2$ tube, and an HCl-gas inlet was used. The addition of $AlCl_3$ and the introduction of HCl gas was timed to take place simultaneously.

The results of the reactions of compounds **5**, **6** (mixed isomers), *cis*-**6**, *trans*-**6**, **14**, **7**, **8**, and **9** are listed in Tables I–VI.

(26) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 110.

Registry No.—**5**, 38899-49-9; *cis*-**6**, 38899-12-6; *trans*-**6**, 38899-13-7; **7**, 38899-57-9; **8**, 38899-58-0; **9**, 38899-51-3; **14**, 31444-36-7; **16**, 14944-23-1; *cis*-**17**, 38899-14-8; *trans*-**17**, 38899-15-9; **21**, 6566-40-1; **22**, 38899-40-0; **23**, 38899-41-1; **24**, 38974-14-0; *trans*-**25**, 38899-10-4; *cis*-**25**, 38899-11-5; aluminum chloride, 7446-70-0; 4-benzyl-2,2-dimethyl-1-tetralone, 38899-42-2; benzyl chloride, 100-44-7.

Acid-Catalyzed Cyclodehydration of Some 4-Benzyl-1-tetralols and 4-Phenylalkanols. Rearrangement of Dibenzobicyclo[3.2.2]nona-2,6-diene by Aluminum Chloride[1]

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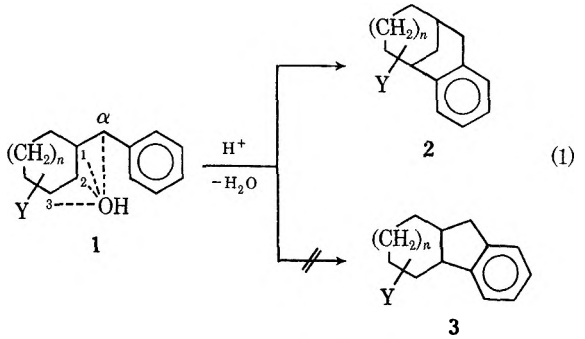
Treatment of 4-benzyl-1-tetralol (**9**) with concentrated sulfuric acid resulted in the formation of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (**12**) in high yield. By the same process, 1-methyl-2,3:6,7-dibenzobicyclo-[3.3.1]nona-2,6-diene (**13**) and 1,8-dimethyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**14**) were obtained from 2-methyl-4-benzyl-1-tetralol (**10**) and 2,2-dimethyl-4-benzyl-1-tetralol (**11**), respectively. The behavioral difference of these homologous 4-benzyl-1-tetralols is discussed from the standpoint of the relative stability of carbonium ion intermediates. In the presence of $AlCl_3$, compound **12** rapidly rearranged to 1-benzyltetralin (**23**) and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**16**). The mechanistic implications are discussed in light of thermodynamic stability of the compounds. Some examples of the cyclodehydration of tertiary 4-phenylalkanols to tetralins are given which illustrate the synthetic utility of this reaction.

The strong protonic acid induced cyclodehydration of phenylalkanols, whereby condensed aromatic compounds are produced, has been the subject of very intensive investigation, resulting in voluminous reports in the literature.[2] In contrast, formation of bridged polycyclic compounds by the same process has not received much attention. Several groups of investigators have reported the production of benzobicyclo-[3.3.1]nonene systems (**2**, $n = 1$) when simple or substituted phenylcyclohexylcarbinols (**1**, $n = 1$, OH at the α position), or benzylcyclohexanols (**1**, $n = 1$, OH at position 1, 2, or 3), or the corresponding olefins were subjected to treatment of strong acids (eq 1, $n = 1$).[3] Analogously, cyclization of phenyl-



(1)

Y = H, CH_2
n = 0, 1

cyclopentylcarbinol (**1**, $n = 0$, OH at the α position), or the benzylcyclopentanols (**1**, $n = 0$, OH at position 1 or 2), or the corresponding olefins gave benzobicyclo-[3.2.1]octenes (**2**, $n = 0$, eq 1).[4] In all these cases, the bridged polycyclic compounds formed have a new six-membered ring fused onto the original compound, indicating a marked tendency for the formation of a six-membered ring, rather than a smaller one, in the cyclization process.[5] These bridged polycyclic compounds are relatively less strained[6] compared to hydrofluorene derivatives (**3**, $n = 1$) or benzobicyclo-[3.3.0]octene derivatives (**3**, $n = 0$).[7] Recently, a bridged polycyclic system has been produced by the action of concentrated sulfuric acid on the acetal **4**, giving isopavine (**5**) (eq 2).[8] On the other hand, the acetals **6** and **7**, although structurally similar to **4**, reacted to give papaverine (**8**) (eq 3).[9]

In our earlier communications, we described the cyclodehydration of some phenylalkanols and diphenylalkanols, whereby indans and tetralins were produced.[10] In continuation of our investigation in this series, we have now chosen to study the behavior of some 4-benzyl-1-tetralols in strong protonic acids, expecting them to cyclize to bridged polycyclic products, some of which we have already obtained in other work.[5,11]

(1) (a) Part XXX of the series "New Friedel–Crafts Chemistry." Part XXIX: R. M. Roberts, K.-H. Bantel, and C.-E. Low, *J. Org. Chem.*, **38**, 1903 (1973). (b) Generous support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

(2) L. R. C. Barclay in G. A. Olah, Ed., "Friedel–Crafts and Related Reactions," Vol. II, Interscience, New York, N. Y., 1964, p 816 ff.

(3) (a) J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 62 (1936); (b) A. A. L. Challis and G. R. Clemo, *ibid.*, 1692 (1947); (c) J. C. Bardhan and R. C. Banerjee, *ibid.*, 1809 (1956); (d) U. R. Ghatak and J. Chakravarty, *Tetrahedron Lett.*, 2449 (1966).

(4) L. H. Grove and G. A. Swan, *J. Chem. Soc.*, 871 (1951).

(5) Studies on other systems have led to the same conclusion; *cf.* R. M. Roberts, G. P. Anderson, Jr., A. A. Khalaf, and C.-E. Low, *J. Org. Chem.*, **36**, 3342 (1971).

(6) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 296; (b) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc. (London)*, 57 (1964).

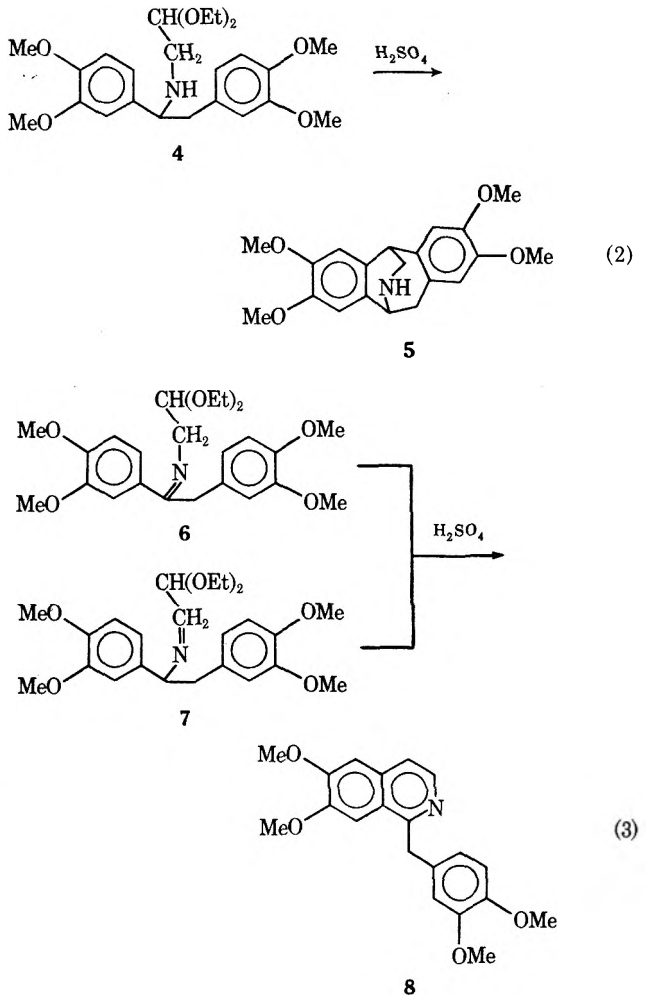
(7) (a) M. Hanack, "Conformational Theory," Academic Press, New York, N. Y., 1965, p 173; (b) reference 6a, p 274.

(8) (a) E. Waldmann and C. Chwala, *Justus Liebigs Ann. Chem.*, **609**, 125 (1957); (b) A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1988 (1958).

(9) (a) P. Fritsch, *Justus Liebigs Ann. Chem.*, **329**, 37 (1903); (b) E. Schlittler and J. Muller, *Helv. Chim. Acta*, **31**, 914 (1948).

(10) (a) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, in press; (b) A. A. Khalaf and R. M. Roberts, *ibid.*, **36**, 1040 (1971); (c) A. A. Khalaf and R. M. Roberts, *ibid.*, **34**, 3571 (1969).

(11) R. M. Roberts, K.-H. Bantel, and C.-E. Low, *J. Org. Chem.*, in press.

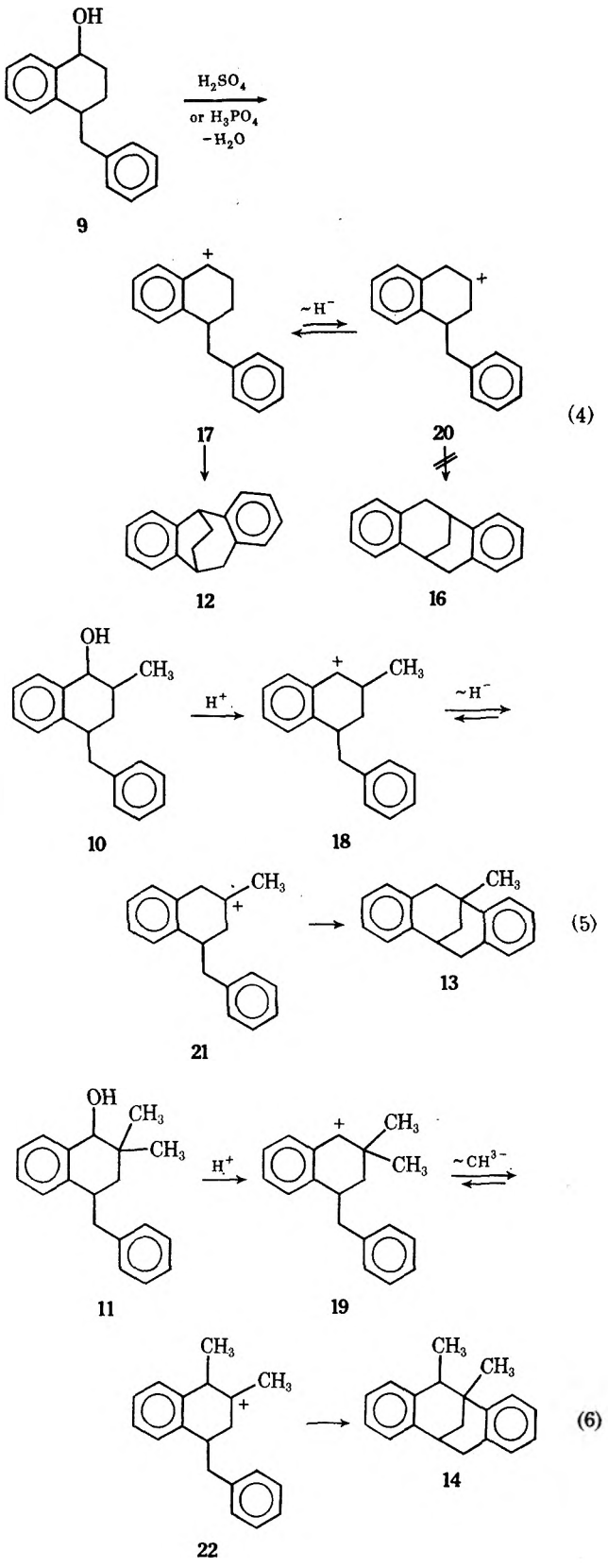


Results and Discussion

The reaction of 4-benzyl-1-tetralol (**9**) in sulfuric acid or phosphoric acid resulted in the isolation of a crystalline product. Its spectroscopic and physical properties were not consistent with those expected for 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**16**),[5,11,12] or tetrahydro-1,2-benzofluorene (**15**),[12] but could be ascribed to 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (**12**) (eq 4).[13]

In sulfuric acid, 2-methyl-4-benzyl-1-tetralol (**10**) cyclodehydrated to give 1-methyl-2,3:6,7-dibenzobicyclo[2.2.1]nona-2,6-diene (**13**) (eq 5). Compound **13** was previously obtained when 3-methyl-1-benzyltetralin was cyclialkylated with $AlCl_3$[5,11] and when 1-chloro-2-methyl-4,5-diphenylpentane was treated with $AlCl_3$.[5] 2,2-Dimethyl-4-benzyl-1-tetralol (**11**) was converted to 1,8-dimethyl-2,3:6,7-dibenzobicyclo-[3.3.1]nona-2,6-diene (**14**) under the same conditions (eq 6). Compound **14** was also formed from 3,3-dimethyl-1-benzyltetralin and 4,4-dimethyl-1-benzyltetralin upon treatment with $AlCl_3$.[11]

Undoubtedly, the products of these reactions are formed *via* carbonium ion intermediates. From **9**, 4-benzyl-1-tetralyl cation **17** is produced, which cyclizes directly to give a seven-membered ring system, **12**. In the latter two cases, however, the initially formed 1-tetralyl cations **18** and **19** undergo 1,2 shift of a hydride or a methide ion to give the 2-tetralyl cations **21** and **22**, which then cyclize to form six-membered bicyclic systems, **13** and **14**, respectively.



It was surprising to observe that compound **9** did not follow the pattern of reaction of the other homologs, even though a seven-membered ring nitrogen analog of **12** had already been reported.[8] The key to the solution of this puzzle lies in the carbonium ion intermediates involved. Species **17**, **18**, and **19**, having the

(12) H. Stetter and A. Reichl, *Ber.*, **93**, 791 (1960).

(13) This compound (**12**) was obtained in a quite different way by E. M. Cioranescu, M. Banciu, R. Jelescu, M. Rentzea, M. Elian, and C. D. Nenitzescu, *Rev. Roum. Chim.*, **14**, 911 (1969).

charge in a benzylic position, and species **21** and **22**, being tertiary and therefore stabilized by hyperconjugation, all possess a high degree of stability. However, species **20**, which would be produced from **17** by a 1,2-hydride shift, would be less stable than **17**, since the charge would no longer be stabilized by the benzene ring. As a result, direct cyclization to the seven-membered ring system takes place.

It will be noted that direct cyclization to the seven-membered ring system can also take place in the case of **18**, but the fact that no such product is observed indicates that this process is unfavorable and that a 1,2-hydride shift takes place. Again, direct cyclization in the case of **19** is unfavorable because of the steric hindrance imposed by the *gem*-dimethyl groups, which makes it difficult for the benzylic carbon to approach the reaction site.

The above argument is supported by the observation that formation of compound **13** was much faster than that of either **12** or **14**, the last being especially slow. This not only bears out the fact that the 1,2 shift of a hydride ion is faster than that of a methide ion,[14] but also that the formation of a six-membered ring is much favored.[5] Since direct cyclization of species **19** is not feasible because of the steric factor and yet this carbonium ion possesses a high degree of stability, there is ample time for a 1,2-methide shift to form **22**, which, upon cyclization, forms compound **14**.

It is expected that a pair of diastereoisomers of **14** should be formed by the cyclodehydration of compound **11**. However, the only available data bearing on this point is the nmr spectrum of **14**. This indicated that the two methyl groups produce a singlet and a doublet, respectively, and the bridge methylene protons form an AB pattern (the high-field half being simple while the low-field half is complex). The benzylic and aromatic protons produced complex resonance peaks (see Experimental Section). Assuming that the methyl groups of the diastereoisomers should exhibit different chemical shifts, being under different environmental influence, the spectrum obtained clearly indicates that only one of the diastereoisomers was produced. Thus, we speculate that a 1,3 fusion of a chair–chair conformation, with the bridgehead methyl group fixed at an equatorial position and the other methyl group pseudoaxial (*i.e.*, the methyl groups cis to each other) should be the energetically preferred conformation, on the basis of both an examination of a molecular model and consideration of the stereochemical course of reaction.

Regarding the assigned structure of compound **12**, another piece of good evidence is provided by its behavior in the presence of $AlCl_3$. When this compound was stirred with 0.5 molar equiv of $AlCl_3$ and the reaction was followed by occasional withdrawal of a small quantity of the reaction mixture, quenching with water, and injection of the organic material into a gas chromatograph, it was found that compound **12** was completely disintegrated within 2 hr, with the concurrent production of 1-benzyltetralin (**23**), 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**16**), and a small quantity of 1,5-diphenylpentane (**24**), plus a trace amount of 1-methyltetralin (**25**). Subsequent reaction was undoubtedly due to the rearrangement of 1-benzyltetralin (**23**) by $AlCl_3$, which we have studied before.[11] The complete results are shown in Table I.

TABLE I

REARRANGEMENT OF 2,3:6,7-DIBENZOBICYCLO[3.2.2]NONA-2,6-DIENE (12) IN $AlCl_3$ AT ROOM TEMPERATURE[a]

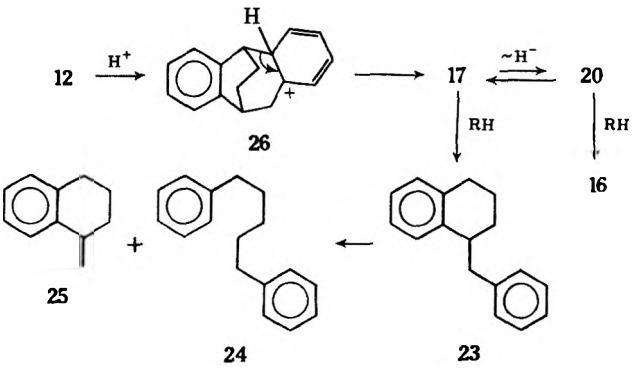
	Product composition %[b]				
Time hr	Unchanged starting material	16	23	24	25
0.5	46	25	29	Trace	Trace
1.0	12	58	30	Trace	Trace
2.0	0	77	21	2	Trace
4.0	0	80	17	3	Trace

[a] Reactant ratios: 12:$AlCl_3$:CS_2 = 5 mmol:2.5 mmol:10 ml. [b] Glpc analysis: 10 ft × 0.125 in. (o.d.) aluminum column impregnated with Bentone-34 (5%) and SE-52 silicone gum rubber (5%) operated at 210° with N_2 carrier gas at 60 psi.

This rearrangement is significant in that it provides direct evidence for the fact that a seven-membered ring (benzosuberane) cannot survive Friedel–Crafts alkylation conditions,[15] and that the assigned structure of **12** is correct.

Mechanistically, the reaction can be formulated as depicted in Scheme I. Protonation of a benzo ring,

SCHEME I



followed by opening of the seven-membered ring (dealkylation[16]), gives the 4-benzyl-1-tetralyl cation **17**, which can either pick up a hydride ion to form 1-benzyltetralin (**23**) or undergo a 1,2-hydride shift to form 4-benzyl-2-tetralyl cation **20**, which then proceeds to cyclize to form 2,3:6,7-dibenzobicyclo [3.3.1]-nona-2,6-diene (**16**).

Since compound **16** is produced in an appreciable quantity right from the beginning of the reaction, the 1,2-hydride shift that converts 4-benzyltetralyl cation **17** to **20** must be very efficient, and direct cyclization of intermediate **20** to the bicyclization product **16** must take place rapidly. The behavior is therefore contrasted sharply with that of the carbonium ion in sulfuric acid, wherein only species **17** exists (*vide supra*). This indicates that the nature of the catalytic effect of $AlCl_3$ and sulfuric acid is very different. The fact that species **20** exists only in $AlCl_3$ even though it

(14) G. W. Wheland, "Advanced Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1960, p 591.

(15) Studies on other systems have also led to this conclusion; see (a) L. R. C. Barclay, B. A. Ginn, and C. E. Milligan, *Can. J. Chem.*, **42**, 579 (1964); (b) reference 2, p 932; (c) reference 5.

(16) R. M. Roberts, E. K. Baylis, and G. J. Fonken, *J. Amer. Chem. Soc.*, **85**, 3454 (1963).

is much less stable than the benzylic cation **17**, confirms that $AlCl_3$ is a very strong acid,[17] for it is only in this strong Lewis acid medium that a less stable carbonium ion species can exist to the extent that a thermodynamically more stable compound can form from it. We have previously reported that $AlCl_3$ is so strong a Lewis acid that it "levels off" the intrinsic difference in the ease of abstraction of a secondary and a tertiary hydride.[1a]

The driving force for the rearrangement of compound **12** to compound **16** is release of strain.[18] Although a Dreiding model does not indicate severe angle strain, the cumulative effect of the boat conformation of the six-membered ring, the torsional strain of the bridgehead carbons, and the slight angular strain of the seven-membered ring probably accounts for its observed instability to $AlCl_3$ treatment. On the other hand, compound **16** can easily assume a pseudo-chair–chair conformation, which approximates a diamondoid structure.

The formation of compound **12** in sulfuric acid effected cyclodehydration of 4-benzyl-1-tetralol (**9**) and the rearrangement of it in $AlCl_3$ to compound **16** serve to illustrate a distinctive difference in the catalytic power between sulfuric acid and $AlCl_3$. It has been estimated that the Friedel–Crafts conjugate acid is 10^5 times more acidic than 100% sulfuric acid.[19] The latter, being of the Brønsted–Lowry type, can function only through its ability to supply a proton, while the former can function, in addition to this,[20] as a hydride ion abstractor. This difference in properties accounts for their difference in activities. It also explains why only the more thermodynamically stable products can be formed in $AlCl_3$.[21]

We have made good use of the fact that tetralin ring formation is facilitated over that of smaller or larger ring size in synthesizing polycyclic compounds.[5,10] In particular, the cyclodehydration process has enabled us to synthesize a number of tetralin derivatives needed in connection with studies which will be published separately.[1a,10] Thus, 2-methyl-5,6-diphenyl-2-hexanol (**29**) cyclodehydrated to give only 1-benzyl 4,4-dimethyltetralin (**30**). No 1,1-dimethyl-4-phenylbenzosuberane was detected. Similarly, 2-methyl-1,5-diphenyl-2-pentanol (**31**) gave 1-benzyl-1-methyltetralin (**32**), 2-methyl-5,5-diphenyl-2-pentanol (**33**) gave 1,1-dimethyl-4-phenyltetralin (**34**), and 2-methyl-5-phenyl-2-pentanol (**35**) gave 1,1-dimethyltetralin (**36**). The starting compounds exhibit a common feature; namely, they all are tertiary carbinols having a phenyl group at the 4 position. Therefore, these reactions may proceed through a rather stable tertiary carbonium ion intermediate and cyclize to a substituted tetralin.

(17) The principle is well documented that a less stable carbonium ion, *i.e.*, a highly electrophilic species, can survive only if it is in a progressively stronger acidic medium. Thus, carbonium ions of very short half-life can be made stable in superacid media. See (a) G. A. Olah, *et al.*, reports appearing in *J. Amer. Chem. Soc.* since 1965; (b) R. J. Gillespie and T. E. Peel, in V. Gold, Ed., *Advan. Phys. Org. Chem.*, **9**, 1 (1971).

(18) Other studies in which a release of strain was observed in $AlCl_3$-catalyzed reactions are found: (a) P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960); (b) H. Stetter and P. Goebel, *Ber.*, **96**, 550 (1963); (c) H. W. Whitlock, Jr., and M. W. Siefken, *J. Amer. Chem. Soc.*, **90**, 4929 (1968); (d) L. A. Paquette, G. V. Meehan, and S. J. Marshall, *ibid.*, **91**, 6779 (1969).

(19) G. A. Olah in G. A. Olah, Ed., "Friedel–Crafts and Related Reactions," Vol. I, Interscience, New York, N. Y., 1963, p 880.

(20) It has been well documented that this catalytic capability of $AlCl_3$ appears only when it is slightly moistened, but under most circumstances, moisture cannot be completely excluded from $AlCl_3$. See ref 19, p 207.

(21) Our studies of the Friedel–Crafts catalyzed rearrangements of alkylbenzenes lead us to the same conclusion.

Experimental Section[22]

2,3:6,7-Dibenzobicyolo[3.3.1]nona-2,6-diene (**16**), 1-benzyltetralin (**23**), and 1,5-diphenylpentane (**24**) were prepared as previously described.[5] 1-Methyltetralin (**25**) was prepared by a known procedure.[10c]

Synthesis of 4-Benzyl-1-tetralols.—4-Benzyl-1-tetralone,[23] 4-benzyl-2-methyl-1-tetralone,[23] or 4-benzyl-2,2-dimethyl-1-tetralone[23] (0.03 mol) was dissolved in 100 ml of methanol in a flask equipped with a thermometer, a reflux condenser and a magnetic stirrer. The contents were cooled in an ice bath, and 0.015 mol of $NaBH_4$ was added portionwise, while the temperature was kept at or below 22°. The reaction mixture was stirred at room temperature for 3 hr after addition. The solvent was then distilled away and the remaining slurry was extracted with ether, washed, dried, and concentrated to give 90% yield in each case of the benzyltetralols.

4-Benzyl-1-tetralol (**9**) had mp 98–100° [lit.[24] bp 185° (0.5 mm)]; ir ν_{max}^{Nujol} 3300, 1470, 1065 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 1.54–1.95 (m, 4, CH_2CH_2), 2.55 (s, 1, OH), 2.63–3.30 (m, 3, benzylic), 4.65 (t, J = 6.0 Hz, 1, CH), 7.20 (m, 8, aromatic), and 7.33–7.55 ppm (m, 1, aromatic); mass spectrum m/e (rel intensity) 238 (10), 221 (87), 220 (29), 147 (46), 129 (100), 117 (33), 91 (88), 77 (14); mass, calcd for $C_{17}H_{18}O$, 238.1358 (found, 238.1365).

4-Benzyl-2-methyl-1-tetralol (**10**) was a very viscous oil: bp 125–128° (0.02 mm); $n^{28}D$ 1.5847; ir ν_{max}^{film} 3350, 1470, 1040 cm^{-1}; nmr (100 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3, CH_3), 1.28–2.00 (m, 3, $CHCH_2$), 2.40–3.40 (m, 4, benzylic and OH, the OH at 2.70 is exchangeable with D_2O), 4.10–4.40 (m, 1, benzylic), 6.96–7.28 (m, 8, aromatic), and 7.33–7.60 ppm (m, 1, aromatic); mass spectrum m/e (rel intensity) 234 (3), 161 (12), 143 (100), 128 (21), 117 (8), 91 (28), 77 (5); mass, calcd for $C_{18}H_{20}O$, 252.1514 (found, 252.1516).

4-Benzyl-2,2-dimethyl-1-tetralol (**11**) had mp 70–72°; ir ν_{max}^{Nujol} 3350, 1462, 1410, 1395, 1042 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.67 (s, 3, CH_3), 1.22–1.58 (m, 2, CH_2), 2.38 (s, 1, OH), 2.50–3.43 (m, 3, benzylic), 4.24 (s, 1, CHOH), 7.12 and 7.38–7.60 ppm (s and m, respectively, 9, aromatic); mass spectrum m/e (rel intensity) 266 (2), 248 (10), 157 (100), 131 (12), 115 (6), 91 (13).

Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.45; H, 8.39.

Cyclodehydration Reaction of the 4-Benzyltetralols.[25]—In a 25-ml flask was placed 1 ml of H_2SO_4 (90% by weight). The benzyltetralol was added in portions to the magnetically stirred acid. After the reaction, the product mixture was quenched by pouring into a beaker containing cold water.[26] The organic layer was taken up in ether, washed, dried, and concentrated.

From 4-benzyl-1-tetralol (**9**), after 14 hr, an 85% yield of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (**12**) was obtained: mp 75° (lit.[12] mp 78–79°); ir ν_{max}^{KBr} 3080, 2945, 1495, 1455, 758, 722 cm^{-1}; nmr (100 MHz, CCl_4) δ 1.88–2.40 (m, 4, bridge CH_2CH_2), 3.15 (apparent s, 3, CH_2 and bridgehead H), 3.73 (overlapping t, 1, CH), and 6.77–7.10 ppm (m with sharp peak at 7.01, 8, aromatic); mass spectrum m/e (rel intensity) 221 (19), 220 (100), 205 (27), 192 (78), 131 (71), 129 (52), 105 (31), 91 (24).

From 2-methyl-4-benzyl-1-tetralol (**10**), after 2.5 hr, a 96% yield of 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**13**) was obtained, mp 88–90°.[5]

From 2,2-dimethyl-4-benzyl-1-tetralol (**11**), after 24 hr, a yield of 70% of 1,8-dimethyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**14**) was obtained, bp 160° (1.5 mm). The product was

(22) All temperatures were uncorrected. The ir spectra were recorded on a Beckman IR-5A instrument. The nmr spectra were taken on a Varian A-60 or a Varian HA-100 instrument, using TMS as internal standard. The mass spectra were recorded on a CEC 21-491 instrument operated at 70 eV.

(23) R. M. Roberts and C.-E. Low, paper in preparation.

(24) Z. J. Vejdelek and B. Kakac, *Collect. Czech. Chem. Commun.*, **20**, 571 (1955).

(25) M. T. Bogert and D. Davidson, *J. Amer. Chem. Soc.*, **56**, 185 (1934).

(26) A glpc analysis of the crude reaction products showed, in addition to the bicyclization product, a 1-benzyl-1,2-dihydronaphthalene derivative, which had a shorter retention time.

purified by column chromatography, using a column of 32 × 3 cm packed with 100–200 mesh silica gel, and *n*-hexane as eluent: ir ν_{max}^{film} 3080, 2945, 1495, 758, 725, 700 cm^{-1}; nmr (100 MHz, CCl_4) δ 1.22 (d, J = 7.0 Hz, 3, CH_3), 1.35 (s, 3, CH_3), 1.59 and 1.72 (d, 1, CH), 2.04–2.13 (two sets of q, 1, CH), 2.50–2.88 and 3.10–3.33 (both m, 4, benzylic), and 6.64–7.27 ppm (m, 8, aromatic); mass spectrum *m/e* (rel intensity) 248 (100), 249 (24), 233 (70), 205 (27), 119 (26), 91 (9); mass, calcd for $C_{19}H_{20}$, 248.1565 (found, 248.1567).

Further Cyclodehydration Reaction of 4-Benzyl-1-tetralol (9).—(1) Water was distilled away from 3.0 ml of 85% phosphoric acid put into a small pear-shaped flask having a thermometer well, until the temperature rose to 240°. To this acid was then added 0.5 g of 4-benzyl-1-tetralol (9), and the temperature was kept at 230–240° for 20 min. Upon cooling, the reaction mixture was poured into a beaker of water. The organic layer was taken up in ether, washed, dried, and concentrated. Analysis by glpc, using a 10 ft × 0.125 in. column of Bentone-34 (5%) and SE-52 silicone gum rubber (5%) at 210° and nitrogen carrier gas at 60 psi, showed that the major product was **12**.

(2) A mixture of 1.0 g of 4-benzyl-1-tetralol (9) in 2.0 ml of 85% (by weight) H_2SO_4 was stirred magnetically at 105° for 3 hr. After working up, the same major product (**12**) was obtained by glpc analysis.

1-Benzyl-4,4-dimethyltetralin (30).—2-Methyl-5,6-diphenyl-2-hexanol (**29**) was first prepared by the Grignard reaction of methylmagnesium iodide with methyl γ,δ-diphenylvalerate, bp 130–132° (0.18 mm). Cyclodehydration of compound **29** gave 1-benzyl-4,4-dimethyltetralin (**30**): bp 109–110° (0.06 mm); $n^{23}D$ 1.5665; ir compatible with the structure; nmr (60 MHz, CCl_4) δ 1.20 (s, 3, CH_3), 1.31 (s, 3, CH_3), 1.52–1.88 (m, 4, CH_2CH_2), 2.51–3.11 (m, 3, benzylic), and 6.98–7.30 ppm (m, 9, aromatic); mass spectrum *m/e* (rel intensity) 251 (0.7), 250 (4), 182 (5), 159 (100), 145 (8), 117 (31), 91 (28); mass, calcd for $C_{19}H_{22}$, 250.1721 (found, 250.1722).

1-Benzyl-1-methyltetralin (32).—2-Methyl-1,5-diphenyl-2-pentanol (**31**), bp 110° (0.12 mm), was prepared by the reaction of 3-phenyl-*n*-propylmagnesium bromide with phenylacetone. Cyclodehydration[26] of compound **31** gave compound **32**: bp 84° (0.12 mm); ir compatible with the structure; nmr (60 MHz, $CDCl_3$) δ 1.21 (s, 3, CH_3), 1.32–1.85 (m, 4, CH_2CH_2), 2.50 (crude t, 2, ring benzylic), 2.82 (AB pattern, J = 12.0 Hz, 2, benzylic), and 6.85–7.25 ppm (m, 3, aromatic).

1,1-Dimethyl-4-phenyltetralin (34).—2-Methyl-5,5-diphenyl-2-pentanol (**33**), nmr (60 MHz, CCl_4) δ 1.05 (s, 6, CH_3), 2.00 (m, 2, CH_2), 2.50 (t, J = 7.2 Hz, 2, CH_2), 3.07 [s (broad), 1, OH], 3.75 (t, J = 7.2 Hz, 1, CH), 7.10 ppm (s, 10, aromatic), was first obtained by the Grignard reaction of CH_3MgI and methyl γ,γ-diphenylbutyrate: bp 188° (11 mm); nmr (60 MHz, neat) δ 2.15 (apparent t, J = 7.0 Hz, 2, CH_2), 2.52 (t, J = 7.0 Hz, 2, CH_2), 3.40 (s, 3, CH_3), 3.88 (t, J = 6.0 Hz, 1, CH), and 7.12 ppm (s, 10, aromatic). Cyclodehydration of **33** gave a 70% yield of **34**: ir compatible with the structure; nmr (60 MHz, $CDCl_3$) δ 1.28 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.52–2.10 (m, 4, CH_2CH_2), 4.02 (t, J = 6.5 Hz, 1, CH), and 6.76–7.38 ppm (m, 9, aromatic).[27]

1,1-Dimethyltetralin (36).—This compound was prepared by cyclodehydration[25] of 2-methyl-5-phenyl-2-pentanol (**35**), obtained by the Grignard reaction of methylmagnesium iodide with methyl 4-phenyl-*n*-butyrate. Compound **36** exhibited the following properties: bp 70° (6.0 mm) [lit.[28] bp 98° (10 mm)]; $n^{23}D$ 1.5255; ir compatible with the structure; nmr (60 MHz, $CDCl_3$) δ 1.22 (s, 6, 2 CH_3), 1.45–2.10 (m, 4, CH_2CH_2), 2.68 (t, J = 6.5 Hz, 2, benzylic), and 6.76–7.38 ppm (m, 4, aromatic).

Rearrangement of 2,3:6,7-Dibenzobicyclo[3.2.2]nona-2,6-diene (12) in $AlCl_3$.—The quantities of reactants employed and the methods used followed those of a reported procedure.[11] The results are recorded in Table I.

Registry No.—**9**, 38899-43-3; **10**, 38899-44-4; **11**, 38899-45-5; **12**, 23417-01-8; **13**, 31444-39-0; **14**, 38899-47-7; **16**, 38899-48-8; **23**, 38899-49-9; **29**, 38899-50-2; **30**, 38899-51-3; **31**, 34663-14-4; **32**, 38899-53-5; **33**, 38899-54-6; **34**, 13556-56-4; **35**, 2979-70-6; **36**, 1985-59-7; 4-benzyl-1-tetralone, 38899-63-7; 4-benzyl-2,2-dimethyl-1-tetralone, 38899-42-2; 4-benzyl-2-methyl-1-tetralone, 38899-65-9; methyl iodide, 74-88-4; methyl γ,δ-diphenylvalerate, 38899-66-0; 3-phenyl-*n*-propyl bromide, 637-59-2; phenylacetone, 103-79-7.

(27) D. L. Ransley, *J. Org. Chem.*, **31**, 3595 (1966).
(28) M. T. Bogert, D. Davidson, and P. M. Apfelbaum, *J. Amer. Chem. Soc.*, **56**, 959 (1934).

Synthesis and Mass Spectral Behavior of Representative 1,1-Dichloro-2-phenylcyclopropanes and 1,1-Dichloro-2-ferrocenylcyclopropanes

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1,1-Dichloro-2-ferrocenylcyclopropanes have been prepared in good yield by the addition of dichlorocarbene to vinylferrocenes under phase transfer catalysis conditions. The mass spectral fragmentation pattern of 1,1-dichloro-2-phenylcyclopropanes and of 1,1-dichloro-2-ferrocenylcyclopropanes are reported here and are found to be similar and quite simple.

1,1-Dichlorocyclopropanes have been of interest to organic chemists since Doering and Hoffmann's classic experiment.[1] Besides chloroform and base a variety of methods for generating dichlorocarbene have since been developed, including the decomposition of halomethylmercurials,[2] pyrolysis of trihaloacetate derivatives,[3] the base-induced decomposition of hexachloroacetone,[4,5] and others.[6,7]

The large number of dichlorocyclopropanes that have been synthesized notwithstanding, only a very limited amount of work has been reported on dichloro-

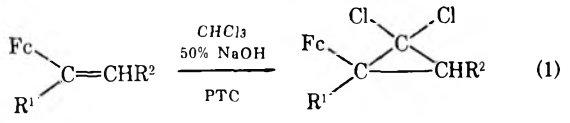
(1) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).
(2) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y. P. Mui, H. D. Simmons, Jr., A. J. H. Treibe, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).
(3) W. M. Wagner, H. Kloosterziel, and S. van der Ven, *Recl. Trav. Chim. Pays-Bas*, **81**, 925, 933 (1961).
(4) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960).
(5) F. W. Grant and W. B. Cassie, *J. Org. Chem.*, **25**, 1433 (1960).
(6) For a recent review see ref 7.
(7) W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971, p 129.

carbene adducts of vinylferrocenes. Such compounds are of interest, since it is well known that substituted ferrocene derivatives possessing a halogen or pseudohalogen α or β to the ferrocene nucleus are extremely labile.[8]

This property has made synthesis of these molecules both difficult and challenging. 1-Ferrocenylethyl chloride, for example, has been prepared only at low temperature, since it decomposes rapidly when warmed.[9] The even simpler compound ferrocenylmethyl chloride remains to be characterized, although it has been implicated in the synthesis of a ferrocenyl amino acid derivative.[10] Fitzgerald reported that 1,1-dichloro-2-ferrocenylcyclopropane was a notable exception to this instability–high reactivity pattern.[11] This is perhaps not surprising, since cyclopropyl halides are well known to solvolyze orders of magnitude more slowly than cyclohexyl halides.[12] This is due principally to two factors: the greater strength of the carbon–chlorine bond attributed to the greater s character of the carbon hybrid orbital forming the bond,[13,14] and strain developed in the ring ("*I*" stain) in going to a planar carbonium ion.[15,16]

Despite this unusual stability reported by Fitzgerald, the low yield (10%) he obtained[11] probably discouraged further work on these compounds. A communication by Horspool and Sutherland is the only other report of the preparation of 1,1-dichloro-2-ferrocencylcyclopropanes.[17] These workers used the thermal decomposition of sodium trichloroacetate in neutral solution to generate dichlorocarbene, which was trapped with vinylferrocenes in moderate (20–66%) yields.

We report here the high-yield synthesis of five representative 1,1-dichloro-2-ferrocenylcyclopropanes (eq 1) by the addition of dichlorocarbene generated by

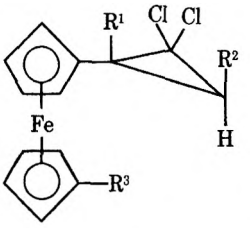


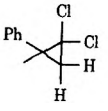
(1)

the phase transfer method to the corresponding vinylferrocenes (see Table I). Makosza and Wawrzyniewicz have shown that dichlorocarbene may be generated efficiently from chloroform and 50% aqueous sodium hydroxide in a heterogeneous system by use of the phase transfer catalyst (PTC) benzyltriethylammonium chloride (**1**), which is soluble in both the aqueous and organic phases.[18] Solution of **1** in the basic aqueous phase followed by anion exchange generates the benzyltriethylammonium hydroxide ion pair, which is soluble in the organic phase. Reaction of hydroxide ion with chloroform gives dichlorocarbene and regenerates **1**.[19] Similar results have been reported by Starks utilizing tetraalkylammonium salts[20] as well as by others.[21–23] We have utilized dichloromethane as a cosolvent to moderate the temperature of this highly exothermic reaction. The isolated yields of analytically pure recrystallized adducts were at least 70%. We believe that the lower temperature required to generate dichlorocarbene by the PTC method compared to those used to generate dichlorocarbene by sodium trichloroacetate pyrolysis[17] may explain our higher yields. In this connection, we have observed that 1,1-dichloro-*trans*-2-ferrocenyl-3-phenylcyclopropane is not stable even at 100° requiring care in recrystallization.

TABLE I

SYNTHESIS OF 1,1-DICHLORO-2-FERROCENYLCYCLOPROPANES UTILIZING THE PHASE TRANSFER CATALYSIS METHOD



Compd	R¹	R²	R³	Yield,[a] %
2	H	H	H	75
3	CH_3	H	H	75
4	Ph	H	H	70
5	H	Ph	H	97
6	Ph	H		71

[a] Yield of pure material.

A stringent test of the reaction's synthetic value was to use it on a diolefinic ferrocene. In this way, we have prepared 1,1′-bis(1-phenyl-2,2-dichlorocyclopropyl)ferrocene (**6**) from 1,1′-bis(α-styryl)ferrocene in 71% yield (after purification) by use of the PTC method.

Despite the broad interest in dichlorocarbene adducts, the only mass spectral data hitherto reported so far is for 1,1-dichloro-2-vinylcyclopropane.[24] We report here the mass spectra of a series of five 1,1-dichloro-2-ferrocenylcyclopropanes and compare them to the spectra of the corresponding 1,1-dichloro-2-phenylcyclopropanes.

The mass spectral fragmentation pattern of 1,1-dichloro-2-phenylcyclopropane (**7**) is outlined in Figure 1 (see Table II for supporting relative intensity and metastable data).[25] High-resolution data indicate that the elemental composition of the base

(8) M. Rosenblum, "Chemistry of the Iron Group Metallocenes," part 1, Wiley, New York, N. Y., 1965, p 136.
(9) W. P. Fitzgerald and R. A. Benkeser, *J. Org. Chem.*, **26**, 4179 (1967).
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(13) A. D. Walsh, *Discussions Faraday Soc.*, **2**, 18 (1947).
(14) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).
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(17) W. M. Horspool and R. G. Sutherland, *Chem. Commun.*, 456 (1966).
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(19) A. W. Herriott and D. Picker, *Tetrahedron Lett.*, 4521 (1972).
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(23) (a) W. P. Weber and G. W. Gokel, *Tetrahedron Lett.*, 1637 (1972); (b) W. P. Weber, G. W. Gokel, and I. K. Ugi, *Angew. Chem., Int. Ed. Engl.*, **11**, 530 (1972).
(24) M. C. Hamming, *Arch. Mass Spectral Data*, **1**, 766 (1970).
(25) Complete mass spectral data has been submitted to the Mass Spectrometry Data Centre, Atomic Weapons Research Establishment, Aldermaston, Berkshire, England. Relative intensity data reported for peaks containing chlorine are the sum of the intensities of the P plus the P + 2 ions.

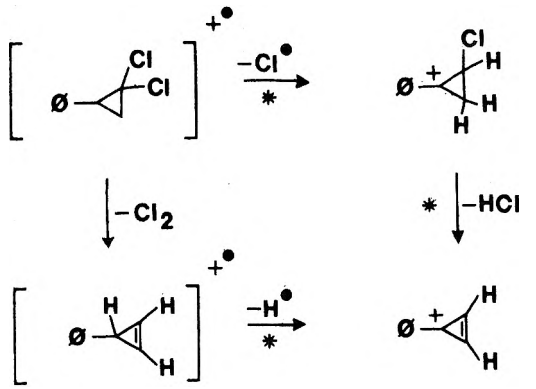

Figure 1.—Mass spectral fragmentation pattern of 1,1-dichloro-2-phenylcyclopropane.

TABLE II
MASS SPECTRAL DATA AT 70 eV FOR 1,1-DICHLOROPHENYLCYCLOPROPANES 7 AND 8

	1,1-Dichloro-2-phenylcyclopropane (7)		1,1-Dichloro-2-methyl-2-phenylcyclopropane (8)	
	Rel intensity	m*	Rel intensity	m*
Parent	47.3		37.0	
P − Cl	80.5	122.6	80.0	136.4
P − Cl_2	43.8		17.0	
[P − Cl] − CH_4			39.0	134.8
[P − Cl] − HCl	100.0	87.4	100.0	100.8 br

peak is C_9H_7.[26] It is not surprising that this peak at mass 115 is intense, since a possible structure for this ion is a phenyl-substituted cyclopropenium cation: a 2-π-electron system which is expected to be particularly stable from the known solution chemistry of these cations.[27-29]

The mass spectrum of 1,1-dichloro-2-methyl-2-phenylcyclopropane (**8**) is quite similar (see Table II). The base peak at mass 129 has an elemental composition of $C_{10}H_9$.[30] A possible structure for this ion is a cyclopropenium cation substituted by phenyl and methyl groups. One new fragmentation process is observed. Loss of CH_4 from the P − Cl ion leads to a pair of ions of mass 149 and 151. A possible structure for these ions is a cyclopropenium cation substituted by a chlorine atom and a phenyl group.

The mass spectrum of 1,1-dichloro-2,2-diphenylcyclopropane (**9**) is somewhat different (see Table III).

TABLE III
MASS SPECTRAL DATA AT 70 eV FOR 1,1-DICHLORODIPHENYLCYCLOPROPANES 9 AND 10

	1,1-Dichloro-2,2-diphenylcyclopropane (9)		1,1-Dichloro-*trans*-2,3-diphenylcyclopropane (10)	
	Rel intensity	m*	Rel intensity	m*
Parent	63.0		3.1	
P − Cl	100.0	196.6	31.7	196.6
P − Cl_2	31.8		23.5	
[P − Cl] − HCl	86.0	160.5	86.7	160.5
[P − Cl] − C_6H_6	85.4	98	100.0	98
[P − Cl − HCl] − H_2	18.3	187.2	29.4	187.2
[P − Cl − HCl] − C_2H_2	40.8	142.5	27.9	142.5

(26) Calculated for C_9H_7, 115.0546; observed, 115.0537.
(27) R. Breslow and H. Chang, *J. Amer. Chem. Soc.*, **83**, 2367 (1961).
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(29) R. Breslow and J. T. Groves, *J. Amer. Chem. Soc.*, **92**, 984 (1970).
(30) Calculated for $C_{10}H_9$, 129.0702; observed, 129.076.

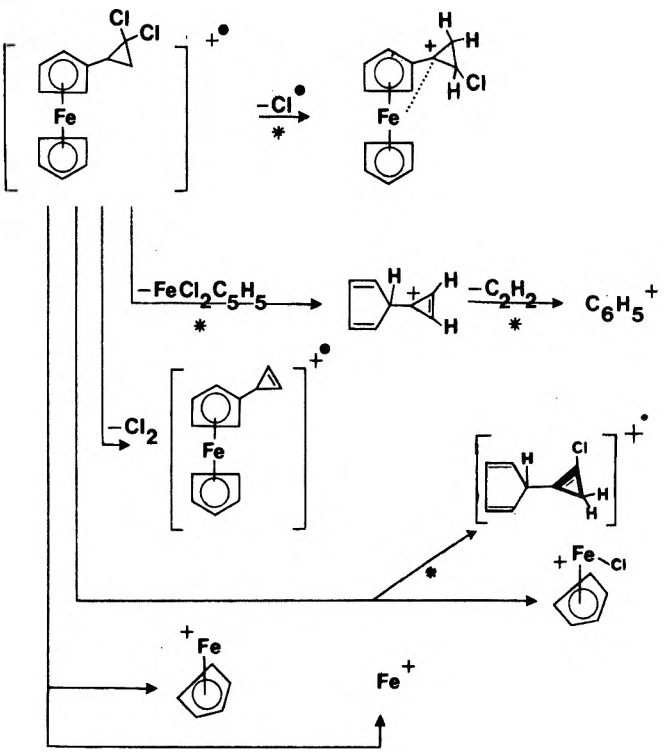

Figure 2.—Mass spectral fragmentation pattern of 1,1-dichloro-2-ferrocenylcyclopropane.

The P − Cl ion is the base peak. Loss of HCl from the P − Cl ion leads to an ion of mass 191 (elemental composition $C_{15}H_{11}$).[31] A possible structure for this ion is the diphenylcyclopropenium cation. The ion of mass 191 further fragments by loss of C_2H_2 to form an ion of mass 165. It also fragments by loss of H_2 to form an ion of mass 189. The P − Cl ion fragments by loss of C_6H_6 to form a pair of ions of mass 149 and 151 as in the spectrum of **8** above.

1,1-Dichloro-*trans*-2,3-diphenylcyclopropane (**10**) fragments in the mass spectrometer in essentially the same way. However, the relative intensities of various fragment ions are quite different. The pair of ions of mass 149 and 151 are the base peak as above.

The mass spectral fragmentation pattern of 1,1-dichloro-2-ferrocenylcyclopropane (**2**) is outlined in Figure 2 (see Table IV). In addition to the parent, P − Cl, and P − Cl_2 ions, fragmentation pathways characteristic of ferrocene compounds are observed,[32,33] including the ion at mass 56 due to Fe^+ and the iron cyclopentadienyl cation at mass 121.[34] Chloro iron cyclopentadienyl cations are observed as a pair at mass 156 and 158. A pair of related ions in which charge is retained by the cyclopropyl-substituted cyclopentadiene ring at mass 138 and 140 is observed (P − $FeClC_5H_5$). The base peak is found at mass 103 (elemental composition C_8H_7).[35] A possible structure for this ion is a cyclopentadiene-substituted cyclopropenium cation. A metastable peak indicates that it is formed directly from the parent ion by loss of $FeCl_2C_5H_5$.

(31) Calculated for $C_{15}H_{11}$, 191.0858; observed, 191.0753.
(32) L. Friedman and G. Wilkinson, *J. Amer. Chem. Soc.*, **77**, 3689 (1955).
(33) D. W. Slocum, R. Lewis, and G. J. Mains, *Chem. Ind. (London)*, 2095 (1966).
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(35) Calculated for C_8H_7, 103.0546; observed, 103.0504.

TABLE IV

MASS SPECTRAL DATA AT 70 eV FOR 1,1-DICHLORO-2-FERROCENYLCYCLOPROPANES 2 AND 3

	1,1-Dichloro-2-ferroeenylcyclopropane (2)		1,1-Dichloro-2-methyl-2-ferrocenylcyclopropane (3)	
	Rel intensity	m*	Rel intensity	m*
Parent	32.2		38.7	
P − Cl	6.1	228.2	3.0	
P − HCl			3.6	
P − Cl_2	8.2		11.3	
P − C_5H_5FeCl	4.9	64.9	18.3	75.0
P − $C_5H_5Cl_2Fe$	100.0	36.2	100.0	44.4
[P − $C_5H_5Cl_2Fe$] − C_2H_2	27.0	57.6	29.0	70.6
[P − $C_5H_5Cl_2Fe$] − H_2			58.0	113.0
C_5H_5FeCl	18.9		9.0	
C_5H_5Fe	6.7		15.3	
Fe	14.4		54.4	

The ion of mass 103 further fragments by loss of C_2H_2 to form an ion of mass 77.

The mass spectrum of 1,1-dichloro-2-methyl-2-ferrocenylcyclopropane (3) is similar (see Table IV) to the nonmethylated derivative discussed above. The base peak is observed at mass 117 (elemental composition C_9H_9).[36] A reasonable structure for this ion is a cyclopropenium cation substituted by methyl and cyclopentadiene residues. Loss of H_2 from the base peak leads to the ion of mass 115. The base peak also fragments by loss of C_2H_2 to form the ion of mass 91.

The mass spectrum of 1,1-dichloro-*trans*-2-phenyl-3-ferrocenylcyclopropane (5) is different (see Table V). In addition to the P − Cl, P − HCl, and P − Cl_2 ions, the parent ion also fragments by loss of $FeClC_5H_5$ to yield a pair of ions of mass 214 and 216. Phenyl substitution appears to favor charge retention in the substituted cyclopentadienyl ring. The parent ion also fragments by loss of $FeCl_2C_5H_5$ in a single step to yield the base peak at mass 179 (elemental composition $C_{14}H_{11}$),[37] whose structure may be a cyclopropenium cation substituted by cyclopentadiene and phenyl groups. Loss of a hydrogen atom from the ion of mass 179 leads to an ion of mass 178 (elemental composition $C_{14}H_{10}$)[38] whose structure may be a phenyl-substituted calicene cation radical.[39] The ion of mass 178 further fragments by loss of C_2H_2 to form an ion of mass 152.

TABLE V

MASS SPECTRAL DATA AT 70 eV FOR 1,1-DICHLOROPHENYLFERROCENYLCYCLOPROPANES

Ion	1,1-Dichloro-*trans*-2-phenyl-3-ferrocenylcyclopropane (5)		1,1-Dichloro-2-phenyl-2-ferrocenylcyclopropane (4)	
	Rel intensity	m*	Rel intensity	m*
Parent	19.4		55.9	
P − Cl	3.2		8.4	
P − HCl	6.1		13.1	
P − Cl_2	44.8		9.5	
P − HCl_2	6.0		10.7	
P − CCl_2	11.9		4.8	
P − $HCl_2C_5H_5$	14.9			
P − $FeClC_5H_5$	13.5	123.9	17.9	123.9
P − $FeCl_2C_5H_5$	100.0	86.6	100.0	86.6
[P − $FeCl_2C_5H_5$] − H	80.6	177, 135.4	95.0	177, 135.4
[P − $FeCl_2C_5H_5$ − H] − C_2H_2	17.9	129.8	23.8	129.8
C_5H_5Fe	14.9		13.1	
Fe	28.4		19.0	

The relative intensities of some fragment ions in the mass spectrum of 1,1-dichloro-2-phenyl-2-ferrocenylcyclopropane (4) are quite different compared to those of 1,1-dichloro-*trans*-2-phenyl-3-ferrocenylcyclopropane (5), but no new fragment ions are observed. The base peak is at mass 179 (elemental composition $C_{14}H_{11}$)[40] while the ion of mass 178 (elemental composition $C_{14}H_{10}$)[41] is almost equally intense.

The mass spectrum of 1,1′-bis(1-phenyl-2,2-dichlorocyclopropyl)ferrocene (6) is quite simple (see Table VI). Three ions dominate the entire spectrum. The cluster of peaks associated with the parent ion, the ion of mass 179 (elemental composition $C_{14}H_{11}$),[42] and the ion of mass 178 (elemental composition $C_{14}H_{10}$)[43] are all of almost equal intensity.

TABLE VI

MASS SPECTRAL DATA AT 70 eV FOR 1,1′-BIS(1-PHENYL-2,2-DICHLOROCYCLOPROPYL)FERROCENE (6)

m/e	Rel intensity	m*
Parent[a]	75.5	
216	8.3	
215	12.3	
214	25.0	
213	15.3	
179	100.0	57.9
178	100.0	177.0
152	25.0	129.8

[a] Relative intensity is sum of peaks associated with the parent ion.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrometer either neat or in chloroform solution and were calibrated against polystyrene film. Nmr spectra were run on a Varian T-60 or HA-100 using 5–10% solutions. TMS was used as the internal standard. Mass spectra were determined on a AEI MS-902 instrument under the following conditions: ionizing voltage 70 eV; filament emission 480 μA; source temperature 100°. Exact mass determinations of the composition of certain important ions were carried out at a resolution of 10,000 by peak matching with peaks of known mass of perfluorokerosene. Microanalysis was done by Elek Microanalytical Laboratory.

All chemicals used were reagent grade. The hexane used for chromatography was redistilled Skellysolve B. Merck alumina was used for chromatography. The phase transfer catalyst used was benzyltriethylammonium chloride (TEBAC).

1,1-Dichloro-2-phenylcyclopropane (7) was synthesized by reaction of styrene with dichlorocarbene generated by the PTC method in 85% yield.[18] The product was purified by distilla-

(36) Calculated for C_9H_9, 117.0702; observed, 117.0674.

(37) Calculated for $C_{14}H_{11}$, 179.0858; observed, 179.0780.

(38) Calculated for $C_{14}H_{10}$, 178.0780; observed, 178.0755.

(39) M. Cais and A. Eisenstadt, *J. Amer. Chem. Soc.*, **89**, 5468 (1967).

(40) Calculated for $C_{14}H_{11}$, 179.0858; observed, 179.0798.

(41) Calculated for $C_{14}H_{10}$, 178.0780; observed, 178.0737.

(42) Calculated for $C_{14}H_{11}$, 179.0858; observed, 179.0869.

(43) Calculated for $C_{14}H_{10}$, 178.0780; observed, 178.0807.

tion: bp 90° (0.5 mm) [lit. bp 78–83° (2 mm)].[44] Its spectral properties were in agreement with literature values.[45]

1,1-Dichloro-2,2-diphenylcyclopropane (9) was prepared by reaction of 1,1-diphenylethylene with dichlorocarbene under phase transfer catalysis conditions in 70% yield:[18] mp 111–112° (lit. mp 115–116°);[46] pmr (100 MHz, $CDCl_3$ δ 2.21 (s, 2 H), 7.26 (m, 10 H).

1,1-Dichloro-*trans*-2,3-diphenylcyclopropane (10) was prepared by reaction of *trans*-stilbene with dichlorocarbene under phase transfer catalysis conditions in 60% yield.[18] The crude reaction product was distilled at 130° (0.2 mm). After distillation, the product crystallized, mp 39–41° (lit. mp 39–40°).[2] Its spectral properties were in agreement with literature values.[2]

1,1-Dichloro-2-methyl-2-phenylcyclopropane (8) was prepared by reaction of α-methylstyrene with dichlorocarbene under phase transfer catalysis conditions in 71% yield.[18] The product was purified by distillation, bp 50° (0.15 mm) [lit. bp 75–77° (1 mm)].[44] Its spectral properties were in agreement with literature values.[2]

1,1-Dichloro-2-ferrocenylcyclopropane (2).—A 500-ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with vinylferrocene[47] (4.5 g, 0.021 mol), $CHCl_3$ (25 ml), 50% aqueous NaOH solution (30 ml), CH_2Cl_2 (100 ml), and finally TEBAC (1 g). The reaction mixture was stirred and spontaneous reflux ensued. The stirring was continued for about 1 hr after reflux had ceased. The reaction mixture was then poured into 200 ml of ice–water and the layers were separated. The organic layer was washed with water, dried over $MgSO_4$, and filtered, and the solvents were removed by evaporation under reduced pressure. The crude product was chromatographed over alumina (150 g). The desired cyclopropane (5.2 g, 88% yield) was eluted with hexane. It was recrystallized from *n*-heptane to give lemon-yellow crystals (4.5 g, 75% yield): mp 81–82° (lit. mp 83–84°);[11] pmr (100 MHz, $CDCl_3$) δ 1.47 (d of d, 1 H, J_{AX} = 8.4, J_{AB} = 7 Hz), 1.87 (d of d, 1 H, J_{AB} = 7, J_{BX} = 11.2 Hz) and 2.59 (d of d, 1 H, J_{AX} = 8.4, J_{BX} = 11.2 Hz, cyclopropane protons), 4.16 (s, 5 H, C_5H_5), 4.00 (m, 4 H), 4.34 (C_5H_4).

2-Ferrocenylpropene.—A 250-ml three-necked round-bottomed flask was charged with phosgene (3.0 g, 0.03 mol), triethylamine (6.0 g, 0.06 mol), and ether (75 ml). The solution was cooled to 0° and 2-ferrocenyl-2-propanol[48] (7.1 g, 0.025 mol) in ether (50 ml) was added dropwise with stirring. The reaction mixture was maintained at 0° for 30 min. It was then allowed to warm to ambient temperature during *ca.* 1.5 hr, at which time no further CO_2 evolution was observed [$Ba(OH)_2$ solution]. The mixture was then poured onto ice (100 g) and water (100 g). A small amount of $Na_2S_2O_4$ was added, and the layers were separated. The ether layer was washed with 5% NaOH (200 ml), water (5 × 200 ml), and brine (200 ml) and finally dried over K_2CO_3. Evaporation of the solvent under reduced pressure left 5.7 g of a brown oil, which was chromatographed on silica gel (Baker 3405, 120 g, 3.5 × 32 cm). Elution with petroleum ether (bp 30–60°)–acetone (4:1, v/v) gave 2.5 g of 2-ferrocenylpropene in the first fraction, and continued elution gave residual starting material (3.1 g): yield (based on unrecovered starting material) 57%; mp 64–66° (lit. mp 66–69°);[49] pmr (100 MHz, CS_2) δ 1.96 (m, 3 H, CH_3), 3.88 (s, 5 H, C_5H_5), 4.00 (t, 2 H) and 4.16 (t, 2 H), (C_5H_4), 4.70 (m, 1 H) and 4.96 (m, 1 H) (=CH_2).

1,1-Dichloro-2-methyl-2-ferrocenylcyclopropane (3).—A 500-ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with 2-ferrocenylpropene (1.8 g, 0.0082 mol), $CHCl_3$ (10 ml), CH_2Cl_2 (100 ml), 50% aqueous NaOH solution (50 ml), and finally 1 g of TEBAC catalyst. Stirring was commenced and the reaction mixture was warmed. The reaction mixture was stirred for *ca.* 2 hr after the exotherm ceased. The reaction was worked up as described previously. The product was chromatographed over alumina; elution with Skelly B, followed by recrystallization from *n*-heptane, gave the cyclopropane as a yellow-orange solid (1.6 g, 75% yield), mp 93.5–94.5°. *Anal.* Calcd for $C_{14}H_{14}FeCl_2$: C, 54.41; H, 4.57; Cl, 22.95. Found: C, 54.33; H, 4.45; Cl, 22.93. Pmr (100 MHz, $CDCl_3$): δ 1.47 (d, 1 H) and 1.70 (d, 1 H) (geminal protons, J_{AB} = 7.5 Hz), 1.78 (s, 3 H, CH_3), 3.97, 4.15, 4.27 (pseudo t, 9 H) (ferrocene protons).

Ferrocenylbenzyl Ketone.—A 500-ml erlenmeyer flask equipped with a magnetic stirring bar and a nitrogen inlet was charged with ferrocene (37.2 g, 0.2 mol), phenylacetyl chloride (31 g, 0.2 mol), and dry CH_2Cl_2 (200 ml). The flask was immersed in an ice bath and aluminum trichloride (28.4 g, 0.22 mol) was added in six equal portions. The mixture turned from brown to wine red and was stirred for 2 hr while warming to ambient temperature. The reaction mixture was poured onto cracked ice. The phases were separated and the aqueous phase was washed once with CH_2Cl_2 (200 ml). The combined organic material was washed with 200 ml each of 10% NaOH solution, water, and brine and then dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a light red powder, 53.4 g (87.5% yield). A small sample was chromatographed over alumina to remove residual ferrocene from the product: mp 128–129° (lit. mp 130°);[50] pmr (100 MHz, CS_2) δ 3.74 (s, 2 H), $-CH_2-$), 3.90 (s, 5, H, C_5H_5), 4.28 (t, 2 H), 4.58 (t, 2 H), 7.14 (s, 5 H, C_6H_5).

1-Ferrocenyl-2-phenylethanol.—Ferrocenylbenzyl ketone (17 g, 0.056 mol) was stirred for 3 hr at ambient temperature with $NaBH_4$ (5.0 g, 0.132 mol) in 500 ml of 95% ethanol. The product was isolated in the normal fashion: yield 15 g (82%); mp 62–63° (lit. mp 64°);[50] pmr (100 MHz, CS_2) δ 1.89 (s, 1 H, –OH), 2.65 (d, 2 H, *J* = 6.4 Hz, $-CH_2-$), 3.96 (s, 9 H, $C_{10}H_9Fe$), 4.35 (t, 1 H, *J* = 6.4 Hz, –CH–), 7.01 (m, 5 H, C_6H_5).

***trans*-2-Ferrocenylstyrene**.—A 500-ml round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet was charged with 1-ferrocenyl-2-phenylethanol (10 g, 0.0326 mol) and 100 ml of dry benzene. Powdered PCl_5 (10 g) was added in one portion, whereupon the benzene solution refluxed vigorously for 15 min. When the reflux had ceased, the reaction mixture was quenched with aqueous sodium carbonate solution. A small amount of sodium dithionite was added to reduce any ferrocinium ion present, and the product was extracted with ether. The organic material was washed several times with water, then dried over $MgSO_4$, and the solvents were removed by evaporation under reduced pressure. The residue was chromatographed over alumina; the product was eluted with Skelly B, yield 6 g (64%), red-orange solid, mp 119–120° (lit. mp 120–122°).[51,52] The olefin was presumed to be the trans isomer on the basis of the vinylic coupling constant, *J* = 17 Hz; pmr (60 MHz, CS_2) δ 3.96 (s, 5 H, C_5H_5), 4.08 (t, 2 H) and 4.26 (t, 2 H) (C_6H_4), 6.36 (d, 1 H) and 6.66 (d, 1 H) (vinyl protons, J_{AB} = 17 Hz), 7.11 (m, 5 H, C_6H_5).

1,1-Dichloro-*trans*-2-phenyl-3-ferrocenylcyclopropane (5).—A 500-ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with *trans*-2-ferrocenylstyrene (2.0 g, 0.007 mol), $CHCl_3$ (10 ml), CH_2Cl_2 (100 ml), 50% aqueous KOH solution (20 ml), and finally 1 g of TEBAC catalyst. The reaction mixture was stirred and began to spontaneously reflux. Stirring was continued for *ca.* 2 hr after reflux had ceased and the solution was worked up as described previously. The crude product was chromatographed over alumina; elution with Skelly B gave 2.6 g (97%) of a red-orange solid, mp 101.5–102.5°. *Anal.* Calcd for $C_{19}H_{16}FeCl_2$: C, 61.50; H, 4.35; Cl, 19.11. Found: C, 61.60; H, 4.41; Cl, 18.94. Pmr (100 MHz, $CDCl_3$): δ 2.89 (s, 2 H, cyclopropane protons), 4.15 and 4.43 (pseudodoublet, 9 H, ferrocene protons), 7.38 (s, 5 H, C_6H_5).

1-Ferrocenylstyrene.—To a solution of triphenylmethylphosphonium iodide (40.4 g, 0.1 mol) in THF (600 ml) was added with stirring a solution of *n*-butyllithium (50 ml, 2.1 *M* in *n*-hexane). Ferrocenophenone[51] (29 g, 0.1 mol) was added as a solid. After the reaction was over, the solution was hydrolyzed and the product was isolated by chromatography over alumina. The olefin eluted with *n*-hexane to give a red-brown oil (21.4 g, 74%): pmr (60 MHz, CCl_4) δ 4.04 (s, 5 H, C_5H_5), 4.16 (t, 2 H) and 4.27 (t, 2 H) (C_5H_4), 5.12 (d, 1 H) and 5.51 (d, 1 H, J_{AB} = 2 Hz), 7.33 (m, 5 H, C_6H_5). The base peak in the mass spectrum of 1-ferrocenylstyrene is the parent ion at *m/e* 288.

1,1-Dichloro-2-phenyl-2-ferrocenylcyclopropane (4).—A 500-

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(52) P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 2990 (1963).

ml round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with 1-ferrocenylstyrene (2.0 g, 0.007 mol), $CHCl_3$ (14 g, 0.12 mol), 50% NaOH solution (50 ml), CH_2Cl_2 (200 ml), and finally 1 g of TEBAC catalyst. The reaction mixture was stirred for *ca.* 5 hr, during which time a mild exotherm was noted. The reaction mixture was worked up as described previously and the crude product was chromatographed over alumina. Elution with Skelly B afforded 2.25 g of the cyclopropane, which was recrystallized from *n*-heptane to give 1.79 g (70%) of a red-orange solid melting at 124–125°. *Anal.* Calcd for $C_{19}H_{16}FeCl_2$: C, 61.50; H, 4.35; Cl, 19.11. Found: C, 61.53; H, 4.32; Cl, 18.97. Pmr (100 MHz, $CDCl_3$): δ 2.07 (d, 1 H) and 2.18 (d, 1 H) (*gem*-protons, J_{AB} = 7.5 Hz), 3.91 (s, 5 H, C_5H_5), 4.04 (m, 2 H) and 4.12 (m, 2 H) (C_5H_4), 7.44 (s, 5 H, C_6H_5).

1,1′-Bis(α-styryl)ferrocene.—A 500-ml three-necked flask equipped with a stirrer, a reflux condenser, an addition funnel, and a N_2 inlet was charged with triphenylmethylphosphonium iodide (33 g, 0.08 mol) and 200° ml of THF. A solution of *n*-butyllithium (40 ml, 2.1 *M* in hexane) was added and the mixture was stirred for *ca.* 10 min. A solution of 1,1′-dibenzoylferrocene[53] (15.6 g, 0.04 mol) in 100 ml of THF was added dropwise. Stirring was continued for 1 hr before hydrolyzing with water. The crude product was chromatographed over neutral alumina (Merck) using Skelly B as eluent: yield 4.0 g (25%) of a red-brown oil; pmr (60 MHz, CS_2) δ 3.95 (t, 4 H, J = 4 Hz), 4.05 (t, 4 H, J = 4 Hz, C_5H_4), 5.03 (d, 2 H, J_{AB} = 2.2 Hz), 5.32 (d, 2 H, J_{AB} = 2.2 Hz), 7.17 (m, 10 H). The base peak in the mass spectrum of 1,1′-bis(α-styryl)ferrocene is the parent ion at *m/e* 390.

(53) M. Rausch, M. Vogel, and H. Rosenburg, *J. Org. Chem.*, **22**, 903 (1957).

1,1′-Bis(1-phenyl-2,2-dichlorocyclopropyl)ferrocene (6).—A 250-ml round-bottomed flask equipped with a stirring bar and a reflux condenser was charged with 1,1′-bis(α-styryl)ferrocene (1.5 g, 0.00384 mol), CH_2Cl_2 (40 ml), $CHCl_3$ (10 ml), 50% aqueous NaOH (20 ml), and finally 0.5 g of TEBAC catalyst. After stirring for *ca.* 5 hr, the reaction mixture was diluted with water and worked up as described previously. The crude product was chromatographed over Merck neutral alumina; elution with Skelly B, followed by recrystallization from *n*-heptane, afforded a yellow-orange solid (1.5 g, 71%). *Anal.* Calcd for $C_{28}H_{22}FeCl_4$: C, 60.47; H, 3.99. Found: C, 60.80; H, 4.05. The compound blackens at ~145°, but is not a mobile liquid below 260°. Pmr (100 MHz, CS_2): δ 1.56 (d, 2 H) and 1.82 (d, 2 H) (cyclopropane protons, J_{AB} = 7.50 Hz), 3.52 (m), 3.62 (m), and 3.75 (m) (total 8 H, C_5H_4), and 7.29 (s, 10 H, C_6H_5).

Registry No.—**2**, 12085-73-3; **3**, 12087-46-6; **4**, 38856-04-1; **5**, 38856-05-2; **6**, 38856-06-3; **7**, 2415-80-7; **8**, 3591-42-2; **9**, 3141-42-2; **10**, 33044-82-5; 2-ferrocenylpropene, 31725-14-1; 2-ferrocenyl-2-propanol, 12093-87-7; ferrocenylbenzyl ketone, 1277-72-1; ferrocene, 102-54-5; 1-ferrocenyl-2-phenylethanol, 12094-28-9; *trans*-2-ferrocenylstyrene, 1272-54-4; 1-ferrocenylstyrene, 35126-64-8; ferrocenophenone, 1272-44-2; 1,1′-bis(α-styryl)ferrocene, 38856-13-2; 1,1′-dibenzoylferrocene, 12180-80-2.

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Organometallic Derivatives of Cymantrene. The Formation of (Fulvalene)hexacarbonyldimanganese[1]

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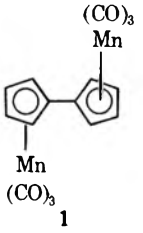
Cymantrene (2) has been found to undergo facile mercuration by reaction with mercuric acetate in the presence of perchloric acid. Chloromercuricymantrene (3) has been converted into a variety of organomanganese derivatives, including cymantrenylmagnesium iodide (8), cymantrenyllithium (10), cymantrenylferrocene (6), and (fulvalene)hexacarbonyldimanganese (1). Complex 1 undergoes Friedel–Crafts acetylation to produce (3-acetylfulvalene)hexacarbonyldimanganese (11).

A recent communication by us[2] reported the synthesis and properties of (fulvalene)hexacarbonyldimanganese (1), one of the first examples in which



1

fulvalene serves as the sole π ligand in an organo transition metal complex.[3] We now wish to describe in detail the preparation of a number of novel organometallic derivatives of cymantrene (2), their utilization as intermediates in the synthesis of 1, and the results of preliminary studies regarding the reactivity of 1 toward electrophilic substitution.[4]

During the course of our studies in cymantrene chemistry it became necessary for us to prepare substantial quantities of the monochloromercuri derivative (3). We were unable in several attempts to reproduce the original direct mercuration procedure described for cymantrene (2),[8] but were successful in reproducing a four-step procedure described by Cais.[9] The latter method was tedious, however, and resulted in low overall yields of product (24% yield of 3 starting

(1) Presented in part at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 9–13, 1968, Abstracts INOR-088.

(2) M. D. Rausch, R. F. Kovar, and C. S. Kraihanzel, *J. Amer. Chem. Soc.*, **91**, 1259 (1969).

(3) For another example of a fulvalene–transition metal π complex, see F. L. Hedberg and H. Rosenberg, *J. Amer. Chem. Soc.*, **91**, 1258 (1969); see also ref 2.

(4) After our program in this area had been completed,[1] the isolation of 1 from (a) the halogenation of triphenylphosphinegoldcymantrene;[5] (b) the reaction of cymantreneboronic acid with copper acetate;[6] and (c) the coupling of cymantrenylmagnesium iodide (8) with cobalt(II) chloride[7] was independently reported.

(5) A. N. Nesmeyanov, K. I. Gandberg, and T. V. Baukova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2032 (1969).

(6) A. N. Nesmeyanov, V. A. Sazonova, and N. N. Sedlova, *Dokl. Akad. Nauk SSSR*, **194**, 825 (1970).

(7) H. Egger and A. Nikiforov, *Monatsh. Chem.*, **100**, 1069 (1969).

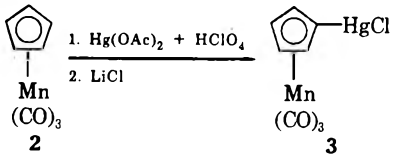
(8) A. N. Nesmeyanov, K. N. Anisimov, and E. P. Valueva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1683 (1962).

(9) N. Cais and J. Kozikowski, *J. Amer. Chem. Soc.*, **82**, 5667 (1960).

from 2). An investigation was therefore begun to develop a more convenient and reliable synthetic route to 3.

Results and Discussion

Cymantrene (2) was found to undergo facile reaction with mercuric acetate *in the presence of perchloric acid.*[10] Treatment of the resulting acetoxymercuri derivative with lithium chloride produced chloromercuricymantrene (3) in 53% yield. The marked effect of perchloric

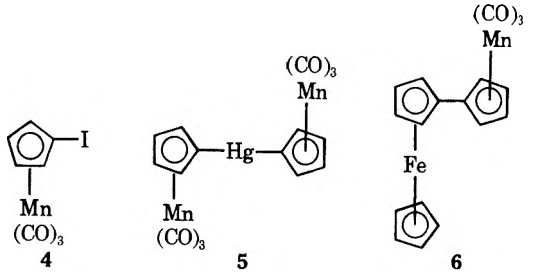


2 3

acid in promoting the mercuration reaction was illustrated by treating 2 with mercuric acetate in the absence of catalyst. Analysis of the reaction mixture by thin layer chromatography indicated the presence of only trace amounts of mercurated product.

A purification procedure was devised which facilitated step-by-step removal of the by-products and unreacted starting material from the crude reaction product. Thus, washing the methylene chloride solution of the crude product with water removed the inorganic salts present, while extraction of the residue from that solution with benzene and subsequent filtration through a dry column of Florisil removed polymercuration products. Evaporation of the benzene eluent and extraction of the residue with hexane removed substantial amounts of unreacted 2. Finally, recrystallization of the residue from methylene chloride–hexane afforded a pure crystalline product which was identical with 3 prepared by the method of Cais.[9] Small amounts of a polymercurated product were obtained by eluting the Florisil column with acetone. The material appeared to be bis(chloromercuri)cymantrene, but attempts at characterization were not completely successful.

Chloromercuricymantrene (3) reacted with iodine in methylene chloride solution to form a dark soluble complex. Iodocymantrene (4) was obtained in 84%



4 5 6

yield by shaking a solution of the complex with aqueous sodium thiosulfate and by chromatographing the crude product on a dry column of Florisil. Attempts to prepare bromocymantrene by treatment of 3 with either bromine or *N*-bromosuccinimide resulted in decomposition of 3 and evolution of carbon monoxide.

Dicymantrenylmercury (5) was prepared according to the procedure reported by Nesmeyanov, *et al.*,[8] by treatment of 3 with aqueous sodium thiosulfate, the yield being nearly quantitative. The physical properties of recrystallized material compared favorably with those reported by Cais.[9] An ir spectrum of 5 was virtually identical with that obtained for 3, exhibiting absorptions due to the terminal carbonyl groups at 2010 and 1900 cm^{-1}.

Our initial attempts to extend the Ullmann biaryl reaction to iodocymantrene (4) were unsuccessful. Reaction of 4 with activated copper bronze[11] yielded cymantrene (2) as the only product. Modification of the procedure by the use of copper–(Zn) powder,[12] however, afforded (fulvalene)hexacarbonyldimanganese (1) in 21% yield. The product was separated from a large amount of hydrogenated product cymantrene (2) by dry column chromatography on Florisil. The first band to be eluted contained 2 as identified by its ir spectrum. Further elution of the column yielded a second band which afforded the desired product (1). The nmr spectrum of 1 exhibited an A_2B_2 pattern, with two sets of triplets centered at τ 5.04 (four α protons) and 5.26 (four β protons). The α protons were deshielded with respect to cymantrene, while the β protons were virtually unaffected. Thus, a cymantrenyl group exerts a deshielding effect in 1 similar to that observed for a ferrocenyl group in biferrocene.[11] The ir spectrum exhibited strong absorptions at 2000 and 1925 cm^{-1} assigned to the terminal carbonyl substituents.

Attempts to prepare the unsymmetrical product cymantrenylferrocene (6) by a mixed Ullmann reaction of 4 with iodoferrocene were unsuccessful, the products being largely biferrocene and 2, together with small amounts of 1.

(Fulvalene)hexacarbonyldimanganese (1) was also formed in 67% yield when 5 was heated at 265° in the presence of silver powder. The temperature of the reaction was found to be a critical factor in determining the yield of product obtained. Thus, when the pyrolysis was run at 230°, cymantrene (2) was the only product obtained. This result is in agreement with an earlier finding that the yield of biferrocene obtained from the pyrolysis of diferrocenylmercury in the presence of silver varies greatly with the reaction temperature.[13]

Pyrolysis of a mixture of diferrocenylmercury (7) and dicymantrenylmercury (5) in the presence of silver powder yielded a substantial amount (39%) of the mixed product, cymantrenylferrocene (6), together with the symmetrical coupling products biferrocene and 1.

Shechter and Helling prepared the ferrocenyl Grignard reagent by the reaction of a mixture of ethylene bromide and bromoferrocene with powdered magnesium in tetrahydrofuran solution.[14] This reaction has now been successfully extended to the cymantrene system, the cymantrenyl Grignard reagent (8) being formed in moderate yield. Treatment of a mixture of ethylene bromide and iodocymantrene (4) (2:1 molar ratio) with powdered magnesium in tetrahydrofuran solution produced a dark reaction mixture. Carbonation of the solution thus formed and subsequent

(10) A. J. Kresg, M. Dubeck, and H. C. Brown, *J. Org. Chem.*, **32**, 745, 752, 756 (1967).

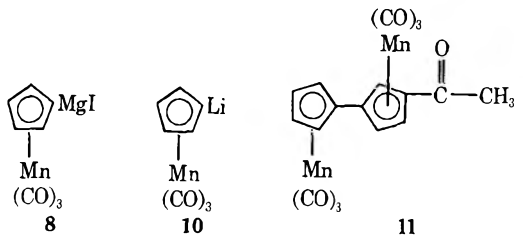
(11) M. D. Rausch, *J. Org. Chem.*, **26**, 1802 (1961).

(12) L. Fieser and M. Fieser, "Advanced Organic Chemistry," Chapman and Hall, London, 1963, p 785.

(13) M. D. Rausch, *Inorg. Chem.*, **1**, 414 (1962).

(14) H. Shechter and J. T. Helling, *J. Org. Chem.*, **26**, 1034 (1961).

hydrolysis afforded cymantrenecarboxylic acid (**9**) in 32% yield. The physical properties of the purified product are in good agreement with properties described for **9** prepared by an alternate procedure.[15,16] A subsequent reaction of **8** with cobalt(II) chloride also produced **1** in 51% yield.



8 **10** **11**

Since earlier attempts to prepare cymantrenyllithium (**10**) had been reported to be unsuccessful,[9] we decided to investigate alternate routes to this potentially useful intermediate. The report by Rausch that treatment of diferrocenylmercury (**7**) with an excess of *n*-butyllithium produced lithioferrocene in high yield[13] prompted us to attempt an extension of this exchange reaction to the cymantrene system. Both chloromercuricymantrene (**3**) and dicymantrenylmercury (**5**) were found to undergo transmetalation with *n*-butyllithium to produce cymantrenyllithium (**10**). Thus, treatment of either **3** or **5** with *n*-butyllithium in ethyl ether–benzene solution and subsequent carbonation of the reaction mixture afforded cymantrenecarboxylic acid (**9**) in yields of 40 and 44% respectively. Furthermore, reaction of **10** prepared from either **3** or **5** with cobalt(II) chloride produced **1** in yields of 13 and 16%, respectively.

Since substitution reactions of **1** followed by oxidation of the $Mn(CO)_3$ groups could conceivably lead to a general route to substituted fulvalenes, it was of interest to determine the relative reactivity of **1** in a typical electrophilic substitution reaction.

Attempted acetylation of **1** in carbon disulfide solution using equimolar amounts of acetyl chloride and aluminum chloride yielded starting material and no products of acetylation. These results indicate a lower reactivity of **1** toward electrophilic substitution as compared to cymantrene (**2**), since the latter compound reacts readily under the above conditions.[17] A reaction of **1** in methylene chloride solution with 2 equiv each of acetyl chloride and aluminum chloride, however, afforded (3-acetylfulvalene)hexacarbonyldimanganese (**11**) in 43% yield. The structural assignment of the product as the 3-acetyl isomer (**11**) was made chiefly on the basis of its proton nmr spectrum, which exhibits a doubly deshielded single proton resonance at τ 4.30 (both the acetyl[18] and cymantrenyl[19] groups are known to be deshielding with regard to adjacent protons on a cyclopentadienyl ring). A very small amount of an apparently diacetylated product was also isolated from the reaction, and its structure is presently under investigation.

(15) R. Riemschneider and K. Pelzoldt, *Z. Naturforsch. B*, **16**, 627 (1960).
(16) Cymantrenylmagnesium iodide (**8**) has also been used successfully in this laboratory in the synthesis of cymantrenyldiphenylphosphine: G. J. Reilly and W. E. McEwen, *Tetrahedron Lett.*, 1231 (1968).
(17) F. A. Cotton and J. R. Leto, *Chem. Ind. (London)*, 1368 (1958).
(18) M. D. Rausch and V. Mark, *J. Org. Chem.*, **28**, 3225 (1963).
(19) R. F. Kovar, Ph.D. Thesis, University of Massachusetts, 1969.

Experimental Section

Ir spectra were recorded on a Beckman IR-10 spectrophotometer and were calibrated using polystyrene. Nmr spectra were recorded on a Varian A-60 spectrometer using $CDCl_3$ as the solvent and TMS and an internal standard. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by the Microanalytical Laboratory, Office of Research Services, University of Massachusetts. Column chromatography was carried out using CAMAG activity I alumina or Florisil (purchased from Fisher Scientific Co.).

Direct Mercuration of Cymantrene (2).—A 500-ml one-necked flask was equipped for magnetic stirring, and a 250-ml addition funnel was attached. A solution of cymantrene (38.6 g, 0.189 mol) dissolved in 100 ml of methylene chloride was added to the flask. Meanwhile, mercuric acetate (20.1 g, 0.063 mol) and 200 ml of methanol were added to a 500-ml erlenmeyer flask equipped for magnetic stirring. Perchloric acid was added dropwise until the white suspension dissolved (a large excess should be avoided). The mercurating reagent thus formed was then added dropwise to the stirring solution of cymantrene. When the addition was complete, a solution containing 5.4 g (0.126 mol) of lithium chloride dissolved in 25 ml of methanol was added, followed by 100 ml of methylene chloride. The contents of the flask were transferred to a 500-ml separatory funnel, and the solution was washed with two 100-ml portions of water to remove perchlorate salts. The organic layer was filtered and dried over anhydrous sodium sulfate. Evaporation of the solvent to dryness yielded yellow crystals. The residue was extracted with three 100-ml portions of boiling benzene, and the cooled extracts were filtered through a 1 in. × 6 in. column of Florisil. Evaporation of the eluent to dryness yielded a light yellow solid. Unreacted cymantrene (22 g) was removed from the residue by extraction with three 100-ml portions of boiling hexane. The pale yellow product which remained was recrystallized from methylene chloride–heptane to yield 14.6 g (53%) of chloromercuricymantrene (**3**) as yellow needles, mp 132–133° (lit.[9] mp 135–136°). An ir spectrum of this material and **3** prepared by Cais' procedure were identical.

Further elution of the Florisil column with acetone yielded small amounts of what appeared to be bis(chloromercuri)-cymantrene. The crude material was converted by reaction with iodine into an iodinated derivative. Analysis of this product by gas chromatography indicated the presence of two components in approximately equal amounts, possibly 1,2- and 1,3-diiodocymantrene.

Preparation of Iodocymantrene (4).—To a stirred solution containing 10.0 g (23 mmol) of chloromercuricymantrene (**3**) dissolved in a minimum amount of methylene chloride was added a saturated solution of iodine in methylene chloride. Addition was continued until the initially fading purple color persisted. The contents of the flask were transferred to a 250-ml separatory funnel shaken vigorously with two 100-ml portions of sodium thiosulfate solution, and then washed with two 100-ml portions of water. The organic layer was filtered through a 1 in. × 6 in. column of Florisil and the eluent was evaporated to dryness. The residual oil was dissolved in hexane and filtered through a 1 in. × 6 in. column of Florisil. Evaporation of the eluent to dryness yielded 6.4 g (84%) of iodocymantrene as a light yellow oil which solidified upon cooling. The mp was 33–34° (lit.[8] mp 33–34°). An nmr spectrum exhibited a triplet at τ 4.95 (two α protons) and a triplet at 5.28 (two β protons).

Preparation of Dicymantrenylmercury (5).—Chloromercuricymantrene (5.0 g, 11 mmol) was added as a solid to a 250-ml flask containing 200 ml of saturated sodium thiosulfate solution. The resulting mixture was stirred for 5 hr, after which time the suspension was filtered, washed with water, and dried at 100°. Recrystallization of the product from methylene chloride–heptane afforded 3.4 g (99%) of dicymantrenylmercury as yellow platelets, mp 174–175° (lit.[9] mp 174.5–175.5°).

Preparation of (Fulvalene)hexacarbonyldimanganese (1) *via* Ullmann Coupling of Iodocymantrene (4).—To a 6-in. test tube equipped with nitrogen inlet and outlet tubes were added 5.0 g of copper–(Zn) powder[12] and 1.0 g (3 mmol) of iodocymantrene. The tube was thoroughly purged with nitrogen and then immersed in an oil bath maintained at 110° for 24 hr. Subsequently, the contents of the tube were extracted repeatedly with methylene chloride until the extracts were colorless. The combined ex-

tracts were evaporated to dryness, and the remaining residue was chromatographed on a 0.5 in. × 6 in. column of dry-packed Florisil. Elution of the column with hexane produced 0.32 g of cymantrene (2) after evaporation of the solvent. Further elution with benzene and subsequent evaporation of the solvent produced 0.13 g (22% yield) of (fulvalene)hexacarbonyldimanganese (1). Recrystallization of the product from methylene chloride–heptane afforded yellow platelets, mp 145–146°.

Anal. Calcd for $C_{16}H_8Mn_2O_6$: C, 47.32; H, 1.99; Mn, 27.06; O, 23.64; mol wt, 406. Found: C, 47.24; H, 2.02; Mn, 27.23; O, 23.59. mol wt 403 (osmometric in benzene), 406 (mass spectrometry).

Attempted Ullmann Coupling of Iodocymantrene (4) with Iodoferrocene.—A 6-in. test tube equipped with nitrogen inlet and outlet tubes was purged with nitrogen. To this tube were added 5.0 g of copper–(Zn) powder, 0.5 g (1.5 mmol) of iodocymantrene, and 2.0 g (6.4 mmol) of iodoferrocene. The tube was again flushed with nitrogen and was then immersed in an oil bath maintained at 130° for 24 hr. The residue was extracted with methylene chloride until the extracts were colorless, and the combined extracts were evaporated to dryness. Thin layer chromatography of the reaction product showed that complete conversion of iodoferrocene into biferrocene had occurred, along with the formation of cymantrene (2) and a very small amount of (fulvalene)hexacarbonyldimanganese (1). There was no evidence for the presence of the mixed product cymantrenylferrocene (6).

Formation of Cymantrenylmagnesium Iodide (8).—A 100-ml three-necked flask was equipped with a nitrogen inlet tube, addition funnel, and magnetic stirrer. Powdered magnesium (4.0 g, 0.16 g-atom) was added, and the flask was thoroughly flamed and purged with nitrogen. Anhydrous tetrahydrofuran (25 ml) was added, followed by several drops of ethylene bromide to activate the magnesium. A solution of 2.0 g (6 mmol) of freshly chromatographed iodocymantrene and 2.3 g (12 mmol) of ethylene bromide dissolved in 10 ml of tetrahydrofuran was added dropwise over a period of 1 hr, the temperature being maintained at 25°. The reaction was then stirred for an additional 1 hr, at which time Dry Ice was added. The contents of the flask were evaporated to dryness *in vacuo*, and the resulting residue was extracted with three 50-ml portions of water. The combined aqueous extracts were filtered and the filtrate was acidified with phosphoric acid. The precipitate which formed was extracted into ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated to dryness, yielding 0.47 g (32%) of cymantrenecarboxylic acid (9). Recrystallization of the products from methylene chloride–heptane produced yellow platelets, mp 195–197° (lit.[15] mp 187–197°). A mixture melting point with an authentic sample of 9 was undepressed and the ir spectra of both compounds were identical.

Reaction of Cymantrenylmagnesium Iodide (8) with Cobalt(II) Chloride.—A solution of cymantrenylmagnesium iodide (6 mmol) was prepared according to the above procedure. To the Grignard reagent, cooled to −20°, was added 7.8 g (60 mmol) of anhydrous cobalt(II) chloride, and the resulting mixture was stirred for 8 hr. The solvent was then evaporated and the residue chromatographed on a 1 in. × 6 in. column of Florisil. Elution of the column with hexane produced 0.9 g of cymantrene. Further elution of the column with benzene produced, after evaporation of the solvent, 0.61 g (51%) of (fulvalene)hexacarbonyldimanganese (1). Recrystallization of the product from methylene chloride–heptane afforded crystals of mp 145–146°. An ir spectrum of the product was identical with that obtained for 1 synthesized by the Ullmann reaction.

Formation of Cymantrenyllithium (10).—A 250-ml three-necked flask equipped with stirrer, nitrogen inlet tube, syringe cap, and addition funnel was thoroughly flamed and purged with nitrogen. Then 1.0 g (1.6 mmol) of dicymantrenylmercury (5) was added, followed by 100 ml of a 3:1 ethyl ether–benzene mixture. The solution was stirred under nitrogen for 15 min and than 4.7 ml (10 mmol) of *n*-butyllithium was added. The solution immediately darkened and became homogeneous. After the solution had been allowed to stir for an additional 30 min, 100 g of Dry Ice was added. The solution was then extracted with two 50-ml portions of dilute potassium hydroxide solution. The combined extracts were acidified with phosphoric acid, and the precipitate which formed was filtered and dried in air, producing 0.32 g (40%) of cymantrenecarboxylic acid (9). Recrystallization of the product from methylene chloride–heptane yielded yellow platelets, mp 194–196° (lit.[15] 187–197°); A mixture melting point with an authentic sample was undepressed and the ir spectra of both compounds were identical.

Reaction of Chloromercuricymantrene (3) with *n*-Butyllithium.—To a stirred solution of chloromercuricymantrene (1.0 g, 2 mmol) dissolved in a 1:1 mixture of benzene–ethyl ether under nitrogen was added 2.0 ml (4 mmol) of *n*-butyllithium in hexane. After the reaction had been allowed to stir for 15 min, solid carbon dioxide was added and the solvent evaporated to dryness. The residue which remained was extracted with two 50-ml portions of water, and the combined aqueous extracts were filtered. The filtrate was acidified with phosphoric acid, and the resulting precipitate was extracted into ethyl ether. The ether extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated to give 0.22 g (44%) of cymantrenecarboxylic acid (9). The product was recrystallized from methylene chloride–heptane, affording crystals of mp 195–197° (lit.[15] mp 187–197°). A mixture melting point with an authentic sample of 9 was undepressed.

Reaction of Cymantrenyllithium (10) with Cobalt(II) Chloride A. Prepared from Dicymantrenylmercury (5).—A solution of cymantrenyllithium (4 mmol) in 3:1 benzene–ethyl ether was prepared from dicymantrenylmercury according to the above procedure. To this solution, cooled to −20°, were added 5.2 g (40 mmol) of cobalt(II) chloride and 20 ml of anhydrous tetrahydrofuran. The reaction mixture was allowed to warm to room temperature and was then stirred for an additional 8 hr. The solution was concentrated to dryness *in vacuo* and the residue which remained worked up in a manner similar to the procedure described previously, producing 0.11 g (14%) of (fulvalene)-hexacarbonyldimanganese (1), mp 146–147°. An ir spectrum was identical with that obtained for a sample of 1 prepared by the Ullmann method.

B. Prepared from Chloromercuricymantrene (3).—A solution of cymantrenyllithium (2 mmol) in 3:1 benzene–ethyl ether was prepared from chloromercuricymantrene according to the procedure previously described. To this solution, cooled to −20°, were added 2.6 g (20 mmol) of cobalt(II) chloride and 20 ml of anhydrous tetrahydrofuran. The reaction mixture was allowed to warm to room temperature and was then stirred for an additional 8 hr. Work-up as described above produced 0.07 g (17%) of (fulvalene)hexacarbonyldimanganese (1), mp 146–147°.

Pyrolysis of Dicymantrenylmercury (5) and Silver Powder.—An intimate mixture of 1.0 g (1.65 mmol) of dicymantrenylmercury and 6.0 g (0.05 g-atom) of silver powder[20] was added to a 1 in. × 8 in. test tube equipped with nitrogen inlet and outlet tubes. The system was flushed with nitrogen and then immersed in bath of Wood's metal maintained at 265°. After 15 hr, the reaction mixture was extracted repeatedly with methylene chloride until the extracts were colorless, and the combined extracts were concentrated to dryness. The residue which remained was chromatographed on a 1 in. × 6 in. column of Florisil. Elution of the column with hexane produced a small initial band containing 63 mg of cymantrene (2). Further elution with benzene and subsequent evaporation of the solvent afforded 0.45 g (67%) of (fulvalene)hexacarbonyldimanganese (1), mp 146–147°. A mixture melting point with a sample of 1 prepared by the Ullmann method was undepressed, and the ir spectra of both compounds were identical.

Preparation of Cymantrenylferrocene (6).—A 1 in. × 8 in. test tube equipped with nitrogen inlet and outlet tubes was thoroughly flushed with nitrogen and an intimate mixture of 1.7 g (2 mmol) of dicymantrenylmercury, 1.2 g (2 mmol) of diferrocenylmercury, and 5.0 g (0.04 g-atom) of silver powder[14] was added. The tube was then flushed with nitrogen and immersed in a bath of Wood's metal maintained at 265°. After 15 hr, the contents of the tube was extracted repeatedly with methylene chloride until the extracts were colorless; the combined extracts were concentrated to dryness. Chromatography of the residue on a 1 in. × 6 in. dry column of Florisil (elution with 6:1 hexane–benzene) produced three bands.

Band I upon evaporation of the solvent yielded 430 mg of biferrocene, identified by its ir spectrum. Band II produced 300 mg (39%) of cymantrenylferrocene (6). Several recrystallization of the product from heptane afforded orange platelets, mp 89–91°.

Anal. Calcd for $C_{18}H_{13}MnFeO_3$: C, 55.71; H, 3.38. Found: C, 55.61; H, 3.38.

(20) G. Brauer, "Handbuch der Praparativen Anorganischen Chemie," Ferdinand Enke Verlag, Stuttgart, 1954, p 766.

An ir spectrum (KBr) exhibited absorptions at 3110 (w), 2000 (s), 1925 (s), 1100 (w), 1100 (m), 1030 (m), 840–880 (m, br), 690 (w), 660 (s), and 635 cm^{-1} (s). An nmr spectrum exhibited a multiplet at τ 5.03 (two α protons on cymantrene ring), a multiplet at 5.24 (two β protons on cymantrene ring), a multiplet at 5.60 (two α protons on ferrocene ring), a multiplet at 5.70 (two β protons on ferrocene ring), and a singlet at 5.87 (five protons on unsubstituted ferrocene ring).

Elution of band III and subsequent evaporation of the solvent afforded 640 mg of (fulvalene)hexacarbonyldimanganese (1), identified by its ir spectrum.

Acetylation of (Fulvalene)hexacarbonyldimanganese (1).—A 100-ml three-necked flask was equipped with a magnetic stirrer, condenser, and a nitrogen inlet tube. To this flask was added 0.5 g (1.2 mmol) of (fulvalene)hexacarbonyldimanganese dissolved in 25 ml of dry methylene chloride, followed by 0.16 g (2.5 mmol) of acetyl chloride and 0.33 g (2.5 mmol) of aluminum chloride. The solution was heated to reflux under nitrogen for 30 min after which time it was poured over 50 g of ice. The organic layer was separated, dried over calcium chloride, and evaporated to dryness. The remaining residue was then subjected to preparative tlc (elution with methylene chloride). Development of the plate yielded three major bands.

Extraction of band I (highest R_f) from the plate and subsequent evaporation of the solvent yielded 0.12 g of unreacted 1, mp 146–147°. Band II was extracted from the plate and the solvent evaporated *in vacuo*. Sublimation of the residue which remained at 120° (0.01 mm) produced 0.24 g (43%) of (3-acetylfulvalene)-hexacarbonyldimanganese (11), mp 116.0–116.5°, as yellow platelets.

Anal. Calcd for $C_{18}H_{10}Mn_2O_7$: C, 48.25; H, 2.25. Found: C, 48.27; H, 2.44.

An ir spectrum (KBr) exhibited absorptions at 2020 (sh), 2000 (s), 1965 (s), 1935 (s), 1915 (s), 1680 (m), 1460 (w), 1425 (w), 1365 (w), 1240 (w), and 620 cm^{-1} (s). An nmr spectrum exhibited a multiplet at τ 4.30 (one proton α to both the acetyl group and the ring junction), a multiplet at 4.50 (one proton α to acetyl group and β to ring junction), a multiplet at 4.92 (three protons; one proton β to acetyl group and α to bridging carbon plus two protons α to bridging carbon), a multiplet at 5.16 (two protons β to bridging carbon), and a singlet at 7.64 (three protons of the acetyl group).

Band III yielded a product tentatively identified as an additional acetylation product of 1. An ir spectrum of the product (KBr) exhibited strong absorptions at 2020, 1970, and 1680 cm^{-1}.

Registry No.—**1**, 31988-02-0; **2**, 12079-65-1; **3**, 12203-10-0; **4**, 12079-63-9; **5**, 12216-27-2; **6**, 37048-11-6; **7**, 1274-09-5; **8**, 38855-99-1; **10**, 38856-00-7; **11**, 38856-01-8; cobalt(II) chloride, 7646-79-9.

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Semiempirical Calculations on the Ring Opening of Substituted Cyclopropanones

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We report the results of INDO and MINDO calculations on the ring openings of cyclopropanone and some of its derivatives and compare the semiempirical results for the parent compound with the *ab initio* results reported earlier. Both semiempirical methods indicate that the substituted cyclopropanones open more readily than the parent compound, but the actual numerical values are not accurate. The major shortcoming of the semiempirical methods is that one never knows when to believe their predictions.

A large number of successful applications of the INDO and MINDO methods have been reported.[2–5] However, in a semiempirical approach the parameters are either not sufficiently flexible or not sufficiently accurate, and examples are bound to exist where these methods fail. It has already been reported that the ring opening of cyclopropanone 1 to singlet oxyallyl 2 is

1 2

such a case.[6] The INDO method predicts a value in excess of 200 kcal/mol, which is certainly too large.[6,7] The MINDO method has been reported to yield a more reasonable value, 78 kcal/mol, for the isomerization.[5] However, as we shall see, this method also fails in several substituted cases, predicting that the corresponding oxyallyls are considerably more stable. An extended Hückel study on the parent system also predicts oxyallyl to be more stable than cyclopropanone,[8] a result now known to be incorrect.[9,10]

An *ab initio* study indicates that singlet oxyallyl is 83 kcal/mol less stable than the closed ketone.[7] Because it does not include correlation, this value is probably too high.

Even allowing for some decrease, the energy difference between 1 and 2 is likely to remain large; yet, in contrast to the parent compound, some derivatives of 1 undergo reactions best explained in terms of an oxyallyl intermediate.[11–16] Concerted reactions need not pass

(1) Address for correspondence.

(2) (a) J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.*, **43**, S129 (1965); (b) J. A. Pople and G. A. Segal, *ibid.*, **43**, S136 (1965).

(3) J. A. Pople and D. L. Beveridge, "Approximate Molecular Theory," McGraw-Hill, New York, N. Y., 1970.

(4) M. J. S. Dewar and E. Haselbach, *J. Amer. Chem. Soc.*, **92**, 590 (1970).

(5) N. Bodor, M. J. S. Dewar, A. Harget, and E. Haselbach, *J. Amer. Chem. Soc.*, **92**, 3854 (1970).

(6) J. F. Olsen, S. Kang, and L. Burnelle, *J. Mol. Struct.*, **9**, 305 (1971).

(7) A. Liberles, A. Greenberg, and A. Lesk, *J. Amer. Chem. Soc.*, **94**, 8685 (1972).

(8) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968).

(9) J. M. Pochan, J. E. Baldwin, and W. H. Flygare, *J. Amer. Chem. Soc.*, **91**, 1896 (1969).

(10) J. M. Pochan, J. E. Baldwin, and W. H. Flygare, *J. Amer. Chem. Soc.*, **90**, 1072 (1968).

(11) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

(12) N. J. Turro, R. B. Gagosian, S. E. Edelson, T. R. Darling, J. R. Williams, and W. B. Hammond, *Trans. N. Y. Acad. Sci.*, **33**, 396 (1971).

(13) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).

(14) A. S. Kende, *Org. React.*, **11**, 261 (1960).

(15) D. B. Sclove, J. F. Pazos, R. L. Camp, and F. D. Greene, *J. Amer. Chem. Soc.*, **92**, 7488 (1970).

(16) S. F. Edelson and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 2770 (1970).

through a true oxyallyl, but a number of reactions remain that do seem to require an oxyallyl. Therefore, these substituted oxyallyls must be formed much more readily than the parent molecule. For example, it has been reported that the racemization of optically active *trans*-2,3-di-*tert*-butylcyclopropanone, which may proceed by way of the corresponding oxyallyl, has a free energy of activation of approximately 27 kcal/mol.[15] It, therefore, seemed quite a proper test of the semiempirical SCF methods to determine their predictions for the ring opening of substituted cyclopropanones.

Ring Opening of Cyclopropanone.—The ring opening of the parent system was first calculated using both the INDO and MINDO methods.[17] The energies of cyclopropanone, using several geometries, are presented in Table I.

TABLE I
THE ENERGY OF CYCLOPROPANONE

Ref	MINDO, eV	INDO, hartrees
a	−759.941	−41.028
b	−759.452	
c	−759.432	
d		−40.996

[a] The experimental geometry of Pochan, Baldwin, and Flygare; see ref 9 and 10. [b] The optimal geometry of Bodor, Dewar, Harget, and Haselbach. The CH_2 angle was 115°. See ref 5. [c] The optimal geometry of Bodor, Dewar, Harget, and Haselbach. The CH_2 angle was 120°. See ref 5. [d] The optimal geometry of Olsen, Kang, and Burnelle; see ref 6.

Apparently, the experimental geometry of Pochan, Baldwin, and Flygare[9,10] is nearly optimal both for the INDO approach and for our version of MINDO.[17] As shown in Table I, we did test the geometry reported to be optimal for MINDO,[5] but the experimental geometry gave a lower energy.

The energy of singlet oxyallyl **2** was next calculated for various internal C_3–C_1–C_2 angles, α. The results are given in Table II.

TABLE II
THE ENERGY OF OXYALLYL FOR VARIOUS INTERNAL ANGLES

α, deg	MINDO, eV	INDO, hartree[a]	INDO, hartree[b]
120	−756.888	−40.600	−40.618
110	−757.031	−40.616	−40.634
100	−757.187	−40.630	−40.647
90	−757.398	−40.640	−40.657
80	−757.753	−40.633	
70	−758.375	−40.535	

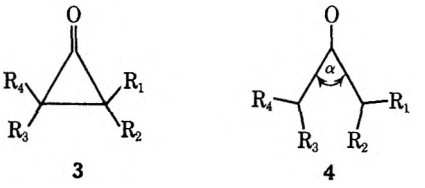
[a] Reference 6. [b] Present work; also see ref 7.

Oxyallyl is predicted by the INDO treatment to have an internal angle equal to 90°. The MINDO method indicates a smaller value for α. Unfortunately, the 60° geometry failed to converge with this method, and the 50° geometry places the endo hydrogens, H_2 and H_3, too close to be practical (d_{HH} = 0.0002 Å). Therefore, the smallest internal angle for which MINDO data are available is 70°.

Since the *ab initio* calculation[7] employed exactly the same bond distances as those used in the present work, it is possible to make a direct comparison of the predictions of the various methods. The INDO approach yields 232 kcal/mol for the ring opening and a value of 90° for α in oxyallyl. The *ab initio* result is 83 kcal/mol for the ring opening and approximately 105° for α. The MINDO method affords a value of 36 kcal/mol and α is in the neighborhood of 70°.[17]

A fuller optimization of the various structural parameters will somewhat change these values but not the conclusions.

Ring Opening of Substituted Cyclopropanones.—The substituted molecules **3** and **4** were derived from



the parent compounds by replacing hydrogens with the appropriate groups. An internal angle of 90° was chosen for the INDO calculations of the oxyallyls, while MINDO results were obtained for both 70 and 90°. The latter value allows a comparison of the two methods when identical bond distances and angles are employed.

Bond distances were obtained from model compounds,[18] and those used are shown in Table III. The

TABLE III
BOND DISTANCES IN SUBSTITUTED CYCLOPROPANONES AND OXYALLYLS

Substituent	3	4
F	1.350	1.340
CH_3	1.530	1.510
CH_3O	1.400	1.350
Methoxy CO	1.420	1.430
Methyl CH	1.100	1.100

energies for the isomerization are given in Table IV. We assumed that the opening of **3** was disrotatory, and of the two disrotatory modes, we chose the one placing bulky groups into positions R_1 and R_4.

The numerical values afforded by the two semiempirical methods are incorrect, but both methods do indicate that substituted cyclopropanones open more readily than the parent compound. The methoxy group, as expected, appears to be an extremely effective stabilizer of the ring-open form. Fluorine also appears to enhance the ring opening, but methyl is calculated to be less effective.

Conclusion

The data in Table IV support the idea that oxyallyls can be viable intermediates in the reactions of cyclopropanones, for both methods indicate that the substituted compounds open more readily than the parent molecule. Unfortunately, the actual numerical values are of little use. One method yields values that are much too large, while the other gives values that are obviously too low. The MINDO values for the parent system and its dimethyl derivative may not seem

(17) The version of MINDO used was QCPE 137, which uses different parameters from those of ref 5 and leads to different results.

(18) "Tables of Interatomic Distances and Configurations in Molecules and Ions," The Chemical Society, London, Special Publications no. 11 and 18.

TABLE IV

THE ENERGY DIFFERENCE BETWEEN SUBSTITUTED OXYALLYLS AND THE CORRESPONDING CYCLOPROPANONES

Registry no.[b]	R_1	R_2	R_3	R_4	ΔE, kcal/mol: MINDO α 70°	MINDO α 90°	INDO α 90°
5009-27-8	H	H	H	H	+36	+59	+232
39050-15-2	F	H	H	F	a	+20	+184
39050-16-3	F	F	H	H	−153	+15	+203
39050-17-4	CH_3	H	H	CH_3	+30	+50	+200
39050-18-5	CH_3O	H	CH_3O	H	−93	+13	+180
39050-19-6	CH_3O	CH_3O	H	H	−96	+2	+174
39050-20-9	CH_3	F	F	CH_3	a	+14	+190
39050-21-0	CH_3O	F	CH_3O	F	−31	+24	+153
39050-22-1	CH_3O	CH_3O	F	F	−32	+30	+150

[a] The oxyallyl calculation failed to converge. [b] For cyclopropanones.

unreasonable, but the values for the fluoro and methoxy derivatives are incorrect, and the major shortcoming of the semiempirical methods is that one never knows when to believe their predictions.

Registry No.—Oxyallyl, 39050-23-2.

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Organic Reactions in Liquid Hydrogen Fluoride. IV.[1] The Fries Rearrangement of Aryl Benzoates

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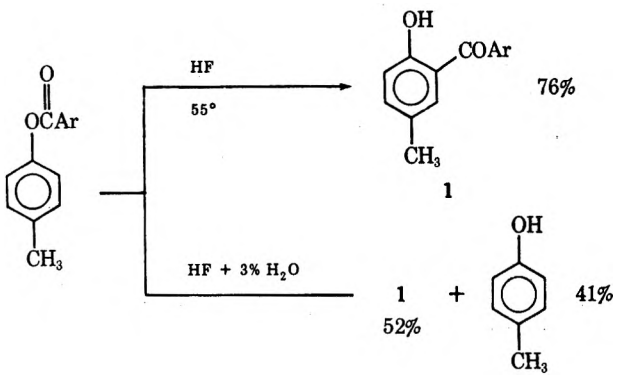
Phenyl and *p*-tolyl benzoates are converted to the corresponding hydroxybenzophenones in 70–75% yields when heated in anhydrous HF at 55°. With *p*-*tert*-butylphenyl benzoate the reaction product is the dealkylated *p*-hydroxybenzophenone, whereas the meta derivative gives 2-hydroxy-4-*tert*-butylbenzophenone in 40% yield. This appears to be the first example of a *tert*-butyl group being retained on a phenolic moiety during an acid-catalyzed Fries rearrangement. Comments on the mechanism and intermolecularity of the reaction are given.

Known as the Fries rearrangement,[2] the reaction of aryl esters in the presence of acidic type catalysts, usually $AlCl_3$, provides a convenient method for preparing hydroxybenzophenones. Hydrogen fluoride has received little attention as a catalyst for the rearrangement, although it has been reported to convert phenyl acetate[3] and some cresolic acetates[4] to the corresponding hydroxy ketones. The yields were low and a temperature of 100° for 24 hr was employed.[3] No work in HF has been reported with *tert*-butyl groups present on the phenolic ring; in fact, nothing in the literature could be found concerning favorable reactions with any *tert*-butylphenyl carboxylates employing any acid catalyst. Dealkylation always prevails, which led Kobsa[5a] to utilize the photo-Fries[5b] reaction for the rearrangement of *tert*-butyl esters.

Results

The present work describes our findings concerning rearrangement of some aryl benzoates in liquid HF, with special emphasis on the reactivity differences due to positions of *tert*-butyl groups on the phenolic ring. A summary of the experimental results is recorded in Table I. Phenyl and *p*-tolyl benzoate yield *p*-hydroxybenzophenone (70% yield) and 2-hydroxy-5-methylbenzophenone (76% yield), respectively, when shaken in liquid HF at 55° for 4–6 hr. The reaction is clean and the HF can easily be removed by distillation (bp 20°) or neutralization with base. No tars or insoluble residues often observed with $AlCl_3$ are obtained. If 3% water is present in the HF when *p*-tolyl benzoate is used as the starting ester, the isolated yield of ketone **1** drops to 52%, and 41% *p*-cresol is recovered resulting from hydrolytic cleavage of the ester.



p-Methoxyphenyl and *p*-chlorophenyl benzoates gave recovered starting material with *p*-methoxyphenol being obtained in the former case under the above con-

(1) For paper III, see J. R. Norell, *J. Org. Chem.*, **37**, 1971 (1972).

(2) For review articles, see (a) M. J. S. Dewar and L. S. Hart, *Tetrahedron*, **26**, 973 (1970); (b) H. J. Shine, "Aromatic Rearrangements," Elsevier, New York, N. Y., 1967, p 72; (c) A. Gerecs in "Friedel-Crafts and Related Reactions," Vol. III, Part I, G. A. Olah, Ed., Interscience, New York, N. Y., 1967, Chapter XXXIII, pp 499–533; (d) A. N. Blatt, *Org. React.*, **1**, 342 (1942).

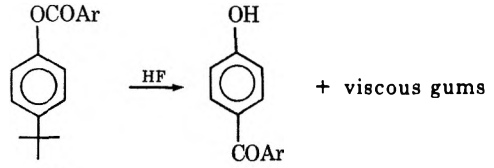
(3) J. H. Simmons, S. Archer, and D. I. Randall, *J. Amer. Chem. Soc.*, **62**, 485 (1940).

(4) O. Dann and G. Mylius, *Justus Liebigs Ann. Chem.*, **587**, 1 (1954).

(5) (a) H. Kobsa, *J. Org. Chem.*, **27**,2 293 (1962); (b) D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967).

ditions. Little evidence was observed for the presence of rearranged ketone. The products isolated from a similar reaction with *p*-ethyl- and *p*-isopropylphenyl benzoates consisted of benzophenones with no unreacted starting materials.

The *tert*-butylphenyl benzoates, both mono- and disubstituted, vary in reactivity depending on the position of nuclear substitution. As equated below, *p-tert*-butylphenyl benzoate (2) gave only *p*-hydroxy-



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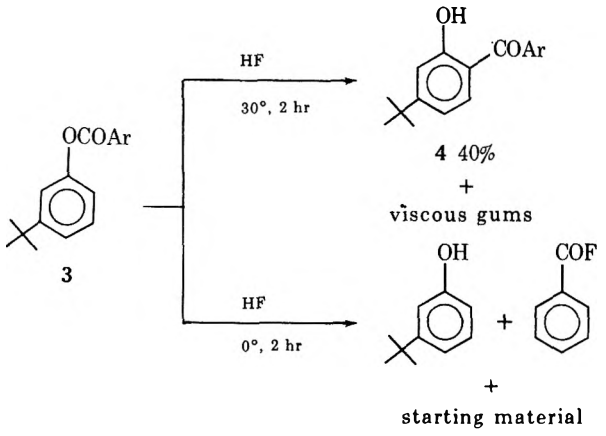
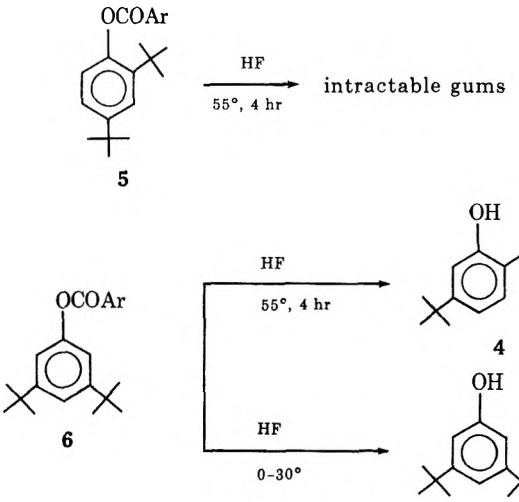
benzophenone under a variety of conditions. The viscous gums are probably polybutylenes and highly substituted phenols. No reaction products were isolated or identified possessing the *tert*-butyl moiety. In contrast, the meta isomer (3) at room temperature



gave a 40% yield of the desired 2-hydroxy-4-*tert*-butylbenzophenone (4). A striking temperature effect exists in that at 0° only the cleavage products, *m-tert*-butylphenol and benzoyl fluoride, are identified in addition to some starting material.

That the above reaction is clearly an artifact of the temperature difference gains credence from two simple observations during work-up. (1) No bands in the infrared attributable to the benzophenone (6.1 μ) are observed in the crude reaction mixtures when run at 0°. This band is very strongly present in the crude mixture of the 30° runs and is characteristic of 4. (2) Compound 4 is bright yellow and imparts this color to the crude mixture in the 30° run, whereas at 0° the crude reaction mixture is cream colored. Whether or not this was a kinetically controlled run is not certain, but, in any case, cleavage products were observed at 0°. To our knowledge this is the first report of a *tert*-butyl group being retained on the phenolic ring under acid-catalyzed Fries rearrangement conditions.

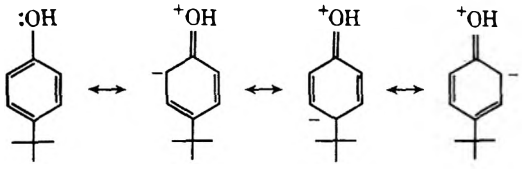
With two *tert*-butyl groups in the molecule the reaction is even more complex. 2,4-Di-*tert*-butylphenyl benzoate (5) yields only a dark oil at 55° after 4 hr, which is typical of many reactions carried out at varying conditions with this isomer. If the *tert*-butyl groups are translated to the next succeeding carbons around the ring, *i.e.*, in 6, the monoalkylated product, 4, is isolated when run at 55° for 4 hr. As with compound



3, a temperature-dependent reaction is observed, for, if 6 is allowed to react at 0° or 30°, the cleavage product, 3,5-di-*tert*-butylphenol, is recovered and none of the ketone is observed.

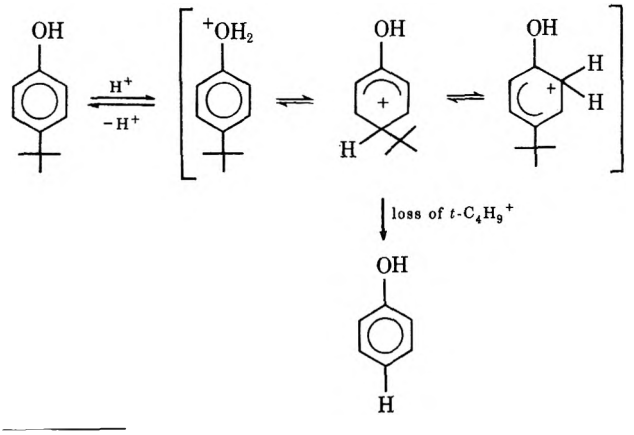
Discussion

The observation that *tert*-butyl groups in the meta position dealkylate to a lesser extent than those in the ortho or para position may be explained by invoking basic resonance and equilibrium principles of aromatic substitution on the free phenol. The electronegative sites on *p-tert*-butylphenol drawn in the canonical forms are shown.



The concept of using the free phenol appears valid, since in HF the cleavage products, the phenol and acyl fluoride, are observed. Dealkylation probably occurs on the free phenol, since a subsequent paper describes such a reaction of *tert*-butylphenols[6] in liquid HF.

On protonation of phenol a reversible attack of the proton can occur at any one of the three sites—two orthos and one para. If a labile group, *i.e.*, a *tert*-butyl, is also present in either the ortho or para position, then at a specific rate dealkylation will occur. The loss of a



(6) J. R. Norell, *J. Org. Chem.*, **38**, 1929 (1973).

TABLE I
REACTIONS OF ARYL BENZOATES IN HF

ArOC$_6$H$_5$, Ar	Registry no.	Mmol	HF, ml	Temp, °C	Time, hr	Product g	Product Recovery, %	Description of product
C_6H_5	93-99-2	76	150	55	4	14.8	99	Orange solids, recrystallized (hexane–$CHCl_3$), 10.5 g, *p*-hydroxybenzophenone (70% yield), mp 132–133.5°.
4-$CH_3C_6H_4$	614-34-6	71	150	55	6	14.5	97	Yellow solids, recrystallized (MeOH), 11.5 g, 2-hydroxy-5-methylbenzophenone (76% yield), mp 83.5–85°.
4-$CH_3C_6H_4$		71	150[a]	55	4	12.1	81	Yellow solids consisting of *p*-cresol (41%), 2-hydroxy-5-methylbenzophenone (52%), and *p*-tolyl benzoate (7%) by glc.
4-$C_2H_5C_6H_4$	3132-15-8	66	150	55	4	14.0	93	Yellow liquid, ir indicated mostly benzophenones; no attempt at characterization.
4-$CH_3OC_6H_4$	1523-19-9	66	150	55	4	11.2	75	Recrystallized (hexane + EtOH), pale yellow solid (6.0 g), mp 72–81°, infrared of crude indicated *ca.* 50% starting ester and 50% *p*-methoxyphenol, very little benzophenone.
4-ClC_6H_4	2005-08-5	64	150	55	4	13.0	87	Recrystallized (pentane), white crystals (8.1 g), mp 84–87°, mostly starting material.
4-*i*-$C_3H_7C_6H_4$	13936-99-7	62	150	55	4	15.2	100	Glc and ir indicated very little starting material, with the principal product being hydroxybenzophenones; no further characterization.
4-*t*-$C_4H_9C_6H_4$	14041-81-7	59	100	25	2	11.7	78	Yellow, viscous liquid, ir indicated no starting material, dilution with pentane gave 2.3 g of *p*-hydroxybenzophenone.
4-*t*-$C_4H_9C_6H_4$		59	150	55	1	14.2	95	Oil which crystallized on standing for several days, pentane trituration gave 3.9 g of *p*-hydroxybenzophenone, mp 131–133°.
3-*t*-$C_4H_9C_6H_4$	13189-56-5	59	100	25	2	13.1	87	Pale yellow liquid, recrystallized (MeOH), 5.6 g of yellow crystals, 2-hydroxy-4-*tert*-butylbenzophenone (37% yield), mp 80–81°.
3-*t*-$C_4H_9C_6H_4$		59	100	0	2	13.7	91	Yellow liquid, infrared indicated *m-tert*-butylphenol, PhCOF, and starting material, no indication of the desired product.
2,4-Di-*t*-$C_4H_9C_6H_3$	39000-49-2	48	150	55	4	12.6	84	Dark oil, very little starting material; no benzophenones were isolated.
3,5-Di-*t*-$C_4H_9C_6H_3$	5723-92-2	48	100	0	2	13.0	87	Pale yellow liquid, crystals separated, washed with pentane, gave 3,5-di-*tert*-butylphenol (3.9 g), mp 92–93.5°.
3,5-Di-*t*-$C_4H_9C_6H_3$		48	100	30	2	13.5	90	Yellow liquid, crystallized to give 3,5-di-*tert*-butylphenol (1.5 g); infrared of crude indicated phenols, Ph-COF, and unreacted ester with no indication of any benzophenone.
3,5-Di-*t*-$C_4H_9C_6H_3$		48	150	55	4	13.4	89	Yellow solids, recrystallized twice, from *i*-PrOH-H_2O then *i*-PrOH, gave 1.25 g of yellow solids, 2-hydroxy-4-*tert*-butylbenzophenone, mp 81–82°, no unreacted ester present.

[a] 5 ml of H_2O was added.

tert-butyl would be much less pronounced when placed in the meta position. The fate of the *tert*-butyl group is probably a combination of oligomerization and transalkylation, giving a large array of products. The disproportionation of *tert*-butylphenols has been studied over zeolites[7] and also was found to occur independently in HF.[6]

Theories and speculations on the mechanism of the Fries rearrangement are nearly as varied as the number of investigators in the field. Furthermore, the type of catalyst and even different quantities of the same catalyst at different temperatures provide interpretations of the reaction path which show little similarity.[2] Dewar and Hart[2a] have recently made an excellent attempt at clearing some of the confusion. The chief difference is whether the reaction is intermolecular or intramolecular, and even here terms such as "pseudo-intramolecular" are recorded.[2] No speculations or mechanistic studies using HF as the catalyst, which differs considerably from the usual aluminum halides,[8] have been recorded. From the data gathered thus far in this work and that gleaned from the literature, we presently favor the intermolecular path as shown below for the rearrangement of phenyl benzoates. The

(7) A. P. Bolton, M. A. Lanenala, and P. E. Pickert, *J. Org. Chem.*, **33**, 3415 (1968).

(8) Reference 2 provides a thorough review of the mechanism of the AlX_3 type of Fries rearrangements.

TABLE II

PREPARATION OF ARYL BENZOATES[a]

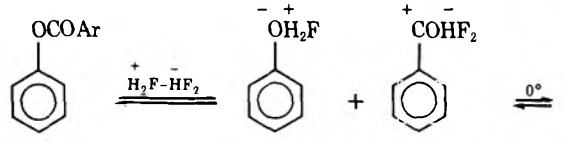
Aryl group	Substituted phenol, mol	C_6H_5COCl, mol	Pyridine, mol	Recrystn solvent	Yield, %	Mp, °C Found	Mp, °C Lit.
p-Tolyl	1.00	1.00	1.10	Hexane	82	70–71.5	70[d]
p-Ethylphenyl	1.00	1.00	1.10	Hexane	72	57–59	60[d]
p-Isopropylphenyl	0.50	0.50	0.50	Hexane	78	72–74	69–70[e]
p-*t*-Butylphenyl	1.00	1.00	1.00	Hexane–EtOH	81	81.5–83	83[f]
m-*t*-Butylphenyl	0.50	0.50	0.53	Liquid	78	136 (0.2 mm)[c]	*g*
2,4-Di-*tert*-butylphenyl	0.75	0.75	0.85	Hexane	45[b]	98–100	98[f]
3,5-Di-*tert*-butylphenyl	0.30	0.30	0.32	MeOH (9)–H_2O (1)	75	80–82	82.5–83[h]
p-Chlorophenyl	1.00	1.00	1.10	*i*-PrOH	83	86–87	88[d]
p-Methoxyphenyl	1.00	1.00	1.10	Hexane–EtOH	80	85–87	87[d]

[a] All reactions were run in toluene (1 l.) at reflux for 18–20 hr. [b] Run for 65 hr. [c] $n^{20}D$ 1.555. [d] N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., 1957, p 680. [e] R. L. Huang and F. Morsingh, *J. Chem. Soc.*, 160 (1953). [f] C. A. Sears, *J. Org. Chem.*, **13**, 120 (1948). [g] Bp 186–188 (11 mm). R. L. Van Etten, G. A. Clower, J. F. Sebastin, and M. L. Bender, *J. Amer. Chem. Soc.*, **89**, 3253 (1967). [h] J. W. Elders and R. P. Mariella, *Can. J. Chem.*, **41**, 1653 (1953).

trimer form of HF is used here as the catalyst, since it displays the more ideal complexation forms, shown below.

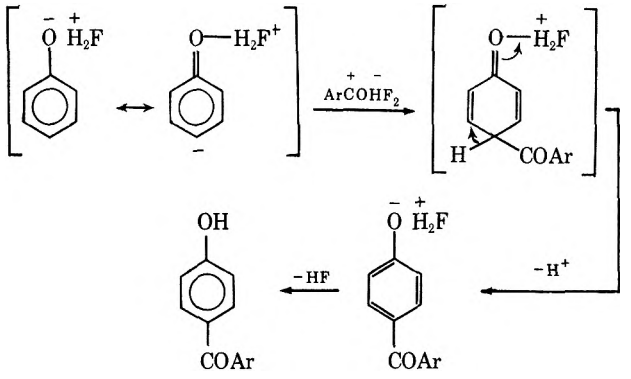
$$3HF \rightleftharpoons H_2F\cdots HF_2$$

Initially a protonic cleavage step occurs, as follows.



phenol + ArCOF

Then, when carried out at 55°, an irreversible acylation takes place.



Although this paper is not intended to be mechanistically inclusive, the foregoing scheme is supported by the following observations.

(1) At 0° the cleavage products are readily isolated, and this step is reversible since benzoyl fluoride and phenol give phenyl benzoate in HF. In the $AlCl_3$ system, the counterpart to an acyl fluoride is not capable of isolation because it exists only as a complex. The reaction of benzoyl fluoride and a phenol in HF to form esters appears to be a novel reaction.

(2) HF is not as strong a π-type complexation agent as is $AlCl_3$ and will tend to be bound more to the oxygen atom rather than form π-coordination complexes with the aromatic ring. Also, HF possesses both Lewis and Brønsted type acid characteristics, which would tend to facilitate protolytic cleavage and an intermolecular reaction. $AlCl_3$ has only Lewis type of acidity.

(3) With phenyl benzoate in HF at 55°, *p*-hydroxybenzophenone is the major product with very little of the ortho derivative being obtained. Dewar and Hart suggest that an intramolecular reaction occurs only when the ortho/para ratio is close to unity. The benzoyl carbonium ion tends to go para in the intermolecular reaction because of the high charge due to the ^+H_2F cation complex in the vicinity of the ortho position.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord; nmr spectra were run on a Varian A-60 spectrometer and the mass spectra were obtained on a CEC mass spectrometer, Model 21-110. Gas chromatography was employed for studying the volatile components with an F & M Model 500 gas chromatograph using a 6-ft, 10% Apiezon L on Chromosorb W.

Chemicals.—*Caution!* When handling anhydrous HF, a face shield, rubber gloves with plastic arm bands, and a protective apron should be worn, and excellent hood facilities are required. Colorless hydrogen fluoride (99.9% from Air Products, Inc., Allentown, Pa.) was withdrawn in the liquid phase by inverting the cylinder and taking off liquid HF through a Monel Hoke valve in addition to the cylinder valve. The liquid HF was allowed to drip directly into a polyethylene graduate, where it readily condensed with very little loss as a fuming liquid; it was then poured into a 300-ml Monel transfer bomb.

Aryl Benzoates.—The starting esters (Table II) were all synthesized by reaction of benzoyl chloride with the appropriately substituted phenol (all commercially available) in refluxing toluene in the presence of pyridine. The example below illustrates a typical run taken from Table II with the other benzoates being prepared similarly.

4-*tert*-Butylphenyl Benzoate.—In a 2-l. flask equipped with a Trubore stirrer, thermometer, reflux condenser, and dropping funnel were placed successively 750 ml of toluene, 150.2 g (1 mol) of *p*-*tert*-butylphenol, and 79.1 g (1.0 mol) of pyridine. Benzoyl chloride (140.6 g, 1.0 mol) was added over a period of 15 min and the mixture was stirred at reflux temperature overnight. After being washed with an equal volume or water, then 10% HCl, water, 10% NaOH, and finally water, the toluene solution was dried over $MgSO_4$. Concentration on a rotating evaporator gave 235.8 g of crude ester. Recrystallization from *n*-hexane–ethanol yielded 205.5 g (81% yield) of white crystals, mp 81.5–83°.

General Procedure for Effecting the Fries Rearrangement in HF.—Either a 300-ml Monel reactor (for reactions above room temperature) or a 450-ml polyethylene vessel was cooled in ice and the specified amount of HF (usually 100–150 ml) was added under a nitrogen stream to exclude moisture. The ester was added and the mixture was shaken in a reciprocating shaker (Monel reactor) or stirred magnetically (polyethylene vessel) at the desired temperature and time. After completion of the reaction the mixture was poured into ice water and extracted with ether. The ether solution was shaken vigorously with saturated $NaHCO_3$ until neutral, washed with water, and dried over $MgSO_4$. Concentration gave the crude products as shown in

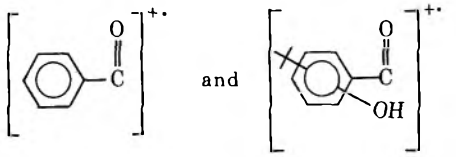
Table I. The residue was purified by crystallization, column chromatography, or distillation. Product characterization was made by comparison with authentically prepared samples, gas chromatography, ir, and nmr. The following two examples display the general method in detail.

2-Hydroxy-4-*tert*-Butylbenzophenone from 3-*tert*-Butylphenyl Benzoate.—Anhydrous HF (100 ml) was added to an ice-cooled 300-ml Monel reactor followed by dropwise addition of 3-*tert*-butylphenyl benzoate. The reactor was capped with a pressure head and shaken at 25° for 2 hr. Most of the HF was allowed to distil from the reactor and the contents were poured on ice. After extraction with ether, the combined organic layers were shaken with saturated NaOH and dried over $MgSO_4$. Concentration provided 14.0 g of a yellow liquid which tended to crystallize on standing. After vacuum distillation [maximum of pot 145° (0.5 mm)] to remove any volatiles, the pot residue, 10.5 g, was recrystallized from methanol to give 5.9 g (40% yield) of yellow crystals, mp 80.5–81.5°. Analysis is detailed below.

2-Hydroxy-4-*tert*-Butylbenzophenone from 3,5-Di-*tert*-Butylphenyl Benzoate.—The ester (15.0 g) was placed in 150 ml of HF in the Monel reactor and heated at 55° for 4 hr. The HF was allowed to evaporate and the residue was poured on ice, neutralized with $NaHCO_3$, extracted with ether, dried ($MgSO_4$), and concentrated to give 13.5 g of a yellow oil. Crystallization was achieved by dissolving the oil in 50% isopropyl alcohol and cooling in a Dry Ice–acetone bath. Recrystallization from isopropyl alcohol gave 1.25 g of yellow crystals: mp 81–82; uv max (EtOH) 3500 m; ir (3.5% $CHCl_3$) 6.17 μ (C=O).

Anal. Calcd for $C_{17}H_{18}O$: C, 80.30; H, 7.12; mol wt, 254. Found: C, 80.23; H, 7.21; mol wt, 260 (osmometry).

Complete structure proof was as follows. The mass spectrum contained a parent ion at 254 with strong peaks observed for the fragments shown at *m/e* 105 and 177, respectively. Ir and nmr

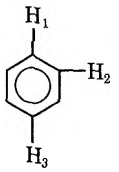


m/e 105 *m/e* 177

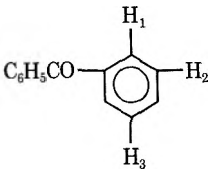
dilution studies indicated that the OH was in the 2 position because of strong intramolecular hydrogen bonding. This was evident by the strong downfield shifting of the hydroxyl proton, −728 Hz.

The position of the *tert*-butyl group was determined by nmr using an NMRIT analysis. An exact fit of the theoretical analysis of the aromatic protons with that of the experimental spectrum was obtained: $W_1 = -450.0$ Hz, $J_{12} = 8.6$ Hz; $W_2 = -410.5$ Hz, $J_{13} = 0.3$ Hz; $W_3 = -422.0$ Hz, $J_{23} = 1.9$ Hz.

It is well known[9] that the ortho coupling constants fall into the range of 7–9 Hz, meta 1–3 Hz, and para 0–1 Hz. Thus J_{12} is an ortho coupling constant, J_{13} para, and J_{23} meta. The proton arrangement is therefore identified as follows.



Irrespective of substituents, the proton ortho to the carbonyl group will experience the maximum of deshielding and will fall in the range of −440 to −470 Hz. Thus the carbonyl must be



located as shown. Since the hydroxy group forms an intramolecular hydrogen bond, the structure is **4**.

3-*tert*-Butylphenyl Benzoate.—Anhydrous HF (100 ml) was placed in a 450-ml high-density polyethylene (Marlex) reactor[10] and cooled to −10°. Benzoyl fluoride (freshly distilled, 12.4 g, 0.10 mol) was added followed by *m*-*tert*-butylphenol (15.0 g, 0.10 mol). The mixture was stirred at −10° for 2 hr, poured on ice, and extracted with ether and the ether extracts were washed with saturated $NaHCO_3$. Drying with $MgSO_4$ and concentration provided 23.2 g of a pale yellow liquid. The infrared spectrum of the crude material indicated the presence of *m*-*tert*-butylphenol, benzoyl fluoride, 3-*tert*-butylphenyl benzoate, and a trace of 4-*tert*-butyl-2-hydroxybenzophenone. Distillation gave 13.4 g of the colorless product, bp 130–134° (0.2 mm). A similar run with *p*-*tert*-butylphenol at −40° gave a 75% yield of *tert*-butylphenyl benzoate, mp 81.5–83°. The pure compounds were characterized by comparison of their physical properties with those of authentically prepared esters.

Registry No.—Hydrogen fluoride, 7664-39-3; *p*-hydroxybenzophenone, 1137-42-4; 2-hydroxy-5-methylbenzophenone, 1470-57-1; 2-hydroxy-4-*tert*-butyl, benzophenone, 39000-51-6; 3,5-di-*tert*-butylphenol, 1138-52-9.

Acknowledgment.—The author wishes to acknowledge the capable laboratory assistance of Mr. Bill Loffer and the helpful discussions with Dr. John E. Mahan.

(9) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 770.

(10) See J. R. Norell, *J. Org. Chem.*, **35**, 1617 (1970), for a description of the reactor.

Organic Reaction in Liquid Hydrogen Fluoride. V. Reactions and Formation of *tert*-Butylphenols

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In temperature ranges of −75 to 100° *o*-, *m*-, and *p*-*tert*-butylphenols (TBP) isomerize and disproportionate in liquid hydrogen fluoride to varying extents depending on the temperature. At −40° the ortho isomer is isomerized exclusively to the para isomer. Above 0° the meta isomer tends to predominate and reaches a maximum of 86% of the total monoalkylated fraction beginning with *o*- or *p*-TBP. At 30–75° transalkylation to phenol and di-TBP occurs with the 3,5-di-TBP being preferentially formed. Above 75° extensive degradation of the molecule occurs with phenol and heavy tars being formed. Phenol is alkylated with isobutylene using catalytic amounts of HF to form the *p*-TBP and 2,4-di-TBP at 25°, but if solvent quantities of HF are used the *m*- and 3,5-di-TBP are obtained.

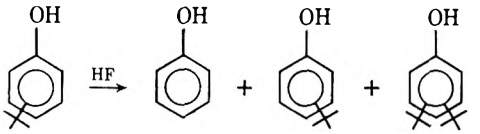
In the preceding paper[1] the Fries rearrangement of substituted phenyl benzoates was discussed. It was shown that when *tert*-butyl groups are on the phenolic ring there is a tendency toward dealkylation. Depending on the ring position, this dealkylation may be very extensive. For example, *p*-*tert*-butylphenyl benzoate gave only dealkylated *p*-hydroxybenzophenone, whereas the meta isomer gave a 40% yield of the Fries product, 2-hydroxy-4-*tert*-butylbenzophenone. We now make similar observations for the free *tert*-butylphenols (TBP), since the most stable TBP in liquid HF is the meta isomer. Also to be expanded in this report is the fact that the 3,5-di-TBP is the most stable disubstituted isomer and that alkylation of phenol with isobutylene in liquid HF can give both *m*-mono- and 3,5-di-TBP instead of the classical ortho and para derivatives.

The literature reports considerable work on reactions of *tert*-butylphenols with various acid catalysts, but no reports could be found in which HF alone was employed.[2] In an excellent study on isomerization of *tert*-butylphenols, Bolton, *et al.*,[3] using type Y zeolite catalysts at 100–200°, found that isomerization is always accompanied by transalkylation. The equilibrium distributions at 200° are approximately 1% ortho, 72% meta, and 25% para in the monophenol fraction with the dialkyl fraction consisting of 2% 2,6-, 83% 3,5-, 5% 2,4-, and 10% 2,5-di-TBP. These workers further demonstrated that the formation of the meta derivatives is attributable to the transalkylation of the ortho and para phenols and not to direct alkylation.

Formation of meta-substituted *tert*-butylphenols from a preparative viewpoint was first reported by Olin,[4] who isomerized *p*-TBP to a mixture containing the meta isomer over a catalyst of sulfuric acid supported on an activated clay. Later Bondy and Moore[5] obtained *m*-TBP from a mixture of *o*- and *p*-TBP on a similar type of catalyst. However, until the recent work by Bolton, *et al.*,[3] no careful study of the isomerization and transalkylation of *tert*-butyl phenols had been carried out. Thus we have investigated this isomerization in liquid HF at much lower temperatures than those for the zeolite work.

Results

Hydrogen fluoride functions as an excellent catalyst–solvent system for studying phenols in that it is nonoxidizing, is a very strong acid ($H_0 = -10$), and possesses a low boiling point (20°) to facilitate easy removal. The work involved dissolving each of the three mono-*tert*-butylphenols in liquid HF at temperatures from −75 to 100° for 2 hr. As shown in Table I, varying ratios of phenol, mono-*tert*-butylphenols, and di-*tert*-butylphenols were isolated by quenching the mixtures with ice followed by ether extraction after neutralization. The product distribution was determined by glc methods using the silylated derivatives (see Experimental Section). Especially at higher



temperatures, large amounts of "heavies" attributable to polyalkylated phenols and butylated oligomers were observed. The quantities of these materials were determined by use of an internal standard in the glc determination; the data in Table I are normalized to provide a ready visual comparison of the relative reactivities.

Pertinent observations gleaned from the results in Table I are as follows. (1) The ortho and para isomers at 30° tend toward the same equilibrium ratio in the monoalkyl fraction of approximately 85% *m*- and 15% *p*-TBP with none or traces of the ortho isomer being observed. This is roughly similar to the equilibrium values obtained by Bolton[2] working at 200° with zeolites. The meta isomer shows only a slight alteration, with the distribution being 98% meta and 2% para, indicating its higher stability. (2) At −75° there is essentially no isomerization and at 100° the molecule is greatly degraded with the principal product being phenol and unidentified oligomers. This effect is independent of the starting isomer. (3) A novel phenomenon occurs with the ortho isomer at −40° in that complete conversion to *p*-TBP is realized. The

(1) J. R. Norell, *J. Org. Chem.*, **38**, 1924 (1973).

(2) A recent review article entitled "Unusual Electrophilic Aromatic Substitutions in Synthesis," by D. E. Pearson and C. A. Buehler, *Synthesis*, 474 (1971), cites use of HF in a table for the transformation of 4-TBP to 3-TBP, but, on careful inspection of the original work, a Ph.D. thesis by R. Wysong, Vanderbilt University, 1967, p 40, it is revealed that actually a mixture of HF and BF_3 was used.

(3) A. P. Bolton, M. A. Lanewala, and P. E. Pickert, *J. Org. Chem.*, **33**, 3415 (1968).

(4) J. F. Olin (to Pennsalt Chemical Corp.), U. S. Patent 3,014,079 (Dec 19, 1961).

(5) M. F. Bondy and F. R. Moore (to Coalite and Chemical Products Ltd.), British Patent 992,629 (May 19, 1965).

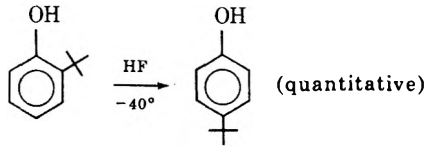
TABLE I

tert-BUTYLPHENOL ISOMERIZATION IN LIQUID HF[a]

tert-Butylphenol	Temp, °C	Amount recovered, %	Heavies, %	Phenolic distribution, wt %			Distribution of mono-TBP, %		
				Phenol	Mono-TBP	Di-TBP[c]	Ortho	Meta	Para
ortho	−75	95	0	2	92	6	98	0	2
ortho	−40	93	0	3	97	0	0	0	100
ortho	−5	93	Tr	10	77	13	0	19	81
ortho	30	95	3	24	24	52	0	86	14
ortho	55	83	8	32	22	46	1	80	19
ortho	75	90	19	42	25	33	6	74	20
ortho	100	81	41	89	8	2	27[b]	73[b]	0
meta[d]	−75	83	0	0	100	0	0	91	9
meta	−40	91	0	3	97	0	0	97	3
meta	−5	93	0	5	87	8	0	97	3
meta	30	96	Tr	12	61	27	0	98	2
meta	55	91	3	25	18	57	0	86	14
meta	75	93	11	30	24	46	0	83	17
meta	100	83	28	100	Tr	0	0	53[b]	47[b]
para	−75	94	0	0	100	0	0	0	100
para	−40	91	0	2	98	Tr	0	0	100
para	−5	93	Tr	9	77	14	0	18	82
para	30	94	22	26	22	52	0	86	14
para	55	91	30	37	22	41	2	84	14
para	75	100	35	45	23	32	3	80	17
para	100	79	22	88	12	0	74[b]	0	26[b]

[a] All runs were made with 15 g (0.10 mol) of *tert*-butylphenol in 100 ml of HF for 2 hr. [b] Where the amount of mono-*t*-BuPhOH is low, the distribution of ortho–meta–para is probably meaningless. [c] The dialkylated phenol is chiefly the 3,5 isomer. [d] Starting purity of *m*-*tert*-butylphenol was 91% meta and 9% para.

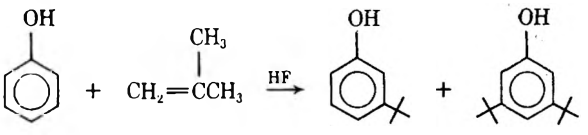
reaction is so "clean" that from the liquid ortho isomer, which readily dissolves in HF, the white crystalline



(quantitative)

para isomer is recovered nearly quantitatively. Further rearrangement, however, occurs as the temperature is increased. (4) Purchased *m*-TBP contained 9% of the para isomer, which was not easily removed by distillation. Increased purity is attained when the 91:9 mixture is placed in HF at 0–30°, since the purity of the monoalkyl fraction increases to 98.2% meta and 1.8% para. (5) The major constituent (>95%) of the dialkylated phenol is the 3,5-di-TBP. This represents a much larger amount than that observed over the zeolites.[2] This material arises *via* a transalkylation step and the method can serve as a synthesis for the 3,5 isomer starting with any of the mono-TBP. The amount of 3,5-di-TBP reaches a maximum of 40–50% at temperatures of 30–50°. Above these temperatures even the most stable 3,5 isomer tends to dealkylate and at 100° phenol *per se* is the chief volatile constituent. Even though the yield of 3,5-di-TBP is only moderate the method is superior to the original, but recent, synthesis which involves four steps.[6] Generally in the preparation of dialkylated phenols the ortho and para isomers, *i.e.*, 2,4-di-TBP, are those expected under normal alkylation conditions, or the 2,6-di-TBP can be obtained using aluminum phenoxide.[7]

In spite of literature reports[8] that phenol is never alkylated in the meta position, the above data on stabilities of *tert*-butyl groups suggested that meta-substituted products could be isolated under alkylation-type conditions, *i.e.*, reaction of isobutylene with phenol in HF. Indeed it was found that, if phenol is alkylated with isobutylene in solvent quantities of HF, *m*-TBP and 3,5-di-TBP are the principal phenols.



A summary of the data (Table II) collected indicates that *p*-TBP forms first and then it isomerizes and transalkylates to the *m*-TBP or 3,5-di-TBP. Preparatively, the method is fair (30% yield) for producing 3,5-di-TBP by direct alkylation because butylene oligomers form in a competing reaction. The reaction is best carried out with a small amount of HF catalyst at 25° to effect the "classical" alkylation in the ortho and para positions. The mixture is cooled and solvent quantities of HF are added so as to effect the isomerization and transalkylation to form the thermodynamically most stable isomers. An alternative method for synthesis of the 3,5 isomer involves the alkylation of *m*-TBP with isobutylene at 0° in 100 ml of HF, which gives a phenolic mixture of 50% 3,5-di-TBP, 7% *p*-TBP, and 43% unreacted *m*-TBP.

When other *tert*-butyl carbonium ion precursors are used, *i.e.*, *tert*-butyl alcohol and *tert*-butyl chloride, the yields are similar except that in the latter case the para isomer predominates, which is probably due to the lower temperature of reaction (Table II). Alkylation

(6) J. W. Elder and R. P. Mariella, *Can. J. Chem.*, **41**, 1653 (1963).

(7) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, p 760.

(8) J. H. Patinkin and B. S. Friedman, "Friedel–Crafts and Related Reactions," Vol. II, Part I, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, pp 75–77.

TABLE II

ALKYLATION OF PHENOL WITH ISOBUTYLENE IN HF

Run	Phenol, mol	Isobutylene, mol	HF, ml	Temp, °C	Time, hr	Product distribution (normalized)[a] Phenol	m-TBP	p-TBP	3,5-Di-TBP	2,4-Di-TBP	Comments
1	0.20	0.64	100	−70	0.7	1	0	35	0	64	C_4H_8 was bubbled in over a period of 1 hr
2	0.20	0.59	130	−78	2	4	0	80	0	17	A mixture of phenol in HF was added to a mixture of C_4H_8 in HF at −78°
3	0.20	0.23	100	0	2	5	11	61	20	3	C_4H_8 was bubbled in over a 2-hr period
4	0.20	0.40	125	−78 to 55	2	50	20	3	27	0	Run as in run 2 except warmed to 55°
5	0.10	0.20	104	−78 to 25	2	31	18	28	21	2	Phenol and 4 ml of HF were mixed at −78°, C_4H_8 was added and allowed to mix for 1 hr; 100 ml of HF was added, stirred for 1 hr at 78°, then warmed to 25°
6	0.16	0.20	104	−78 to 25	3	22	18	13	47	0	Phenol and 4 ml of HF were mixed at 78°, C_4H_8 was added and the reactor was shaken at 25° for 1 hr. A rapid exotherm occurred at 25–45°. After cooling to −78° 100 ml of HF was added and the mixture was again warmed to 25° for 2 hr
7	0.16	0.45	100	−70 to 25	2	28	13	48	11	0	Reactants were mixed at −78° and allowed to warm to 25°
8	0.20	0.40[b]	100	55	2	38	26	10	26	0	
9	0.10	0.20[c]	100	0	2	3	14	60	23	0	
10	0.24	0.49	10 g[d]	150	2	30	8	40	0	22	Benzene (50 ml) was used in a solvent

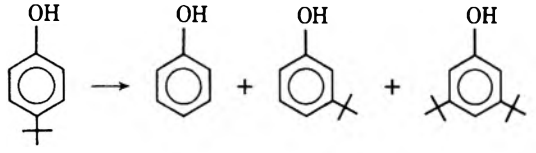
[a] Depending on the amount of excess isobutylene, the oligomer found varied to as much as 30%; therefore, the phenolic distribution has been normalized. [b] *tert*-Butyl alcohol was used in place of isobutylene. [c] *tert*-Butyl chloride was used in place of isobutylene. [d] Zeolon H, an acidic molecular sieve from Norton Chemical Co. which had been treated at 600° for 4 hr, was used in place of HF.

of phenol with isobutylene employing an acidic zeolite, Zeolon H, at 150° in benzene gave very little *m*-TBP and no detectable 3,5-di-TBP; *p*-TBP and 2,4-di-TBP were the chief products. Zeolon H is probably a much less acidic zeolite than the type Y used by Bolton, *et al.*,[3] and hence no meta isomers were produced.

Discussion

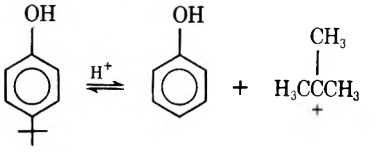
The kinetic experiments of Bolton, *et al.*, over zeolites at 200° coupled with our observations over a wide temperature range in liquid HF support the concept that isomerization of *tert*-butylphenols proceeds *via* a transalkylation mechanism rather than an intramolecular rearrangement.

For *p*-TBP the chief products found are as follows.

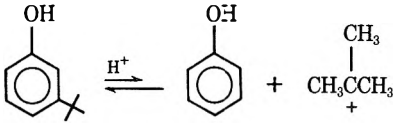


The meta derivatives tend to be more stable because during protonation of the phenol the meta position is less vulnerable to dealkylation, as presented in our previous paper.[1] Other than the 3,5 isomer, very little of the other dialkylated phenols are observed in liquid HF. This may be due to the fact that each experiment is run exhaustively rather than kinetically as reported for the zeolite case.[3]

The observation that the meta isomer is preferentially formed in solvent quantities of HF whereas the para isomer is the chief product when catalytic amounts of HF are employed during alkylation of phenol with isobutylene is best rationalized on an understanding of the reversibility of the reaction. In essence *p*-TBP and *o*-TBP, when placed in solvent quantities of HF, react reversibly as follows.



With the meta derivative this equilibrium lies much further to the left. Thus the *tert*-butyl carbonium ion



can attack in the ortho or para position or lose a proton forming an olefin, which is the equivalent of adding isobutylene to the reaction. Oligomers can be formed that utilize the *tert*-butyl carbonium ion. However, once attack occurs in the meta position reversibility is much less pronounced and hence a build-up of the meta isomer is observed. The same holds true for the 3,5-di-TBP. With catalytic amounts of catalyst the initial attack is at the electron-rich ortho and para centers and since insufficient HF is present for cleavage of the *tert*-butyl group, the para and 2,4 isomers are those isolated. Although some reports have been found for the formation of ortho derivatives and ethers in alkylation with acids,[8] we were unable to find any such materials in the reaction in HF. The rapid interconversion of ortho to para at −40° probably accounts for such observations.

Experimental Section

Apparatus.—All reactions above 0° were carried out in a 300-ml Monel vessel equipped with a pressure gauge and Hoke valves. Heating and mixing were supplied by shaking the reactor in an Eberbach thermostated reciprocating shaking water bath. For reactions at 0° and lower a polyethylene vessel was constructed (450-ml capacity) with two openings so that a thermometer could be inserted into the liquid. The reactor was placed in a coolant at the desired temperature and magnetically stirred.

Chemicals.—Hydrogen fluoride was obtained from Air Products Co. It was withdrawn in the liquid phase and was used directly without further purification. Note precautions to be observed when using HF.[1] All the *tert*-butylphenols (TBP) were obtained from Aldrich Chemical Co. The para isomer was used as received and the ortho and meta isomers were distilled prior to usage. Even after distillation, the composition of the latter was 91% *m*- and 9% *p*-TBP.

Analytical Procedure.—A variety of gas chromatographic procedures was employed throughout the course of this work for analyses of phenol, and the mono- and di-*tert*-butylphenols, with the most satisfactory method being described below. A total determination is based on a combination of glc chromatograms on both silylated and nonsilylated phenols using a Hewlett-Packard Model 5752-B gas chromatograph (T. C. cells). The column used was based on work by Duvall and Tulley[9] and consisted of a 60:40 mixture of silicone 550 and Carbowax 20M on silanized (DMCS) Chromosorb W, acid-washed, 60/80 mesh, packed in a 10 ft × 0.25 in. stainless steel column. Loading of the liquid phase was 9% on the support for the silylated samples and 17% for the free phenols. Samples were silylated with Regisil, *N,O*-bis(trimethylsilyl)trifluoroacetamide from Regis Chemical Co., 100–200-mg sample/1 ml Regisil, and column conditions were as follows: 3-min postinjection period, programmed from 140° to 165° at 10°/min, held for 20 min.

Under these conditions, the following elution times were observed for the silylated derivatives (Table III).

TABLE III

Component	Retention time, min:sec	Correction factors
Phenol	4:10	0.92
o- and *m*-TBP	9:25	1.05
p-TBP	10:12	1.05
3,5-di-TBP	14:55	1.17
2,4-di-TBP	16:45	1.17
2,5-di-TBP	17:35	1.17

Prior to silylation all the expected components are separable except the meta and para isomers, whereas after silylation the *o*- and *m*-*tert*-butylphenols are not separable. Thus, two chromatograms are required for each sample and the exact amount of each isomer is determined by arithmetic methods. Elution times for the nonsilylated phenols on a similar column except isothermally at 225° gave the following retention times (Table IV).

Quantitative measurements were made by use of a Disc Integrator which gave the number of counts per peak. Correction factors were determined by use of carefully weighed knowns for both the silylated and nonsilylated samples. The percentages of heavies, *i.e.*, butylene oligomers, heavily alkylated phenols, and other material not eluting on the column, were determined by weighing a known amount of *p*-cresol into the sample, as an internal standard, prior to glc analysis. This technique was employed only on nonsilylated samples. The equation from which the percentage of heavies was determined is

$$\% \text{ heavies} = \frac{\text{wt of sample} - \text{wt of std} \times \frac{\text{total peak ct}}{\text{std ct}}}{\text{wt of sample}} \times 100$$

TABLE IV

Component	Retention time, min:sec	Correction factors
Phenol	4:07	0.92
2,6-di-TBP	6:27	1.00
o-TBP	7:21	1.05
m- and *p*-TBP	9:36	1.05
2,4-di-TBP	12:07	1.00
3,5-di-TBP	16:05	1.17

Standard Procedure for Reactions above 0°.—The phenol was placed in a 300-ml Monel reactor cooled in ice under a N_2 flow. Liquid hydrogen fluoride was added, and the reactor was capped and placed in the shaker bath at the desired temperature. After the allotted time, the reactor was cooled, the valve was opened, and the HF was bled off. The reactor was opened and the reaction mixture was poured into ice water, neutralized with $NaHCO_3$, and extracted with ether. After drying over $MgSO_4$–K_2CO_3 mixture, the extracts were concentrated to give the crude phenol mixture as recorded in Table I.

Standard Procedure for Reaction below 0°.—The 450-ml polyethylene reactor containing 100–150 ml of HF was cooled in the suitable collant until the temperature reached that specified. The phenol was added and stirred magnetically for the allotted time. The entire mixture was quickly poured on ice, neutralized with $NaHCO_3$, and extracted with ether. After drying, the extracts were concentrated to give the crude phenol mixtures.

General Procedure for Alkylation Reactions (Table II).—The phenol was placed in either the Monel or polyethylene reactor and HF was cautiously added. The mixture was cooled or heated to the desired temperature and isobutylene or other *tert*-butyl carbonium ion source was added. Isobutylene was usually added slowly through a Gilmont gas flow meter. The reactor was then shaken or stirred at the specified time and temperature. The contents were poured on ice, and ether extracted, and the combined ether extracts were neutralized by shaking with saturated $NaHCO_3$ solution. After drying over $MgSO_4$ and concentration the resulting, usually viscous, residues were analyzed by glc techniques described above. The data displayed in Table II are representative runs of many experiments under a variety of conditions. Because the various methods employed for carrying out the reaction greatly affect the product distribution, a column entitled "Comments" is included in Table II.

Registry No.—Hydrogen fluoride, 7664-39-3; *o*-*tert*-butylphenol, 88-18-6; *m*-*tert*-butylphenol, 585-34-2; *p*-*tert*-butylphenol, 98-54-4; phenol, 108-95-2; isobutylene, 115-11-7.

Acknowledgment.—The helpful discussions with Dr. John E. Mahan and the capable laboratory assistance of Mr. Bill Loffer are gratefully recognized.

(9) A. H. Duvall and W. F. Tulley, *J. Chromatogr.*, **11**, 38 (1963).

The Stereochemistry of Febrifugine. I. The Equilibrium between *cis*- and *trans*-(3-Substituted 2-piperidyl)-2-propanones

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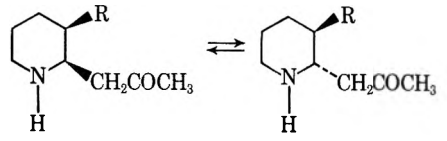
A facile thermal equilibration of *cis*-(3-methoxy-2-piperidyl)-2-propanone and some analogous *cis*-(3-substituted 2-piperidyl)-2-propanones with their trans isomers is reported. The effects on the equilibrium of temperature, solvent, pH, and the size of the 3 substituent were investigated. Chemical and nmr spectral data and conformational free-energy calculations are presented to support the assignment of the trans configuration to the more stable isomer. A revised synthesis of the title compounds is reported. The title compounds are intermediates in the synthesis of febrifugines.

The hydrangea alkaloid, febrifugine, and many of its synthetic analogs have been extensively investigated because of their antimalarial[1] and anticoccidial[2] activity. In the course of the synthesis of some febrifugines using a route first developed by Baker, *et al.*,[3] it was discovered that the intermediate **1a** readily undergoes isomerization. It was subsequently found that the analogous compounds **1b–d** undergo a similar isomerization.

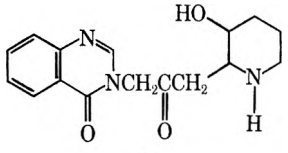
It would be expected that the compounds **1**, which are synthesized by hydrogenation of the corresponding



1 **2**

a, R = OCH_3; **b**, R = OC_2H_5; **c**, R = $OCH(CH_3)_2$; **d**, R = CH_3

pyridines (**5**), would possess the cis configuration and that they would equilibrate to mixtures favoring the trans isomers (**2**). However, our initial thinking on this subject was complicated by the fact that Baker had assigned the cis configuration to febrifugine (**3**).



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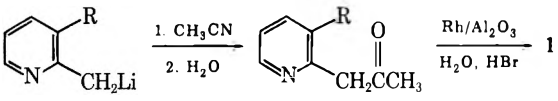
He was unaware of the easy isomerization of **1a** and interpreted his results as further confirmation of the cis configuration, originally assigned on the basis of other work.[4] Because of this conflicting evidence we studied the isomerization in some detail. In this paper we will present the evidence that the configurations of **1** and **2** are as expected, and part II[5] will present the evidence that febrifugine (**3**) has the isomerized or trans configuration.

We found it convenient to synthesize *cis*-(3-alkoxy-2-piperidyl)-2-propanones (**1a–c**) and *cis*-(3-methyl-2-piperidyl)-2-propanone (**1d**) *via* Scheme I. This sequence is more convenient than the longer route of Baker, *et al.*,[3] involving condensation of **4** with acetaldehyde followed by hydrogenation and chromic acid oxidation of the secondary alcohol. Rhodium on alumina in water in the presence of 1 equiv of hydrobromic acid at 3–4 atm and ~50–70° is quite selective for the reduction of the pyridine ring in the presence of the ketone. A high degree of selectivity is achieved only when the (3-substituted 2-pyridyl)-2-propanones (**5**) are carefully purified by distillation. Otherwise the impurities present act as catalyst poisons, and, as the rate of hydrogenation diminishes, the selectivity is also lost.[6] The hydrogenation product is a single isomer to the limits of detectability by nmr (>95%), and the available evidence in the literature[7] suggests that under these conditions the cis isomer would predominate. Our observations on the isomerization also support this conclusion. Additionally, we tried hydrogenation of the free base in methanol over rhodium on carbon, of the free base in acetic acid over rhodium on alumina or palladium on carbon, and of the hydrobromide salt in methanol or the free base in acetic acid over platinum oxide, but none of these systems gave a rapid selective reduction.

SCHEME I



4 **5**

a, R = OCH_3; **b**, R = OC_2H_5; **c**, R = $OCH(CH_3)_2$; **d**, R = CH_3

Equilibrium between **1** and **2** is established by heating for ~1 hr on a steam bath under nitrogen or in refluxing toluene. Equilibration occurs in ~3–4 weeks at room temperature, and it is essentially complete after 10 months' storage at 5°. Depending upon

(1) R. I. Hewitt, W. S. Wallace, E. R. Gill, and J. H. Williams, *Am. J. Trop. Med. Hyg.*, **1**, 768 (1952).

(2) E. Waletzky, G. Berkelhammer, and S. Kantor, U. S. Patent 3,320,124 (1967).

(3) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).

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(5) D. F. Barringer, Jr., G. Berkelhammer, and R. S. Wayne, *J. Org. Chem.*, **38**, 1937 (1973).

(6) Unpublished work of Dr. J. R. Giacin, American Cyanamid Co., Agricultural Division.

(7) H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Amer. Chem. Soc.*, **56**, 2425 (1934); R. A. Robinson, *J. Org. Chem.*, **16**, 1911 (1951); J. Pliml, E. Knoblock, and M. Protiva, *Chem. Listy*, **46**, 758 (1952); F. Galinovsky, O. Vogl, and W. Moroz, *Monatsh. Chem.*, **83**, 242 (1952); F. Galinovsky and H. Langer, *ibid.*, **86**, 449 (1955); F. Bohlmann, A. Englisch, N. Ottawa, H. Sander, and W. Weise, *Chem. Ber.*, **89**, (1956); M. Freifelder, D. A. Dunnigan, and E. J. Baker, *J. Org. Chem.*, **31**, 3438 (1966); B. van de Graff, H. van Bekkum, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **87**, 777 (1968).

the pot temperature used, it can also occur during a vacuum distillation.

To study the isomerization, a convenient method for determining the isomeric composition was needed. The nmr spectrum turned out to be very well suited for this determination. Depending upon the solvent chosen, either the protons of the methyl group in the acetonyl substituent or the protons on the α carbon of the alkoxy group exhibit different chemical shifts in the two isomers. We used either benzene or toluene as the solvent, and in these solvents the protons of the methyl group on the acetonyl substituent appeared at 3 Hz higher field in the trans isomer. The two peaks were well resolved, and the results were quite reproducible. Unfortunately we were unable to determine the stereochemistry directly from the ring protons α to the substituents because of the complexity of the spectra.

The effects of temperature, solvent, pH, and the steric requirement of the 3 substituent on the equilibrium were studied. The temperature of the equilibration in toluene had no demonstrable effect on the position of the equilibrium. *cis*-(3-Ethoxy-2-piperidyl)-2-propanone (**1b**) was isomerized at 80°, reflux (110.6°), and 140° in a sealed tube to 68:32, 69:31, and 67:33 trans–cis mixtures, repectively.[8] These values are the same within experimental error. The isomerization required 23–31 hr, ~3 hr, and slightly more than 0.5 hr at the three temperatures.

The effects of various solvents on the equilibration are summarized in Table I. Only in the case of water

TABLE I

EFFECT OF SOLVENTS ON THE CIS ⇄ TRANS EQUILIBRIUM OF (3-ETHOXY-2-PIPERIDYL)-2-PROPANONE

Solvent	Concn, %	Temp, °C	Time, hr[a]	% trans
Water[c]	5	98–102	20 min[d]	76
Cyclohexanol	10	98–100	1	67
tert-Butyl alcohol	10	Reflux (82.6)	4[e]	69
Neat		78–82	1.5[b]	51
Neat		96–101	0.5[b]	60
Neat		96–101	1[b]	67
Neat		96–101	1.5[b]	70
Toluene	10	95–100	22.5[f]	70
Toluene	10	Reflux (110.6)	3	69

[a] For runs in solution, this is the time after which no further change in isomer ratio occurred as was determined by at least one measurement after the time listed. For neat runs, see *b*. Started with 100% cis isomer. [b] Not necessarily complete equilibration. At 96–101° the 1-hr and 1.5-hr ratios are probably the same within experimental error. [c] pH 10.6 (pH meter). [d] 55% trans at 7 min, 75% trans at 30 min. [e] 52% trans at 1.5 hr, 65% trans at 3 hr. [f] Almost complete at 6.5 hr.

is the isomer ratio significantly different from that obtained in toluene or in the absence of solvent. The increase in the proportion of trans isomer in water solution is probably due to coordination of the solvent with the ether oxygen and/or the nitrogen, which would increase the steric interactions in the cis isomer.

(8) Febrifugines synthesized from trans–cis mixtures such as these for **1a–c** usually contained 90% or more trans isomer, as was determined by quantitative thin layer chromatography. The difference in trans content between the intermediates and the febrifugine products is probably due to the preferential solubility of salts of the *cis*-febrifugines in ethanol, the solvent used for purification.

Apparently the two alcohols do not bond tightly enough to have a measurable effect. All three polar hydroxylic solvents enhanced the rate of the isomerization compared with toluene. The minimum time for equilibration in toluene is probably not very much greater than 6.5 hr (footnote *f*, Table I), while the minimum in cyclohexanol is 1 hr or less and in water 20 min or less. The demonstrated effect of solvent polarity would be expected where charge separation is present in the transition state.

The effect of pH on the position of the equilibrium in water solution was examined. A 5% solution of equilibrated (3-ethoxy-2-piperidyl)-2-propanone (**2b**, 68% trans) in water had a pH of 10.6. The pH of the other samples was adjusted up or down with aqueous sodium hydroxide or hydrochloric acid. The solutions were heated in a bath at 94–100°, and the free base was isolated and dissolved in toluene for nmr measurements (see Experimental Section).

The results are shown in Table II. The % trans isomer decreases with decreasing pH in the range

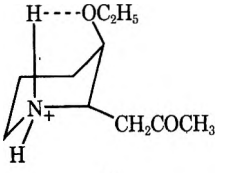
TABLE II

EFFECT OF pH ON THE CIS ⇄ TRANS EQUILIBRIUM OF (3-ETHOXY-2-PIPERIDYL)-2-PROPANONE

	% recovery			% trans isomer		
pH[a]	3 hr	5.5 hr	20 min	3 hr	4 hr	5.5 hr
0.5 *N* NaOH[b]	92			75		
0.1 *N* NaOH	91	86		76		75
10.6[c]			76[c]			
9.9	88	84		72		71
8.0[d]					56[d]	
6.9	94	79		46		47
5.9	91	87		61		48[e]
4.8[a]	76	88		63		48

[a] The pH remained constant during each run except the one at 4.8, which increased to 6.4 after 5.5 hours, presumably owing to loss of HCl. [b] Not completely homogeneous. Ir after run showed evidence of decomposition. [c] Started with cis isomer. Equilibrium reached in 20 min. [d] Run at 105–110°. [e] 5.5-hr sample redissolved in water at pH 6.0 and heated for 3 hr more at 98–99°. No further change in % trans isomer.

where the proportions of free base and hydrochloride salt are varying, and it remains fairly constant above and below this range. The probable explanation for this effect is transannular hydrogen bonding in the salt **6**. This would reduce the conformational free



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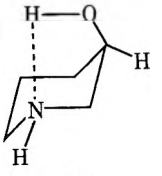

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energy penalty for the axial ethoxy group in the cis isomer. Similar hydrogen bonding has been observed in 3-piperidinol (**7**) and its *N*-alkyl derivatives.[9] Hydrogen bonding would be expected to be much less important in the free base of **6** since the evidence at this time favors the hypothesis that a proton bonded to nitrogen has greater steric requirements than an

(9) G. Hite, E. E. Smissman, and R. West, *J. Amer. Chem. Soc.*, **82**, 1207 (1960); R. E. Lyle, D. H. McMahon, W. E. Grueger, and C. K. Spicer, *J. Org. Chem.*, **31**, 4164 (1966).

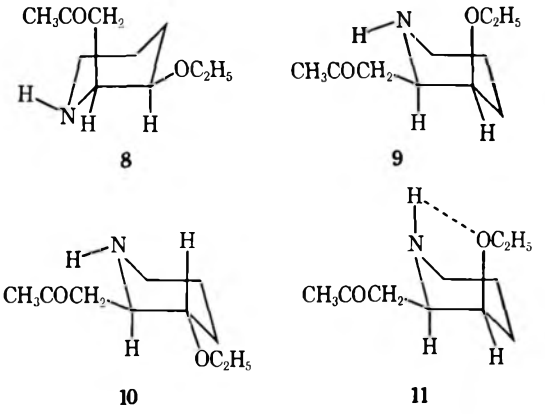
electron pair,[10] and ammonium ions would be expected to form stronger hydrogen bonds than free amines. The rate of isomerization is less at pH values below 7 than above 7, in agreement with a base-catalyzed mechanism.

When a pyridine solution of the hydrochloride of 68% *trans*-(3-ethoxy-2-piperidyl)-2-propanone (**2b**) was heated on a steam bath for 3.5 hr, the equilibrium shifted slightly toward the cis isomer, giving a trans:cis ratio of 1.83:1 (65% trans). Presumably this reflects a small contribution from structure **6** in this medium.

There were no significant differences in the extent of isomerization of the (3-alkoxy-2-piperidyl)-2-propanones (**1a**, **1b**, and **1c**) studied (69, 68, and 67%). This is what one would expect, since the conformational free energies for methoxy, ethoxy, and isopropoxy groups are about the same. When a methyl group (*vide infra*) was placed in the 3 position, however, there was a large shift in favor of the trans isomer (**2d**). This can be explained by the larger conformational free energy of a methyl group and the lack of any stabilization of the cis isomer by transannular hydrogen bonding.

The theoretical position of the cis $\rightleftarrows$ trans equilibrium of (3-ethoxy-2-piperidyl)-2-propanone (**1b** $\rightleftarrows$ **2b**) can be approximated using conformational free-energy differences determined for substituents on cyclohexane systems.[11] The conformational free-energy difference for an acetonyl substituent apparently has not been determined, but the value of 1.7 kcal/mol for a methyl group can be used as a minimum value. The value for an ethoxy group is 0.9 kcal/mol.

To simplify the computations, two conformations (**8** and **9**) were considered for the cis isomer and one



(**10**) for the trans isomer. The other conformation for the trans isomer has the two large groups axial and would be expected to be essentially absent. Only conformations with the proton on the nitrogen in the equatorial position were considered. Since an axial group in the 3 position of piperidine has only one 1,3-diaxial interaction with hydrogen, the conformational free energy was reduced by one-half to a value of 0.45. It is probably true that the hydrogen-bonded conformation (**11**) contributes some extra stability to the cis isomer, but, since we have no data from which to estimate the contribution of **11**, it was ignored in the computation.

On the basis of these assumptions the equilibrium mixture of the isomeric (3-ethoxy-2-piperidyl)-2-propanones (**1b** and **2b**) was calculated to contain 73% trans at 25° and 69% trans at the boiling point of toluene (111°). These values compare well with the experimentally observed trans concentration of about 70%.

cis-(3-Methyl-2-piperidyl)-2-propanone (**1d**) was synthesized and isomerized as an intermediate for a febrifugine analog. A similar calculation on this equilibrium predicts 85% trans at 25° and 79% at 111°. The amount of cis isomer in the mixture is too small to be determined accurately by the nmr method, but it appears to be ~10% in the crude product and considerably less after distillation. Since in this case there is no opportunity for transannular hydrogen bonding to give unusual stability to the cis isomer, it is quite certain that the more stable isomer is trans. Since the synthesis route and equilibrium results with the (3-alkoxy-2-piperidyl)-2-propanones were analogous, initial formation of the cis isomers followed by predominant isomerization to trans must also have occurred in this series. The differences in the compositions of the equilibrium mixtures also agree well with the predictions based on conformational free energies.

A further confirmation of the stereochemistry of the (3-methyl-2-piperidyl)-2-propanones can be found in the nmr resonance of the 3-methyl group. In the cis isomer this resonance is a doublet (J = 6.5 Hz) centered at δ 0.96. In the trans isomer it is a partly resolved, unequal doublet (J = 3.5 Hz) centered at δ 0.82. This same effect was reported in the case of the isomeric 2,3-dimethylpiperidines,[12] and it was attributed to the effect of the strong upfield shift of the proton on the adjacent ring carbon on going from the cis to the trans configuration.

The mechanism of the isomerization can be described as a base-catalyzed β elimination followed by a Michael addition, analogous to a mechanism proposed for the racemization of pelletierine (**12**)[13] (Scheme II).

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord Model 137. Nmr spectra were recorded on a Varian A-60.

(3-Methoxy-2-pyridyl)-2-propanone (5a).—The reaction was run in a stirred flask under a nitrogen atmosphere. A hexane solution (397.4 g) containing 0.924 mol of *n*-butyllithium was introduced into the flask along with 909 g of absolute ether. 3-Methoxy-2-picoline (103.3 g, 0.840 mol) was added dropwise at 0–5°. The 3-methoxy-2-picolyllithium partially precipitated as a yellow solid. The mixture was allowed to warm briefly to 10°, and 37.9 g (0.924 mol, 48.4 ml) of acetonitrile was added dropwise at 4° over a 1.5-hr period. The mixture was allowed

(10) P. J. Brignell, A. R. Katritzky, and P. L. Russell, *Chem. Commun.*, 723 (1966); N. L. Allinger, J. G. Carpenter, and F. M. Karkonski, *Tetrahedron Lett.*, 3345 (1964); *J. Amer. Chem. Soc.*, **87**, 1232 (1965); F. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 218 (1961); *J. Chem. Soc.*, 2637 (1962); N. W. Pumphrey and M. J. Robinson, *Chem. Ind. (London)*, 1903 (1963). However, J. B. Lambert and R. G. Keske [*J. Amer. Chem. Soc.*, **88**, 621 (1966)] have presented evidence that the hydrogen may have smaller steric requirements than the electron pair.

(11) E. Eliel, N. Allinger, S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 11, 44.

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(13) F. Galinovsky, G. Bianchetti, and O. Vogl, *Monatsh. Chem.*, **84**, 1221 (1953).

TABLE III

(3-SUBSTITUTED 2-PYRIDYL)-2-PROPANONES (5)

R	Yield, %	$n^{25}D$	Bp, °C (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
OC_2H_5	72	1.5179	94 (0.4)	67.02	7.31	7.82	66.94	7.62	8.25
$OCH(CH_3)_2$	69		32 (0.2)	68.37	7.82	7.25	68.59	7.88	7.40
CH_3	72	1.5338	68 (0.15)	Not analytically pure					

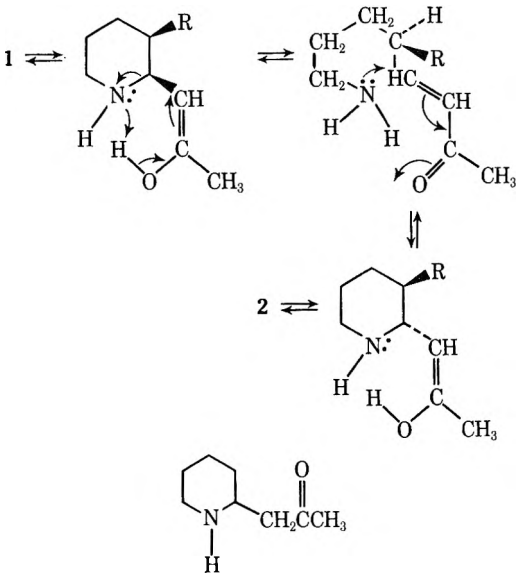
TABLE IV

TRANS-RICH (3-SUBSTITUTED 2-PIPERIDYL)-2-PROPANONES (2)

R	Yield, %	Bp, °C (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Br	Found, % C	Found, % H	Found, % N	Found, % Br
OC_2H_5[a]	68	88–93 (1.25)	45.11	7.47	5.26	30.01	45.39	7.70	5.21	29.79
$OCH(CH_3)_2$	95+[b]									
CH_3[c]		54–61 (0.4)	69.63	11.04	9.02		69.67	10.99	9.11	

[a] Analyzed as the hydrobromide, mp 164–167°, prepared by passing HBr into a toluene solution of the free base, followed by trituration in and recrystallization from acetone. Isolation of the free base from this salt gave samples containing 85–95% trans isomer. [b] Crude yield. Structure assigned on the basis of nmr spectrum and subsequent conversion to a *trans*-febrifugine. [c] Analyzed as the free base.

SCHEME II



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to warm to 10° yielding a dark red solution. One liter of 3 *N* sulfuric acid was added cautiously at 20–30°. The layers were separated, and the aqueous layer was adjusted to pH 10 with 10% sodium hydroxide. The product was extracted with 4 × 500 ml of chloroform. Evaporation of the solvent yielded 173 g of an oil which was distilled under vacuum through a Vigreux column to yield 105.7 g (76%) of a yellow oil: bp 86–89° (0.1 mm); $n^{26.5}D$ 1.5284; principal ir bands at ν_{max}^{neat} ~2950 (five peaks), 1720, 1645, ~1675 (three peaks), 1455, 1430, 1355, 1280, 1120, 1025, 802 cm^{-1}. *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 64.9; H, 6.6; N, 8.9.

Other (3-substituted 2-pyridyl)-2-propanones (5) synthesized by this route are listed in Table III.

cis-(3-Methoxy-2-piperidyl)-2-propanone (1a).—A solution of 20.37 g (0.1235 mol) of (3-methoxy-2-pyridyl)-2-propanone in 250 ml of water was adjusted to pH 2 with 48% hydrobromic acid. This solution was hydrogenated over 2.0 g of 5% rhodium on alumina in a Parr apparatus at an initial pressure of 50.3 psi and a temperature of 55° measured in an external thermometer well. After 7.5 hr the mixture was cooled to room temperature. The pressure drop was 32.5 psi (101% of theory). The catalyst was filtered out, the solution was basified to pH >12 with sodium hydroxide, and the product was extracted with methylene chloride. The methylene chloride solution was dried and evaporated under vacuum to yield 18.87 g (0.1162 mol, 94%) of a yellow oil. This compound was not purified owing to its instability with respect to thermal isomerization. Principal infrared bands appeared at ν_{max}^{neat} 3330, 2930, 1710, 1460, 1440, 1360, 1100 cm^{-1} (broad). There is no absorption between 1710 and 1460 cm^{-1}. The spectrum is not very sensitive to small amounts of the corresponding secondary alcohol. This by-product is formed in the reduction of impure starting material, and its formation is accompained by a reduced rate of hydrogenation and spectral evidence for the presence of the pyridine ring (band at 1675 cm^{-1}) even after consumption of the theoretical amount of hydrogen.

Phenyl Isothiocyanate Derivative.—When 5 ml each of 0.2 *M* ether solutions of *cis*-(3-methoxy-2-piperidyl)-2-propanone and phenyl isothiocyanate were mixed and left standing for 15 min at room temperature and overnight in a refrigerator, a pale yellow crystalline derivative, mp 129–130°, was obtained in 40–60% yield: ir (mineral oil mull) ν_{max} 3260, 1590, 1330, 1080, 820 cm^{-1}; $\lambda_{max}^{0.1\ N\ NaOH}$ 214 nm (ϵ 19,700), 242 (broad, 19,300); λ_{max}^{MeOH} 225 nm (ϵ 17,700), 255 (15,300). *Anal.* Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.7; H, 7.24; N, 9.14; S, 10.5. Found: C, 62.7; H, 7.00; N, 9.31; S, 10.5.

The other *cis*-(3-substituted-2-piperidyl)-2-propanones (1) were prepared in similar fashion.

Isomerization of *cis*-(3-Methoxy-2-piperidyl)-2-propanone to *trans*-(3-Methoxy-2-piperidyl)-2-propanone.—This reaction was run either with or without a solvent (see Table I). The liquid was kept under a nitrogen atmosphere while hot to retard decomposition. The crude product was isolated from organic solvents by evaporation at moderate temperatures (<50°) on a rotary vacuum evaporator. Isolation from water solutions was effected by making the solution alkaline with sodium hydroxide and extracting with methylene chloride or chloroform. In a typical preparation 4.99 g (0.0292 mol) of *cis*-(3-methoxy-2-piperidyl)-2-propanone was dissolved in 100 ml of toluene, and the solution was heated under reflux for 3.5 hr. The solvent was evaporated under vacuum and the residue was distilled to yield 4.11 g (0.0240 mol, 82%) of the trans-rich equilibrium mixture as a nearly colorless oil: bp 88–93° (2.5 mm); principal ir bands at ν_{max}^{neat} 3380, 2940, 1704, 1460, 1440, 1360, 1100 cm^{-1} (broad). *Anal.* Calcd for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.18. Found: C, 63.5; H, 10.2; N, 8.57. The phenyl isothiocyanate derivative, prepared as for the cis ketone, had mp 165–169° and principal ir bands (mineral oil mull) at ν_{max} 3230, 1700, 1600, 1320, 1080 cm^{-1}; $\lambda_{max}^{0.1\ N\ NaOH}$ 214 nm (ϵ 20,100), 242 (broad, 19,000); λ_{max}^{MeOH} 224 nm (ϵ 17,800), 255 (14,400). *Anal.* Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.7; H, 7.24; N, 9.14; S, 10.5; OCH_3, 9.72. Found: C, 62.2; H, 7.34; N, 9.01; S, 10.2; OCH_3, 9.99.

Other trans-rich (3-substituted 2-piperidyl)-2-propanones (2) prepared in the same manner are listed in Table IV.

Determination of Isomer Ratios in (3-Alkoxy-2-piperidyl)-2-propanones and (3-Methyl-2-piperidyl)-2-propanone.—The isomer ratios were determined by comparing the nmr integrals for the methyl group α to the carbonyl in each of the isomers (Table V). The best solvents for this comparison were benzene or toluene. A 10% solution of the equilibrium mixture of the isomeric (3-ethoxy-2-piperidyl)-2-propanones gave nmr peaks at δ 1.76 and 1.82 for the trans and cis isomers. The peaks were well resolved when a 100-Hz sweep width was used on a Varian A-60.

TABLE V
PRINCIPAL NMR OF (3-SUBSTITUTED 2-PIPERIDYL)-2-PROPANONES

	Nmr[a]			
	Cis		Trans	
R	$COCH_3$	CCH_3	$COCH_3$	CCH_3
OCH_3	1.80		1.75	
OC_2H_5	1.82		1.76	
$OCH(CH_3)_2$	1.88		1.82	
CH_3	2.23	0.96	2.11	0.82

[a] 10% toluene solutions except for the 3-methyl compound which was 50% in chloroform. Chemical shifts given in δ (parts per million) from tetramethylsilane.

A 30% solution shows the peaks shifted to δ 1.84 and 1.88 with incomplete resolution. The results were similar in benzene and for the other alkoxy substituents. In the case of the 3-methyl analog, the peaks were at δ 2.11 and 2.23 in $CHCl_3$ for the trans and cis isomers. When toluene is the solvent, care must be taken to avoid interference from the spinning side bands of the solvent methyl group.

Registry No.—**1a**, 39037-79-1; **1a** phenyl isothiocyanate derivative, 39037-80-4; **1b**, 39037-81-5; **1c**, 39037-82-6; **1d**, 39037-83-7; **2a**, 39037-84-8; **2a** phenyl isothiocyanate derivative, 39037-85-9; **2b**, 39004-80-3; **2c**, 39037-86-0; **2d**, 39037-87-1; *cis*-**3**, 39037-92-8; *trans*-**3**, 39037-90-6; **4a**, 39049-96-2; **4b**, 39049-97-3; **4c**, 39049-98-4; **4d**, 39049-99-5; **5a**, 6652-00-2; **5b**, 6651-69-0; **5c**, 39050-02-7; **5d**, 39050-03-8; 3-methoxy-2-picoline, 26395-26-6; acetonitrile, 75-05-8.

The Stereochemistry of Febrifugine. II. Evidence for the Trans Configuration in the Piperidine Ring

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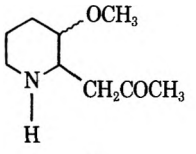
Evidence from nmr spectra and thin layer chromatography is presented pointing to the conclusion that the substituents on the piperidine ring of the hydrangea alkaloid, febrifugine, are in the trans configuration. The absolute stereochemistry proposed is (2′*S*,3′*R*)-3-[3-(3-hydroxy-2-piperidyl)acetonyl]-4(3*H*)-quinazolinone.

The discovery of the facile isomerization of (3-methoxy-2-piperidyl)-2-propanone (**1**),[1] a key inter-



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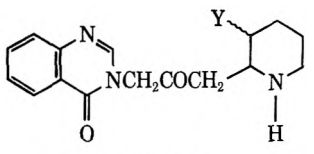
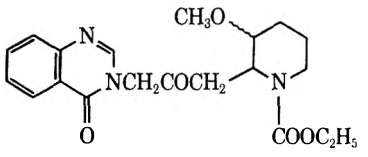


2a, Y = OH, trans
b, Y = OH, cis
c, Y = $OCOCH_3$, trans

mediate in one synthesis of the hydrangea alkaloid, febrifugine (**2a**),[2] led to a reconsideration of the stereochemistry of the piperidine moiety of febrifugine. Baker, *et al.*, synthesized a second intermediate (**3**)[2]



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from (3-methoxy-2-piperidyl)-2-propanone (**1**) and showed that it was identical with a sample prepared by two other routes.[3] Compound **3** had previously been converted into febrifugine by removal of the blocking groups and had been assigned the cis configuration (**2b**). However, test results against coccidiosis in chicks with both synthetic isomers of febrifugine and some analogs with substituents on the aromatic ring clearly showed that the trans isomers possessed the expected biological activity. The *trans*-febrifugines are approximately ten times as effective as the *cis*-febrifugines against coccidia in chickens. The activity of the cis isomers is substantially, if not entirely, due to contamination with the trans isomer which is estimated to be present to the extent of 5–10% from thin layer chromatograms.

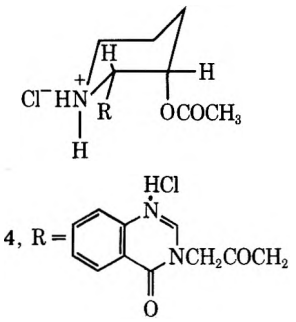
We isolated a sample of febrifugine dihydrochloride from hydrangea according to the procedure of Ablondi, *et al.*[4] The melting point, specific rotation, and ir spectrum all checked with the published data. The free base was prepared according to Hutchings, *et al.*,[5] and its melting point of 156.5–158.5° agreed well with the reported melting point of 154–156°[6] for the higher melting dimorph. The cis and trans racemic febrifugines (**2a,b**) were synthesized by published procedures[1,2] from the isomeric (3-methoxy-2-piperidyl)-2-propanones. Although *trans*-(3-methoxy-2-piperidyl)-2-propanone synthesized by our usual procedure contains from 25–35% of the cis isomer, purification of the febrifugine salts by recrystallization removes the cis isomer and affords the trans compound in high purity.

Thin layer chromatography (see Experimental Section) showed that the *trans*-febrifugine was pure, while the cis isomer contained a small amount of the trans. The compound isolated from hydrangea had the same R_f value as the synthesized *trans*-febrifugine. The melting point of the synthesized racemic *trans*-febrifugine, 178.5–180.5°, was higher than that of the naturally occurring dextrorotatory compound. The cis isomer melted at ~134–136°. It was impossible to obtain a precise melting point since the cis isomer underwent a rapid isomerization to the trans compound

(1) D. F. Barringer, Jr., G. Berkelhammer, S. D. Carter, L. Goldman, and A. E. Lanzilotti, *J. Org. Chem.*, **38**, 1933 (1973).
(2) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).
(3) (a) B. R. Baker, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 132 (1952); (b) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *ibid.*, **18**, 153 (1953).
(4) F. Ablondi, S. Gordon, J. Morton, II, and J. H. Williams, *J. Org. Chem.*, **17**, 14 (1952).
(5) B. L. Hutchings, S. Gordon, F. Ablondi, C. F. Wolf, and J. H. Williams, *J. Org. Chem.*, **17**, 19 (1952).
(6) J. B. Koepfli, J. F. Mead, and J. A. Brockman, Jr., *J. Amer. Chem. Soc.*, **71**, 1048 (1949).

near its melting point, and the melting point could be observed only on very rapid heating. The ir spectra of the three compounds were run in arsenic trichloride solution. The spectra of the natural product and the synthesized *trans*-febrifugine were identical while the spectrum of the cis isomer differed in the 900–1250-cm^{-1} region.

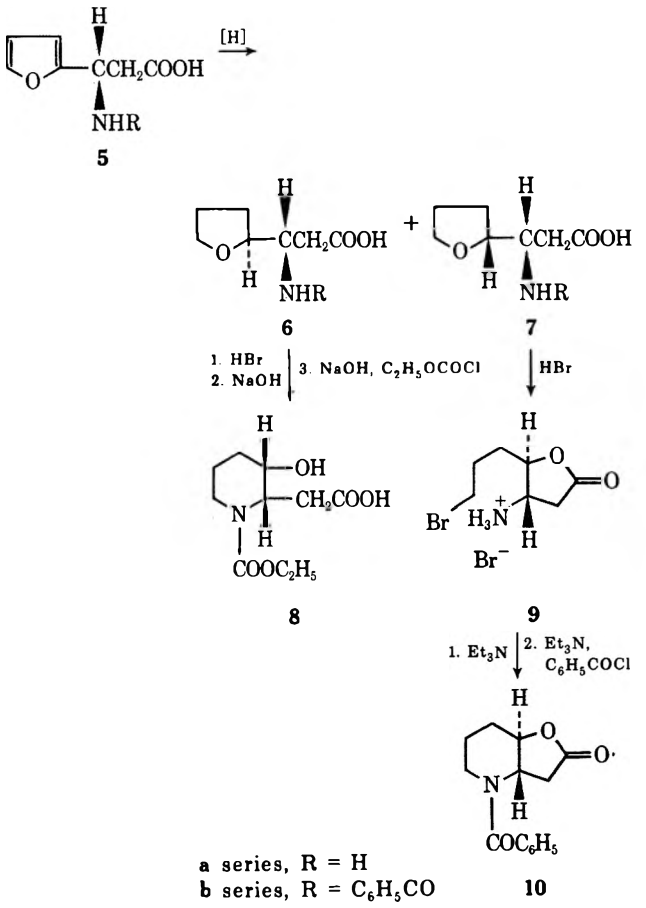
The 100-MHz nmr spectra of the diacidic salts of the acetate esters of the natural product and the synthesized *trans*-febrifugine (**2c**) were compared and found to be identical. Acetylation of the cis isomer could not be accomplished; so its nmr spectrum could not be compared with the other two. The resonance of the proton at the point of attachment of the acetonyl side chain in the piperidine ring appeared as a quartet centered at δ 3.98 with a splitting of 7 Hz. This assignment was made by irradiating the sample at the absorption frequency of the side-chain methylene adjacent to the piperidine ring, which collapsed the quartet to a doublet (J = 7 Hz). A coupling constant of 7 Hz for the two methine hydrogens on the piperidine ring is somewhat smaller than would be expected for the trans-diaxial hydrogens in a normal trans disubstituted six-membered ring in the chair conformation, but it is also much too large for the cis isomer. The cis isomer would be expected to prefer the conformation **4** where the acetate ester group is in



the axial position. In this conformation both methine hydrogens are anti coplanar with electronegative heteroatoms. The axial–equatorial coupling constants observed in similar situations are of the order of 1–2 Hz or less.[7] The resonance for the methine (at 100 MHz) adjacent to the acetate ester function appears as a multiplet centered at δ 5.0. The separation between the outermost lines is about 20 Hz and the pattern seems to fit for coupling constants of about 4–5, 7, and 9–10 Hz. These values indicate that this hydrogen is probably in an axial position.

Since our data all pointed to the conclusion that febrifugine was trans rather than cis as Baker, *et al.*, have proposed,[3b] we decided to examine the earlier work for a possible key to the resolution of this difference. The original stereochemical assignment was made on the basis of the chemistry of intermediates in a synthesis other than the one we used.[3b] This synthesis begins with hydrogenation of a derivative of β-(2-furyl)-β-alanine (**5a**). Baker, *et al.*, reported that, when β-(2-furyl)-β-alanine was hydrogenated over platinum oxide and the crude mixture of tetrahydro compounds (**6a** and **7a**) was treated sequentially with hydrobromic acid at 100°, sodium hydroxide at 100°, and ethyl chloroformate in the presence of sodium hydroxide in the cold, a 1-ethoxycarbonyl-3-hydroxy-2-piperidylacetic acid (**8**) (Scheme I) was obtained which

SCHEME I



was unreactive toward alcohol derivatizing reagents, even after several hours in boiling acetyl chloride. This compound was converted into an isomer of febrifugine and therefore has the "wrong" relative stereochemistry in the piperidine ring.

On the other hand, if *N*-benzoyl-β-(2-furyl)-β-alanine (**5b**) was hydrogenated over palladium on carbon the major product was **7**. When this compound was treated with hydrobromic acid at 100°, the crystalline lactone (**9**) was isolated. This lactone, in the presence of triethylamine in chloroform, cyclized to the lactone of 3-hydroxy-2-piperidylacetic acid. Benzoylation of this amino lactone in the presence of triethylamine yielded the lactone **10**, which was converted into febrifugine.

Baker, *et al.*, concluded that the lactonizable hydroxy acid was cis and the unreactive one trans.[3b] Since our work required the opposite assignment, it was decided to reinvestigate these intermediates. The sequence **5b–7b–9–10** was repeated, and the melting points and chemical properties of all the compounds agreed with those reported.[3b] The ir spectra were in accord with the assigned structures. The nmr spectrum of 1-benzyol-3-hydroxy-2-pyridylacetic acid lactone (**10**) was measured at 60 MHz. The resonance of the proton at C_2 of the piperidine ring appeared as a quartet (J = 8.5 Hz) centered at δ 5.15. The resonance for the C_3 proton appeared as a multiplet centered at δ 4.68

(7) H. Booth, *Tetrahedron Lett.*, 411 (1965); H. Booth and G. C. Gidley, *Tetrahedron*, **21**, 3429 (1965).

which was made up of two triplets (J = 8.5 Hz) separated by 5.0 Hz.

A technique for relating nmr coupling constants to conformation, called dihedral angle estimation by the ratio method (DAERM), has recently been reported.[8] The DAERM method requires a proton coupled to a vicinal methylene group. The dihedral angles are calculated from the ratio (eq 2), of the two Karplus equations (1) using the observed values for J_1 and J_2,

$$J_1 = k_1 \cos^2 \phi_1 - C \qquad 0 \leq \phi_1 \leq 90° \qquad (1a)$$

$$J_2 = k_2 \cos^2 \phi_2 - C \qquad 90 \leq \phi \leq 180° \qquad (1b)$$

$$(J_1 + C)/(J_2 + C) = (k_1/k_2)(\cos^2 \phi_1/\cos^2 \phi_2) \qquad (2)$$

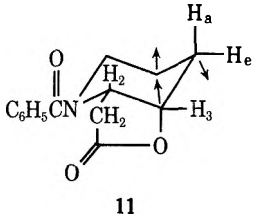
C = 0.28 and k_1/k_2 = 0.9, and substituting $W - \phi_1$ and $W + \phi_1$ for ϕ_2, where W is the H–C–H dihedral angle (usually 120°). The nmr spectrum of 1-benzoyl-3-hydroxy-2-piperidylacetic acid lactone (**10**) reveals that the proton at C_2 of the piperidine ring is coupled to the protons at C_α of the lactone and C_3 of the piperidine ring with J values of 8.5 Hz. The proton at C_3 is in turn coupled to those at C-4 with J values of 5.0 Hz and 8.5 Hz. Using these values and the further condition that at least one dihedral angle (ϕ_1) must be <90° to avoid large strains in the ring, the values in Table I were calculated.

TABLE I

DAERM CALCULATIONS OF 5.0 HZ- AND 8.5 HZ-COUPLINGS

	Obsd coupling constants		Calculated dihedral angles		Calcd Karplus constants	
Set	J_1	J_2	ϕ_1	ϕ_2	k_1	k_2
1	5.0	8.5	40	160	9.00	9.93
2	5.0	8.5	64	56	27.36	28.14
3	8.5	5.0	56	64	28.14	27.36
4	8.5	5.0	15	135	9.41	10.56

Sets 2 and 3 are equivalent and correspond to the cis conformer **11** with an axial oxygen. This structure



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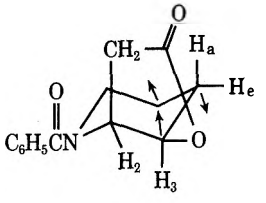

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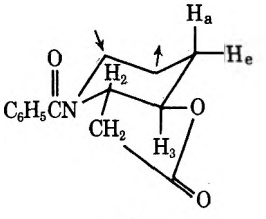

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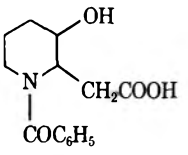
can be eliminated because the Karplus constants are much too large. Sets 1 and 4 have reasonable Karplus constants. The dihedral angles around the C_3–C_4 axis are about the same in the Dreiding models of the cis conformer **12** with the lactone α-methylene in the axial position and in the trans isomer **13**. They are in the range of 40–60 and 160–180°, corresponding quite well with the values calculated in set 1. Using the Karplus equations calculated for set 1, the H–C_2–C_3–H dihedral angle (J = 8.5 Hz) was calculated to be either 9 or 160°. The 160° value compares well with the 160–170° angle shown by the model of the trans isomer, but the angle in the cis conformer **12** is 40°. The angle approaches 0° as **12** is flipped into the boat conformation as indicated by the small arrows. The trans isomer **13** can be flipped into a twist conformer, as indicated by the small arrows, with hardly any change in the dihedral angles of the C_2–C_3–C_4 substituents. Set 4 in Table I requires that the groups on C_3 and C_4 be nearly eclipsed. This does not occur in any of the Drieding models, but it would be the case at some intermediate stage while flipping the conformer **11** into a boat conformer as indicated by the arrows. Thus, while it is not possible to rule out a cis configuration on the basis of the nmr spectrum of 1-benzoyl-3-hydroxy-2-piperidylacetic acid lactone (**10**), the couplings observed seem more easily accommodated by the trans configuration.

It is instructive to compare the reactivity of 1-benzoyl-3-hydroxy-2-piperidylacetic acid (**14**) with the



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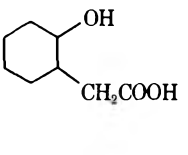

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reactivity of the cis and trans isomers of (2-hydroxycyclohexyl)acetic acid reported by Newman and VanderWerf.[9] The lactone **10** was hydrolyzed with 10% sodium hydroxide. Acidification of the resultant solution with 12 N hydrochloric acid at room temperature precipitated the hydroxy acid **14**. This compound was stable up to its melting point of 157–158°, but was relactonized upon refluxing in acetic anhydride solution for 1 hr. This behavior is similar to that of *trans*-(2-hydroxycyclohexyl)acetic acid (*trans*-**15**), which can be isolated by careful acidification of a cold alkaline solution, but is lactonized by heating to 200° or refluxing several hours in dilute hydrochloric acid solution. The cis isomer of **15**, in contrast, lactonizes spontaneously when an alkaline solution of the salt is neutralized at 0° with the stoichiometric amount of acid. The inertness of (1-ethoxycarbonyl-3-hydroxy-2-piperidyl)acetic acid (**8**) compared to the (2-hydroxycyclohexyl)acetic acids may be due to interaction between the hydroxyl and amide functions. This interaction would be expected to be greater in the cis isomer where the hydroxyl group will be largely in the axial position.

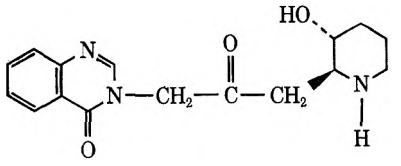
We made some attempts at the resynthesis of *cis*-(1-ethoxycarbonyl)-2-piperidyl)acetic acid (**8**) to compare its spectral and chemical properties with *trans*-(1-benzoyl-3-hydroxy-2-piperidyl)acetic acid. In our hands the hydrogenation of β-(2-furyl)-β-alanine (**5a**) over platinum oxide or 5% rhodium on alumina gave what seemed to be a mixture of the isomeric tetrahydro compounds **6a** and **7a**. However, the subsequent reactions afforded the trans compounds **9** and **10** as the only isolable crystalline products. Thus, we were unable to prepare **8**. Since we did not have pure samples

(8) K. N. Slessor and A. S. Tracey, *Can. J. Chem.*, **49**, 2874 (1971).

(9) M. S. Newman and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **67**, 233 (1945).

of the individual diastereomers **6a** and **7a**, we cannot explain this failure to obtain any **8**.

While some of the chemistry of the intermediates related to febrifugine remains unclear, our results definitely point toward a trans configuration in the piperidine ring. Since Hill and Edwards[10] have determined that the absolute configuration of the 2′ position is *S*, we propose (2′*S*,3′*R*)-3-[3-(3-hydroxy)piperidyl]-acetonyl-4(3*H*)-quinazolinone (**16**) as the structure of



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febrifugine. The absolute configuration of the hydroxyl group is the same as that in δ-hydroxylysine,[11] which is a plausible precursor, and also the same as 5-hydroxypipecolic acid.[12]

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord, Model 137. Nmr spectra were recorded on a Varian A-60 or a Varian HA100.

Febrifugine Dihydrochloride (16 2HCl).—The alkaloid was isolated according to Ablondi, *et al.*, method II.[4] The yield from 1320.65 g of dried hydrangea cuttings (common Easter variety) was 315 mg of the dihydrochloride salt: mp 222–225° dec. (lit.[4] mp 223–225°); ir spectrum (mineral oil mull) identical with the published spectrum;[4] $[\alpha]^{25}D$ +15.3° (standard deviation 3.3°, c 0.75, H_2O) {lit.[4] $[\alpha]^{31}D$ +12.8° (c 0.85, H_2O)}. *Anal.* Calcd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.3; H, 5.7; N, 11.2; Cl, 19.0. Found: C, 51.5; H, 5.4; N, 11.3; Cl, 19.0.

***dl-trans*-Febrifugine Hydrobromide (2a HBr).**—This compound was synthesized from (3-methoxy-2-piperidyl)-2-propanone containing ~70% trans isomer[1] according to a modification of the method of Baker and McEvoy[1,2] using allyl chloroformate rather than ethyl chloroformate to block the secondary amine function. The crude product was recrystallized from 95% ethanol to give the pure trans isomer, mp 229–231°. *Anal.* Calcd for $C_{16}H_{19}N_3O_3 \cdot HBr$: C, 50.3; H, 5.3; N, 11.0; Br, 20.9; OCH_3, 0.0. Found: C, 50.0; H, 5.0; N, 10.9; Br, 20.7; OCH_3, 0.2.

***dl-cis*-Febrifugine Dihydrobromide (2b 2HBr).**—This compound was synthesized from *cis*-(3-methoxy-2-piperidyl)-2-propanone using the same sequence as for the trans isomer, mp 199–201°. *Anal.* Calcd for $C_{16}H_{19}N_3O_3 \cdot 2HBr$: C, 41.5; H, 4.6; N, 9.1; Br, 34.5; OCH_3, 0.0. Found: C, 40.5; H, 4.6; N, 8.5; Br, 33.7; OCH_3, 0.3.

Febrifugine Free Bases.—The free base of the natural product was prepared from the dihydrochloride according to the procedure of Hutchings, *et al.*,[5] in 81% yield, mp 156.5–158.5° (lit.[6] mp 154–156° for the higher melting dimorph).

The synthetic stereoisomeric febrifugines were liberated from their salts in the same fashion. The *dl*-trans compound **2a** had mp 178.5–180.5° and the *dl*-cis compound had mp 134–136° (resolidified and remelted at 178.5–181.5°).[13]

Comparison of the spectra in arsenic trichloride solution and the R_f values demonstrated that the naturally occurring compound was the trans isomer. The tlc chromatograms were run by spotting solutions of the alkaloid salts on E. Merck alumina G plates, overspotting with aqueous sodium carbonate, and developing with 5% methanol in benzene. The spots were located by spraying the developed plates with 50% sulfuric acid and heating. R_f values were 0.15 for the trans compounds and 0.3 for the cis.

Febrifugine Acetate Dihydrochloride (2c 2HCl).—This compound was prepared in 43% yield from the natural product according to the procedure of Hutchings, *et al.*:[5] mp 190–194° (lit.[5] mp 184–188°); nmr (100 MHz, D_2O) δ 1.5–2.4 m, 4 H, CH_2CH_2, 2.20 (s, 1 H, CH_3CO), 3.0–3.6 (m, 2 H, NCH_2), 3.43 (d, J = 7 Hz, 2 H, CH_2CO), 3.98 (q, J = 7 Hz, 1 H, NCH), 4.75 (s, exchangeable H), 5.0 (m, 1 H, OCH), 5.26 (s, 2 H, NCH_2CO), 7.65–8.24 (m, 4 H, aromatic), 8.91 (s, 1 H, N=CHN). *Anal.* Calcd for $C_{18}H_{21}N_3O_4 \cdot 2HCl$: C, 51.9; H, 5.6; N, 10.1; Cl, 17.0. Found: C, 52.2; H, 5.6; N, 10.3; Cl, 16.7.

The trans synthetic compound was acetylated in the same manner to give a 71% yield of a diacidic salt, mp 228–229° (from 2B ethanol), which contained 69% chloride and 31% bromide. It was homogeneous by tlc on alumina G (10 and 20% methanol in chloroform and 5 and 20% methanol in benzene). Its nmr spectrum was identical with that of the compound derived from the natural product. *Anal.* Calcd for $C_{18}H_{21}N_3O_4 \cdot 1.38HCl \cdot 0.62HBr$: C, 49.1; H, 5.3; N, 9.6; Br, 9.8; Cl, 11.7. Found: C, 48.7; H, 5.3; N, 8.9; Br, 10.2; Cl, 11.8.

No satisfactory conditions were found for acetylating the *cis* synthetic compound.

1-Benzoyl-3-hydroxy-2-piperidylacetic Acid Lactone (10).—This compound was synthesized according to the procedure of Baker, *et al.*:[3b] mp 99–101° (lit.[3b] mp 99–101°); nmr (60 MHz, $CDCl_3$) δ 1.25–2.60 (m, 4 H, CH_2CH_2), 2.75 (d, J = 8.5 Hz, 2 H, CH_2CO), 3.08 (m, 1 H, axial CH_2N), 3.88 (d of t, 1 H, equatorial CH_2N), 4.69 (m, J = 8.5, 8.5, and 5.0 Hz, 1 H, OCH), 5.15 (q, J = 8.5 Hz, 1 H, NCH), 7.46 (s, 5 H, aromatic).

Registry No.—**2a**, 39037-90-6; **2a** HBr, 39037-91-7; **2b**, 39037-92-8; **2b** 2HBr, 39000-93-6; *trans*-**2c** 2HCl, 39037-93-9; **16** 2HCl, 39037-94-0; *trans*-(3-methoxy-2-piperidyl)-2-propanone, 39037-95-1; *cis*-(3-methoxy-2-piperidyl)-2-propanone, 39037-96-2.

(10) R. K. Hill and A. G. Edwards, *Chem. Ind. (London)*, 858 (1962).
(11) B. Witkop, *Experientia*, **12**, 372 (1956).
(12) B. Witkop and C. M. Foltz, *J. Amer. Chem. Soc.*, **79**, 192 (1957).
(13) The lower melting point is observed only on rapid heating. When the cis isomer is heated slowly, it isomerizes without melting (melting point and mixture melting point).

Nor Steroids. X. Synthesis of *A*-Nor Steroids *via* the Dieckmann Condensation[1,2]

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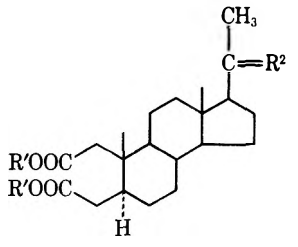
Dieckmann condensation of dimethyl 2,3-seco-5α-pregnan-20-one-2,3-dioate (Ia) gave an 84% yield of 3α-carbomethoxy-*A*-nor-5α-pregnane-2,20-dione (IIc). Alkylation of IIc with methyl iodide gave a 91% yield of a 1:1 mixture of the 3α- and 3β-methyl β-keto esters IId,e. Hydrolysis and decarboxylation of the mixture gave a mixture of 3α- and 3β-methyl-*A*-nor-5α-pregnane-2,20-diones (IIf,g) (80–85% 3α-methyl isomer). The same sequence of reactions in the cholestane series gave the β-keto ester IIIa in 70% yield, and alkylation of this with methyl iodide gave a mixture of the 3-methyl epimers IIIb,c in 69% yield. Hydrolysis and decarboxylation gave a 70% yield of 3α-methyl-*A*-nor-5α-cholestane-2-one (IIId).

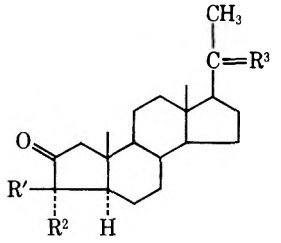
In a previous study[1] the application of the Dieckmann condensation, followed by the methylation of the resulting β-keto ester, to prepare 3-methyl-*A*-nor-androstanes was described. This synthesis has now been extended to the pregnane and cholestane series.

In an earlier investigation[4] the condensation of dimethyl 2,3-seco-5α-pregnan-20-one-2,3-dioate (Ia) using sodium methoxide in benzene gave none of the desired product, but gave a 40% recovery of starting material and a 13% yield of *A*-nor-5α-pregnane-2,20-dione (IIa), apparently formed by loss of the carbomethoxy group under the conditions of the reaction. Using sodium in toluene, only starting material was recovered.

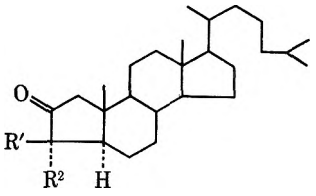
Since it seemed possible that in the earlier study the active hydrogens of the 21-methyl group might be interfering with the condensation, the 20,20-ethylenedioxy derivative (Ib) of the seco ester was prepared,



Ia, R′ = CH_3; R^2 = O
b, R′ = CH_3; R^2 = OCH_2CH_2O
c, R′ = H, R^2 = O



IIa, R′ = R^2 = H; R^3 = O
b, R′ = H; R^2 = CO_2Me; R^3 = OCH_2CH_2O
c, R′ = H; R^2 = CO_2Me; R^3 = O
d, R′ = CH_3; R^2 = CO_2Me; R^3 = O
e, R′ = CO_2Me; R^2 = CH_3; R^3 = O
f, R′ = CH_3, R^2 = H; R^3 = O
g, R′ = H; R^2 = CH_3; R^3 = O



IIIa, R′ = H, R^2 = CO_2Me
b, R′ = CH_3; R^2 = CO_2Me
c, R′ = CO_2Me; R^2 = CH_3
d, R′ = H; R^2 = CH_3

and the Dieckmann condensation was carried out using potassium *tert*-butoxide in benzene and *tert*-butyl alcohol. A 70% yield of the desired *A*-nor-β-keto ester IIb was obtained, and its structure was established by hydrolysis and decarboxylation to the known *A*-nor-5α-pregnane-2,20-dione (IIa).

Although this result seemed to substantiate the hypothesis that the 21-methyl group was causing the trouble in the earlier study, the condensation of the seco ester 20 ketone Ia was repeated, but with potassium *tert*-butoxide in place of sodium methoxide. In this instance an 84% yield of the desired 3α-carbomethoxy-*A*-nor-5α-pregnane-2,20-dione (IIc) was obtained, thus eliminating the interference of the 21-methyl group as the cause of the decarboxylation. The reasons for the lack of success in the earlier experiments are not known.

Although Fuchs and Loewenthal in an earlier study[5] had claimed that the condensation of the seco ester in the cholestane series gave the 3β-carbomethoxy isomer, the nmr data on the β-keto esters in the pregnane series indicated that the carbomethoxy group was α. The C-3 hydrogen appeared as a doublet at δ 3.08 (J = 13 Hz) for the β-keto ester 20-ethylene ketal IIb.

Molecular models indicate that the dihedral angle for the hydrogens at C-3 and C-5 in the 3β-carbomethoxy isomer is approximately 30°, while the angle for the 3α isomer is about 150°. Using the Williamson–Johnson modification[6] of the Karplus equation,[7] the β isomer should show J = 7.5 Hz for the 3α hydrogen, and the α isomer should show J = 13 Hz for the 3β hydrogen. The observed J value of 13 Hz indicates that the condensation product is indeed the 3α-carbomethoxy isomer IIb.

The condensation product from the 20-keto compound IIc showed absorption of the C-3 hydrogen at δ 3.01 (J = 13 Hz), again indicating that the product

(1) For the previous paper in the series see H. R. Nace and J. L. Pyle, *J. Org. Chem.*, **36**, 81 (1971).

(2) Supported in part by the USPHS under Grant No. 5R01 AM 11024-02MCHA.

(3) Abstracted from the Ph.D. Thesis of A. H. S., Brown University, 1968.

(4) D. H. Nelander, Ph.D. Thesis, Brown University, 1963.

(5) B. Fuchs and H. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(6) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

(7) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

was the 3α-carbomethoxy isomer. These structures are in accord with those assigned in the androstane series by Nace and Pyle,[1] and in the cholestane series by Paranjape and Pyle[8] and the present authors (see below).

The β-keto ester (20-keto series) IIc was alkylated with potassium *tert*-butoxide and methyl iodide to give a mixture of the 3α- and 3β-methyl β-keto esters IId,e in 91% yield. Integration of the nmr peaks for the 3α- and 3β-$OCOCH_3$ (δ 3.62 and 3.65) indicated that the mixture was 1:1.

The alkylated β-keto ester was hydrolyzed and decarboxylated by heating in a mixture of hydrochloric and acetic acids, to give a mixture of 3α- and 3β-methyl-*A*-nor-5α-pregnane-2,20-diones (IIf,g). The nmr spectral data (see Experimental Section) indicated that the mixture contained 80–85% of the 3α-methyl isomer IIg. Once the β-keto acid is decarboxylated, the 2 ketone can readily equilibrate to give the observed ratio, in which the 3α-methyl compound is the more stable, by analogy with the results obtained for the unalkylated β-keto ester.

In order to clear up any ambiguity about the structure of Fuchs and Loewenthal's β-keto ester,[5] their work was repeated. Dimethyl 2,3-secocholestane-2,3-dioate was treated with potassium *tert*-butoxide to give the β-keto ester IIIa in 70% yield, with physical constants identical with those reported. In the nmr spectrum the C-3 hydrogen appeared at δ 3.08 (J = 13 Hz), indicating that it was β, as discussed above. Accordingly, the carbomethoxy group must be α, contrary to the previous assignment. No change in the J value was observed at 40 MHz.

Alkylation of the β-keto ester with methyl iodide and potassium *tert*-butoxide gave the 3-methyl derivative IIIb,c in 69% yield, as a mixture of isomers epimeric at C-3.

Hydrolysis and decarboxylation proved to be difficult, but prolonged heating with acetic acid and hydrogen bromide gave 3α-methyl-*A*-nor-5α-cholestan-2-one (IIId) in 70% yield. The 100-MHz nmr spectrum showed a doublet at δ 1.03 (J = 7 Hz) for the 3α-methyl group, and there was no indication that any of the 3β isomer was present.

On the basis of these results and those previously reported, the alkylation of *A*-nor-β-keto esters offers an attractive route for introduction of a methyl group into the five-membered ring.

Experimental Section[9]

2,3-Seco-5α-pregnan-20-one-2,3-dioic Acid (Ic).—To a solution of 12.6 g (40.0 mmol) of 5α-pregnane-3,20-dione in 535 ml of 95% acetic acid was added 12.6 g of chromium trioxide, the solution was heated at 60° for 10 hr, then 500 ml of water was added and the mixture was allowed to stand overnight at room temperature. Then it was extracted with 10 × 300 ml of ether, and the extract was washed with water and evaporated to dryness under reduced pressure. The residue was added to 1 l. of 20% K_2CO_3 solution and additional K_2CO_3 was added to pH 9. After washing with 4 × 200 ml of ether the solution was acidified with concentrated HCl and the resulting precipitate was collected, washed with water, and air dried. Recrystallization from acetic acid–water gave 5.46 g (38%) of seco diacid: mp 216–217.5° (lit.[10] mp 218°); $[\alpha]D$ +91° (c 0.48, $CHCl_3$); R_f 0.69 (3:1:1 benzene–ether–acetic acid); ir ($CHCl_3$) 3500–2600 and 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.62 (C-18 CH_3), 0.82 (C-19 CH_3), 2.13 (C-21 CH_3), and 8.38 (COOH); mass spectrum (70 eV) m/e (rel intensity) 364 (0.3) (M^+), 44 (base peak).

Dimethyl 2,3-Seco-5α-pregnan-20-one-2,3-dioate (Ia).—A solution of 1.02 g (2.8 mmol) of 2,3-seco-5α-pregnan-20-one-2,3-dioic acid in 240 ml of a 10% methanolic hydrogen chloride solution was boiled under reflux for 3 hr, allowed to stand overnight at room temperature, and then evaporated to dryness under reduced pressure. Water (100 ml) was added to the residue, then K_2CO_3 to pH 9, and the mixture was extracted with 4 × 50 ml of ether. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to give 942 mg (86%) of a colorless oil which could not be crystallized: R_f 1.00; ir ($CHCl_3$) 1735 and 1702 cm^{-1}; $[\alpha]D$ +71° (c 0.9, $CHCl_3$); nmr (CCl_4) δ 0.57 (C-18 CH_3), 0.80 (C-19 CH_3), 2.05 (C-21 CH_3), and 3.63 (s, 6, OCH_3).

Dimethyl 2,3-Seco-20,20-ethylenedioxy-5α-pregnane-2,3-dioate (Ib).—A solution of 1.20 g (3.0 mmol) of the seco diester and 80 mg of *p*-toluenesulfonic acid in 40 ml of benzene and 12.5 ml of ethylene glycol was boiled under reflux with a Dean–Stark trap for 24 hr while 20 ml of distillate was removed. Then 25 ml more of benzene was added and refluxing was continued for 20 hr. The reaction mixture was extracted with 3 × 20 ml of benzene, and the extract was washed with alcoholic KOH, water (2 × 20 ml), and 25 ml of saturated brine, dried (Na_2SO_4), and evaporated to give 1.28 g (94%) of a pale yellow solid. Recrystallization from methanol gave the product as white needles: mp 128–129.5°; ir (CCl_4) 1745 cm^{-1}; $[\alpha]D$ +63° (c 0.96, $CHCl_3$); R_f 1.15; nmr (CCl_4) δ 0.70 (C-18 CH_3), 0.78 (C-19 CH_3), 1.20 (C-21 CH_3), 3.28 (broad, 4, $-OCH_2CH_2O-$), and 3.58 (s, 6, OCH_3); mass spectrum (70 eV) m/e (rel intensity) 421 (1.7) ($M^+ - CH_3$), 87 (base peak).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.78; H, 9.23. Found: C, 69.68, 69.95; H, 9.16, 9.33. Further recrystallization and drying did not improve the analytical values, and the high value for carbon is anomalous.

3α-Carbomethoxy-20,20-ethylenedioxy-*A*-nor-5α-pregnan-2-one (IIb).—Under nitrogen, 0.07 g (1.8 mg-atom) of potassium was added to 5 ml of *tert*-butyl alcohol and 5 ml of benzene (solvents dried for 24 hr over calcium hydride and distilled), and after the potassium had reacted, a solution of 150 mg (0.34 mmol) of the seco ester Ib in 10 ml of benzene was added with a syringe with stirring. The solution was then boiled under reflux (nitrogen atmosphere) with a Dean–Stark trap for 17 hr, during which time 5 ml of solvent was removed. The dark orange solution was cooled to room temperature, 15 ml of water, 20 ml of benzene, and 1 ml of dilute HCl were added, the benzene layer was washed with water, 5% $NaHCO_3$, and water (to neutrality) and dried (Na_2SO_4), and the solvent was evaporated to give 97 mg (70%) of white solid. Recrystallization from methanol gave the *A*-nor compound IIb as white needles: mp 177–179°; $[\alpha]D$ +98° (c 1.01, $CHCl_3$); ir ($CHCl_3$) 1755 and 1725 cm^{-1} (an acetone solution gave a green color with ferric chloride); nmr ($CDCl_3$) δ 0.80 (C-18 CH_3), 0.88 (C-19 CH_3), 1.30 (C-21 CH_3), 3.08 (d, J = 13 Hz, C-3 β-H), 3.75 (s, 3, OCH_3), and 3.93 (m, 4, OCH_2CH_2O) (at 40 MHz the 3.08 doublet had J = 12.5 Hz); mass spectrum (70 eV) m/e (rel intensity) 389 (2.3) ($M^+ - CH_3$), 87 (base peak).

(8) B. V. Paranjape and J. L. Pyle, *J. Org. Chem.*, **36**, 1009 (1971).

(9) Melting points were determined with a Herschberg apparatus and Anschutz thermometers and are corrected. Analytical determinations were by Schwarzkopf Microanalytical Laboratory or Midwest Microlab, Inc. Nmr spectra were determined on Varian Models HR-60 and A-60A spectrometers at 60 MHz, unless specified otherwise. TMS was used as internal standard and peak positions are reported in parts per million (δ) downfield from TMS. The authors are indebted to Dr. J. MacReed of the Plastics Department, E. I. du Pont de Nemours and Co., for the two 100-MHz spectra. Mass spectra were obtained with a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer equipped with an MG-150 solid sample direct inlet into the ionization chamber. Thin layer chromatography (tlc) was performed on type K 301 R Eastman chromagram sheets coated with silica gel, the tlc's were developed with 3:1 benzene–ether, and the spots were visualized by spraying with 2,4-dinitrophenylhydrazine in phosphoric acid–ethanol solution, or exposure to iodine vapor. The R_f values were measured relative to 5α-pregnane-3,20-dione. Vapor phase chromatography (vpc) was performed on an Aerograph Model 204 chromatograph, equipped with a flame ionization detector, and a 4-ft column packed with a 1% QF-1 coating on Gas-Chrom Z support. The T_R values refer to retention times relative to that of *A*-nor-5α-pregnane-2,20-dione as the standard at the temperature specified.

(10) R. E. Marker, O. Kamm, and D. M. Jones, *J. Amer. Chem. Soc.*, **59**, 1595 (1937). This procedure consistently gave low yields, *ca.* 15%, in our hands.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.57; H, 9.24.

Hydrolysis and Decarboxylation of the A-Nor Ketal IIb.—A solution of 100 mg (0.25 mmol) of the above *A*-nor compound in 15 ml of glacial acetic acid and 5 ml of concentrated HCl was boiled under reflux for 70 hr (2 ml of water added after 48 hr) and cooled to room temperature, 20 ml of water was added, and the mixture was extracted with ether. The ether was evaporated, 50 ml of water was added to the residue, K_2CO_3 was added to neutralize acetic acid, and the mixture was extracted with 3 × 20 ml of ether. The extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated to give 50 mg (67%) of solid which was recrystallized from ethanol–water to give *A*-nor-5α-pregnane-2,20-dione (IIa), mp 174–177° (lit.[11] mp 176–179°). The ir and nmr spectra and R_f were identical with those of an authentic sample; mass spectrum (70 eV) *m/e* (rel intensity) 302 (75.6) (M^+), 43 (base peak).

Dieckmann Condensation of Dimethyl 2,3-Seco-5α-pregnan-20-one-2,3-dioate (Ia).—The ester (450 mg, 1.15 mmol) in 26 ml of benzene was added to 0.15 g of potassium dissolved in 12.5 ml of *tert*-butyl alcohol and 17.5 ml of benzene, heated as above for 17 hr, and worked up as above to give 345 mg (84%) of 3α-carbomethoxy-*A*-nor-5α-pregnane-2,20-dione (IIc). A 240-mg sample was chromatographed on 10 g of silica gel and elution with 5% ether in benzene gave 200 mg of white solid: mp 144–150°; ir ($CHCl_3$) 1755, 1725, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 0.63 (C-18 CH_3), 0.90 (C-19 CH_3), 2.10 (s, 3, C-21 CH_3), 3.01 (d, 1, J = 13 Hz, C-3 β-H), and 3.73 (s, 3, $OCOCH_3$). The addition of 2 drops of D_2O had no effect on the spectrum, but a few crystals of K_2CO_3 caused an immediate decrease in the intensity of the doublet at δ 3.01, and after 5 *min* the doublet had virtually disappeared. No other change was apparent in the spectrum, even after 24 hr.

Mass spectrum (70 eV) showed *m/e* (rel intensity) 360 (58.6) (M^+), 43 (base peak); $[\alpha]_{589}$ +167°, $[\alpha]_{578}$ +179°, $[\alpha]_{546}$ +205°, $[\alpha]_{436}$ +467°, $[\alpha]_{365}$ +1176° (*c* 0.3, $CHCl_3$). A portion was sublimed at 130° (0.25 mm) to give the analytical sample, mp 147–150°.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.10; H, 8.93.

Methylation of the A-Nor Ester IIc.—To a solution of 800 mg (2.22 mmol) of 3α-carbomethoxy-*A*-nor-5α-pregnane-2,20-dione (IIc) in 5 ml of benzene was added a solution of 400 mg (2.8 mmol) of potassium *tert*-butoxide in 40 ml of *tert*-butyl alcohol (all carried out in a drybox under nitrogen), and the solution was stirred for 45 min. Then 430 mg of methyl iodide (distilled from zinc dust) was added, and the solution was stirred for 2 hr and then boiled under reflux under nitrogen overnight. After cooling, 10 ml of 6 *N* hydrochloric acid and 100 ml of benzene were added, and the benzene layer was removed, washed with water, K_2CO_3 solution, water again to neutrality, and saturated brine, dried ($MgSO_4$), and evaporated to give 758 mg (91%) of 3-carbomethoxy-3-methyl-*A*-nor-5α-pregnane-2,20-dione (IId,e) as a colorless oil which could not be crystallized: ir ($CHCl_3$) 1750, 1725, and 1700 cm^{-1}; R_f 1.06; nmr ($CDCl_3$) δ 0.67 (C-18 CH_3), 0.92 (broad, shoulder at 0.88, C-19 CH_3), 1.30 and 1.37 (C-3 α- and β-CH_3's), 2.13 (C-21 CH_3), 3.67 and 3.68 (C-3 α- and β-$OCOCH_3$'s); in CCl_4, δ 3.62 and 3.65 (C-3 α- and β-$OCOCH_3$'s, integration indicated a 1:1 mixture).

3-Methyl-*A*-nor-5α-pregnane-2,20-dione (IIf,g).—A solution of 878 mg (2.35 mmol) of the methylated *A*-nor ester in 80 ml of glacial acetic acid and 80 ml of concentrated HCl was heated at 97° for 6 days (20 ml of water was added after the first day), then cooled to room temperature and added to 400 ml of water. Solid K_2CO_3 was added to basicity and the solution was extracted with ether. The extract was washed to neutrality with water, then with saturated brine, dried ($MgSO_4$), and evaporated to give 550 mg of brown solid, which was chromatographed on 40 g of silica gel. Elution with 10% ether in benzene gave 262 mg of a yellow solid, a mixture of 3α- and 3β-methyl-*A*-nor-5α-pregnane-2,20-dione (IIf,g): nmr ($CDCl_3$) δ 0.65 (C-18 CH_3), 0.8–1.18 (m, 7, C-19 and C-3 CH_3's, plus one proton from the steroid nucleus, indicating a mixture of C-3 epimers), and 2.12 (C-21 CH_3).

The 100-MHz spectrum ($CDCl_3$) showed δ 0.64 (s, C-18 CH_3), 0.87 (d, J = 1 Hz, C-19 CH_3), 0.88 (d, J = 6.5 Hz, C-3 CH_3), 1.02 (d, J = 6 Hz, epimeric C-3 CH_3's), and 2.11 (s, C-21 CH_3); in benzene-d_6, δ 0.52 (s, C-18 CH_3) and 1.18 (s, C-21 CH_3). The C-19 CH_3 was shifted upfield to δ 0.54. The larger of the C-3 CH_3 doublets remained relatively unshifted at δ 1.00 (J = 7 Hz) and was assigned to the C-3 α-CH_3. The smaller doublet was shifted upfield to δ 0.62 (J = 7 Hz) and was assigned to the C-3 β-CH_3. Integration of these two doublets indicated a mixture of 80–85% of the α-methyl and 15–20% of the β-methyl epimer, ir ($CHCl_3$) 1735 and 1698 cm^{-1}.

The solid was sublimed at 90° (0.25 mm) to give 190 mg (25%) of the methyl *A*-nor ketone mixture, mp 125–135°, R_f 1.10 (elongated spot). A portion of this material was resublimed at 90° (0.4 mm) to give an analytical sample, mp 126–134°, mass spectrum (70 eV) *m/e* (rel intensity) 316 (49.2) (M^+) and 43 (base peak).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 78.92; H, 10.10.

A second fraction (250 mg) was also eluted from the column with 10% ether in benzene, and the brown solid appeared to be a mixture of two components, R_f 0.61 and 1.17, the latter the epimeric C-3 methyl mixture, based on the nmr spectrum.

Dimethyl 2,3-Secocholestane-2,3-dioate.—A solution of 1.31 g (3.06 mmol) of 2,3-secocholestane-2,3-dioic acid ln 270 ml of 10% methanolic hydrogen chloride was allowed to stand at room temperature for 4 days, and then the solvent was removed under reduced pressure and the residue was triturated with 150 ml of K_2CO_3 solution (pH 10). The mixture was extracted with benzene, and the extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated to give 1.40 g of white solid. This was chromatographed on 50 g of silica gel and elution with benzene gave 1.35 g (95%) of the dimethyl ester: mp 61–63° (lit.[5] mp 62–64°); ir ($CHCl_3$) 1730 cm^{-1}; R_f 1.56; T_R^{215} 2.03; $[\alpha]_D$ +21° (*c* 0.75, $CHCl_3$); nmr δ 0.65 (C-18 CH_3), 0.78 (C-19 CH_3), 0.88 (side chain CH_3's), and 3.68 (s, 6, OCH_3's).

3α-Carbomethoxy-*A*-nor-5α-cholestan-2-one (IIIa).—A solution of 790 mg (1.5 mmol) of the seco ester in 36 ml of dry benzene was added rapidly to a stirred solution of 0.15 g (3.7 mg-atom) of potassium in 17.5 ml of benzene and 17.5 ml of *tert*-butyl alcohol (both solvents distilled from calcium hydride) and the resulting solution was boiled under reflux (nitrogen atmosphere, Dean–Stark trap) for 17 hr while 25 ml of distillate was collected in the trap. The solution was then cooled to room temperature, 30 ml of water and 10 ml of dilute HCl were added, the water layer was removed, and the organic layer was made up to 150 ml with benzene. It was then washed with water, 5% $NaHCO_3$, and water and dried ($MgSO_4$), and the solvent was removed to give 636 mg of an oil which solidified on standing. Recrystallization from methanol gave 517 mg (70%) of 3α-carbomethoxy-*A*-nor-5α-cholestan-2-one: double mp 109.5–110.5° and 121–123° (lit.[5] mp 110–111° and 120–121°); ir ($CHCl_3$) 1755 and 1725 cm^{-1}; $[\alpha]_D$ +99° (589 nm), +105° (578), +124° (546), +268° (436), and +658° (365) (*c* 0.71, $CHCl_3$) (lit.[5] $[\alpha]_D$ +119°); R_f 1.40; T_R^{215} 1.30; nmr δ 0.67 (C-18 CH_3), 0.80 (C-19 CH_3), 0.85, 0.90 (side chain CH_3's), 2.16 (d, 2, C-1-CH_2), 3.08 (d, 1, J = 13 Hz, C-3 H), and 3.75 (s, 3, OCH_3) (at 40 MHz, the C-3 H appeared as a doublet, J = 12.9 ± 0.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 430 (42) (M^+), 275 (base peak).

3α-Methyl-*A*-nor-5α-cholestan-2-one (IIId).—To a solution of 150 mg (0.35 mmol) of the β-keto ester in 7.5 ml of dry benzene was added a solution of 60 mg (0.42 mmol) of sublimed potassium *tert*-butoxide in 7.5 ml of *tert*-butyl alcohol, the solution was stirred for 0.5 hr, and then 37.5 μl (1.3 equiv) of methyl iodide (distilled from Zn dust) was added, and the solution was stirred for 3 hr. All of the preceding operations were carried out in a dry box under a nitrogen atmosphere. Then 10 ml of dilute HCl and 40 ml of benzene were added, the water layer was removed after shaking, and the organic layer was washed with water, saturated K_2CO_3 solution, and water and then dried ($MgSO_4$) and evaporated to give 113 mg (69%) of 3-carbomethoxy-3-methyl-*A*-nor-5α-cholestan-2-one (IIIb,c) as a colorless oil which solidified to a low-melting solid on standing: ir ($CHCl_3$) 1749 and 1725 cm^{-1}; nmr ($CDCl_3$) δ 0.68 (s, C-18 CH_3), 0.83 and 0.92 with shoulders at 0.90 and 0.95 (C-19 CH_3 and side chain CH_3's), 1.30 and 1.35 (C-3 CH_3), and 3.67 with a shoulder at 3.75 (C-3 $OCOCH_3$); in benzene, δ 0.63 (C-18 CH_3), 0.90, 1.00, 1.05, and 1.10 (C-19 CH_3 and side chain CH_3's), 1.35 (C-3 CH_3), 3.32 with a shoulder at 3.33 (C-3 $OCOCH_3$). The nmr data indicated that two isomers, epimeric at C-3, were present.

(11) H. R. Nace and A. C. Watterson, Jr., *J. Org. Chem.*, **31**, 2109 (1966).

A 100-mg (0.26 mmol) sample of the mixture in 5 ml of glacial acetic acid and 4 ml of concentrated HCl was boiled under reflux for 4 days and poured into 40 ml of water, and the mixture was extracted with benzene (3 × 15 ml). The extract was washed with water until neutral, with 10 ml of saturated K_2CO_3 solution, and with water (4 × 10 ml) and dried ($MgSO_4$), and the solvent was removed to give 88 mg of white solid, nmr (CCl_4) δ 3.60 (C-3 $OCOCH_3$, half the area of the C-18 CH_3 at 0.67, indicating only about 50% hydrolysis). The mixture was taken up in 4 ml of glacial acetic acid and 4 ml of 48% hydrobromic acid and boiled under reflux for 2.5 days. After work-up as above 63 mg (70%) of a white solid was obtained; the nmr spectrum showed no methoxy absorption at δ 3.60. After recrystallization from methanol, 54 mg of 3α-methyl-*A*-nor-5α-cholestan-2-one (IIId) was obtained: double mp 124–125.5° and 131.5–133°; $[\alpha]_{589}$ +110°, $[\alpha]_{578}$ +113°, $[\alpha]_{546}$ +138°, $[\alpha]_{436}$ +296°, $[\alpha]_{365}$ +754° (*c* 0.15, $CHCl_3$); $T_R^{115°}$ 1.26; R_f 1.40; nmr ($CDCl_3$) δ 0.70 (s, C-18 CH_3), 0.83, 0.88, 0.93, and 0.97 (C-19 CH_3 and side chain CH_3's), and a new peak at 1.08 (part of doublet for C-3 CH_3); nmr (100 MHz) ($CDCl_3$) δ 0.70 (s, C-18 CH_3), 0.85, 0.90, 0.92, and 0.95 (s, C-19 CH_3 and side chain CH_3's), and 1.03 (d, J = 7 Hz, C-3 CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 386 (68) (M^+) and 231 (base peak).

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.65; H, 12.09.

Registry No.—Ia, 39010-42-9; Ib, 39010-43-0; Ic, 26654-59-1; IIb, 39010-45-2; IIc, 39010-46-3; IId, 39010-47-4; IIe, 39010-48-5; IIf, 39010-49-6; IIg, 39010-50-9; IIIa, 27460-19-1; IIIb, 39010-52-1; IIIc, 39010-53-2; IIId, 39010-54-3; 5α-pregnane-3,20-dione, 566-65-4; 2,3-secocholestane-2,3-dioic acid, 1178-00-3; dimethyl 2,3-secocholestane-2,3-dioate, 1180-24-1.

Hydride Reductions of Naphthalic Anhydrides[1]

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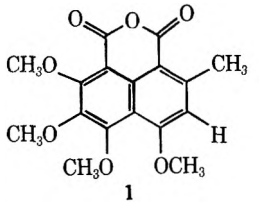
Diborane reduction, at room temperature, of 1,8-naphthalic anhydrides yields the corresponding cyclic ether (2,1,3-*peri*-naphthopyran) as sole isolable product. Reduction with diborane of 1,8-naphthalide also yields only the *peri*-naphthopyran, but in twice the yield obtained from the anhydride. If both the 2 and 7 positions in the anhydride are occupied, reduction fails to occur. Diborane reduction of 1,2-naphthalic anhydride, or of the adduct from anthracene and maleic anhydride, yields only the corresponding diol. Lithium aluminum hydride reduction, at room temperature, of 1,8-naphthalic anhydride yields no *peri*-naphthopyran, but a mixture of diol and 1,8-naphthalide; 1,2-naphthalic anhydride gives similar results. 2,7-Dimethoxy-1,8-naphthalic anhydride, on lithium aluminum hydride reduction in refluxing tetrahydrofuran, yields no diol but a mixture of naphthalide and cyclic ether, with increase in ratio of cyclic ether as reaction time is increased. The data indicate that the naphthalide (lactone) is a common intermediate for formation of either diol or cyclic ether and that diol is not an intermediate in cyclic ether formation. The first step in the sequence proceeds at a higher rate with lithium aluminum hydride, whereas the second step is faster with diborane. 7-Methyl-2,3,4,5-tetramethoxy-1,8-naphthalic anhydride (1), on lithium aluminum hydride reduction, yields only one of the two possible naphthalides; structure **7** has been assigned on the basis of nmr data.

In the course of our earlier investigation[2] of methods for synthesis of substituted 1,8-naphthalic anhydrides, it was discovered that diborane rapidly reduces this type of anhydride, at room temperature, to the corresponding cyclic ether, the 2,1,3-*peri*-naphthopyran. This result was unexpected, since diborane fails to reduce acid chlorides at room temperature,[3] and even sodium borohydride, used by us for preparation of the diborane *in situ*, reduces aromatic acid chlorides only slowly at steam bath temperature.[4] The present investigation is concerned with additional study of reductions with diborane and with lithium aluminum hydride.

1,8-Naphthalic anhydride, as well as 3-methoxy-1,8-naphthalic anhydride, give about the same yield (40%) on reduction at room temperature with diborane, and no other products could be isolated; however, when both the 2 and 7 positions were occupied, reduction failed to occur. Starting material was recovered when there was utilized either 2,7-dimethoxy-1,8-naphthalic anhydride or 7-methyl-2,3,4,5-tetramethoxy-1,8-naphthalic anhydride[5] (1). When the same reaction conditions were used for reduction of 1,8-naphthalide (2), 2,1,3-*peri*-naphthopyran was again obtained, but in



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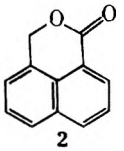
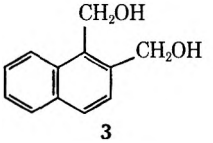


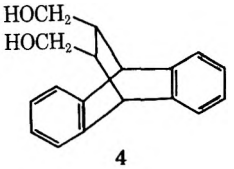
2

~80% yield.[6] Thus, the intermediacy of 2 in the reduction of 1,8-naphthalic anhydride is suggested.

When 1,2-naphthalic anhydride was subjected to diborane reduction, the sole product isolable from the reaction was the diol, **3**. Similarly, when the adduct of



3



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maleic anhydride and anthracene was reduced, the only product obtained was diol **4**. Thus in absence of the notably stable 2,1,3-*peri*-naphthopyran system, cyclic ether is not formed. Much of the chemistry of the peri-substituted naphthalenes is dominated by the stability of this ring system. For example, 1,8-naphthalic anhydride fails to react with alcohols; indeed,

(1) This investigation was supported in part by a research grant (G-9866) from the National Science Foundation.

(2) J. Cason, A. Weiss, and S. A. Monti, *J. Org. Chem.*, **33**, 3404 (1968).

(3) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).

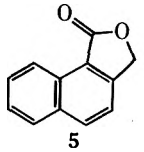
(4) S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949).

(5) J. Cason and D. M. Lynch, *J. Org. Chem.*, **31**, 1883 (1966).

(6) There have been several reports of hydride reductions of esters, including lactones, to ethers. The pioneering report of reduction of lactones to tetrahydropyrans by diborane seems to be that of G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

heating of 1,8-naphthalic acid with methanol or ethanol yields 1,8-naphthalic anhydride. Additional consistent behavior of peri-substituted naphthalenes is reported in the investigation[7] concerned with isolation of anhydride **1** as a degradation product of the naturally occurring pigment herqueinone.

In spite of the stability of the 2,1,3-*peri*-naphthopyran system, reduction of 1,8-naphthalic anhydride with lithium aluminum hydride at room temperature yields none of the cyclic ether. There results a mixture of naphthalide (2) and the diol, 1,8-bis(hydroxymethyl)naphthalene. Indeed, with this reducing agent, results with the 1,2-naphthalic anhydride are the same; products are diol **3** and the 1,2-naphthalide. In view of the significant hindrance exerted by an adjacent peri position in naphthalene, it seems safe to assume that the single 1,2-naphthalide obtained from the reaction has structure **5**. In further evidence of the



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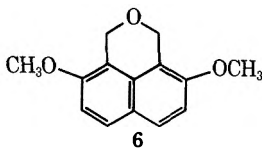

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impact of hindrance in this reaction, 2,7-dimethoxy-1,8-naphthalic anhydride is reduced by lithium aluminum hydride, after 3 hr at reflux in tetrahydrofuran, to yield the cyclic ether, 4,9-dimethoxy-2,1,3-*peri*-naphthopyran (**6**). After a brief period of reflux, the principal product is the intermediate 2,7-dimethoxy-1,8-naphthalide.

The experimental results indicate that the reaction sequence with lithium aluminum hydride also involves the naphthalide as a common intermediate, and the cyclic ether is not formed by dehydration of the diol. Formation of the cyclic ether *via* the diol is also contraindicated by the report[8] that the diol is obtained in good yield when the lithium aluminum hydride reduction of 1,8-naphthalic anhydride is carried out with 3 hr of heating under reflux in a benzene–ether mixture, with distillation of the ether toward the end of the reflux period. In diborane reduction of 3-methoxy-1,8-naphthalic anhydride, recovered alkali-soluble material consisted of starting material, not the naphthalide. Thus, our combined data reveal that with diborane the second step (lactone to cyclic ether) is the faster step, whereas with lithium aluminum hydride the second step is the slower one, regardless of whether the product is diol or cyclic ether.

Lithium aluminum hydride reduction of the highly substituted anhydride, **1**, proved to yield a single 1,8-naphthalide; careful examination failed to detect a second isomer. On the basis of the location of the resonance line in nmr (*cf.* Table I) for the methylene hydrogens at τ 4.23, structure of this lactone is assigned as **7**, with the methylene hydrogens on the side with methyl. 1,8-Naphthalide displays this line at τ 4.10, while 2,7-dimethoxy-1,8-naphthalide has it at τ 4.31. Thus, structure **7**, with the methylene hydrogens not adjacent to methoxyl, seems required, because the methylene hydrogens are significantly downfield from

(7) J. Cason, J. S. Correia, R. B. Hutchison, and R. F. Porter, *Tetrahedron*, **18**, 839 (1962).

(8) W. J. Mitchell, R. D. Topsom, and J. Vaughan, *J. Chem. Soc.*, 2526 (1962).

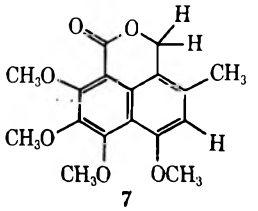
TABLE I

NMR SPECTRA OF ANHYDRIDE 1 AND LACTONE 7

Type H	τ values[a] (number of H's) 1	7
Ar H	3.20 (1)	3.12 (1)
Ar CH_2O		4.23 (2)
Ar OCH_3	5.83 (6)	5.77 (3)
Ar OCH_3	5.90 (3)	5.86 (6)
Ar OCH_3	5.97 (3)	5.93 (3)
Ar CH_3	7.11 (3)	7.00 (3)

[a] All lines are singlets.

the location in the 2,7-dimethoxy-1,8-naphthalide, where they must be adjacent to methoxyl. Buttressing effect of additional methoxyls in **7** might shift the



7

methylene hydrogens further upfield, but not downfield. In additional support of structure **7**, the resonance line for the aromatic methyl hydrogens in **7** is located at τ 7.00, as compared to 7.11 in anhydride **1** (Table I); so a different environment for the aromatic methyl in the two structures is revealed. No conclusions concerning structure may be reached by comparing positions of methoxyl hydrogens, on account of the relatively large effects of vicinal methoxyls on each other;[7] indeed, the lowest field line results from six methoxyl hydrogens in **1**, whereas six hydrogens are accounted for in the middle line of the three resonance lines in **7** (Table I).

Experimental Section[9]

Reduction of 1,8-Naphthalic Anhydride. A. With Diborane.—To a solution of 1.36 g (36 mmol) of $NaBH_4$ in 37 ml of purified diglyme, stirred at room temperature in an atmosphere of N_2, was added portionwise 3.96 g (20 mmol) of powdered 1,8-naphthalic anhydride. To the reddish turbid mixture was next added dropwise, during ~30 min, a solution of 6.8 g (48 mmol) of boron trifluoride etherate in 15 ml of purified diglyme. The ratio of $NaBH_4$:BF_3 is 3:4, as required stoichiometrically for formation of B_2H_6. Stirring at room temperature was continued for 2 hr. After about one-fourth of the BF_3 had been added, the initially reddish solution turned clear yellow, and, after about three-fourths of the addition, a precipitate began to separate. The reaction mixture was worked up by addition of 100 ml of ice–water, followed by filtration, washing, and drying of the precipitate. Crystallization from commercial mixed hexanes yielded 1.36 g (40%) of 2,1,3-*peri*-naphthopyran: mp 76–80° [sublimation raised this to 82–83° (lit.[10] mp 83–83.5°)]; ir clear in carbonyl region, aromatic absorption at 6.20 μ; picrate mp 176–178° (lit.[10,11] mp 177.5–178, 173.5–175°).

A similar run using double the ratio of $NaBH_4$ gave 50% yield, mp 82–84°.

B. With Lithium Aluminum Hydride.—To a suspension of 396 mg (2 mmol) of 1,8-naphthalic anhydride in 10 ml of purified tetrahydrofuran (THF), stirred in an atmosphere of N_2, there was added dropwise at room temperature, during 30 min, a solution of 228 mg (6 mmol) of $LiAlH_4$ in 20 ml of absolute ether.

(9) Melting points are corrected. Nmr spectra were recorded on a Varian A-60 instrument, in deuteriochloroform as solvent, with TMS as internal reference. Microanalyses were by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

(10) A. J. Weinheimer, S. W. Kantor, and C. R. Hauser, *J. Org. Chem.*, **18**, 801 (1953).

(11) J. Cason and J. D. Wordie, *J. Org. Chem.*, **15**, 608 (1950).

After stirring had been continued for 1 hr, excess $LiAlH_4$ was destroyed by adding 15 ml of water, followed by 15 ml of 2 *M* H_2SO_4. The resultant two-phase solution was extracted with three portions of ether, and solvent was removed from the washed extracts. Repeated systematic crystallization of the residue from $CHCl_3$ yielded 100 mg (27%) of 1,8-bis(hydroxymethyl)naphthalene, mp 156–157° (lit.[10] mp 154–154.5°), ir and melting point identical with those of a sample synthesized by reduction of dimethyl 1,8-naphthalate with $LiAlH_4$. Combined mother liquors from isolation of the diol were evaporated to dryness, and the residue was systematically recrystallized from ethanol to yield 143 mg (39%) of 1,8-naphthalide (2), mp 159–161°, ir and melting point identical with those of an authentic sample,[11] but lit.[11] melting point of same sample is 156.6–157.2°. Another sample of 2, purified *via* extraction into basic solution, had mp 157–161° (lit.[12,13] mp 156–157, 159–160°). The substance appears to be polymorphic.

Reduction of 1,8-Naphthalide (2) with Diborane.—Reduction of 184 mg of 2 by the same procedure described for 1,8-naphthalic anhydride, except that one-half the ratio of reducing agent was used, yielded, after crystallization, 135 mg (80%) of product, mp 80–83°.

Reduction of 3-methoxy-1,8-naphthalic anhydride[2] with diborane by the same procedure described for the unsubstituted anhydride yielded 43 mg of crude product from 72 mg of starting material. The crude product was heated under reflux for 15 min with 23 ml of 1 *N* NaOH (to dissolve any naphthalide present), and the cooled mixture was extracted with three portions of ether. Work-up of the alkaline solution yielded no naphthalide, but 10 mg of starting material, which, after crystallization from glacial acetic acid, had mp 246–250° (lit.[2] mp 249–250°). Product recovered from the ether extracts was recrystallized from hexane to yield 24 mg (38%), mp 80–83°, of **5-methoxy-2,1,3-*peri*-naphthopyran**. By sublimation and further recrystallization was obtained an analytical sample: mp 82–84°; ir clear in carbonyl region, aromatic absorption at 6.27 μ.

Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0. Found: C, 77.6; H, 6.0.

Reduction of 1,2-Naphthalic Anhydride. A. With Diborane.—A 396-mg sample of 1,2-naphthalic anhydride,[14] mp 169–171°, was reduced as described for the 1,8 isomer. Recrystallization of the product from benzene yielded 240 mg (63%), mp 122–123°, of **1,2-bis(hydroxymethyl)naphthalene (3)**.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.6; H, 6.2.

B. With Lithium Aluminum Hydride.—A 396-mg sample of the anhydride was reduced as described for the 1,8 isomer, and the product was first crystallized from benzene to yield 170 mg (45%) of diol **3**, mp 122–123°, ir and melting point identical with those of sample from diborane reduction. Recrystallization from methanol of material recovered from the mother liquors yielded 84 mg, mp 157–158°, of **1,2-naphthalide**, assigned structure **5**.

Anal.[15] Calcd for $C_{12}H_8O_2$: C, 78.25; H, 4.4. Found: C, 78.3; H, 4.45.

Diol 4.—A 5.52-g sample of the adduct from anthracene and maleic anhydride was reduced with diborane as described for 1,8-naphthalic anhydride, and the product was crystallized from benzene to yield 3.6 g (68%) of diol **4**, mp 225–226° (lit.[16] mp 221°). In view of the minor discrepancy in melting point and the previous report in a patent,[16] a sample was analyzed.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.2; H, 6.9.

A 100-mg sample of diol 4 was converted to the **cyclic ether** by heating it under reflux for 20 hr with 5 ml of 35% H_2SO_4, yield 79 mg (85%), mp 182–183° from methanol (lit.[16] mp 180–181°).

2,7-Dimethoxy-1,8-naphthalic Anhydride.—Following the procedure previously developed[2] for synthesis of 3-substituted acenaphthenequinones, 3.04 g (16.2 mmol) of 2,7-dimethoxynaphthalene (from acid-catalyzed methylation of commercial diol, mp 139–141° from ethanol, lit.[17] mp 139°) and 4.48 g (16.2 mmol) of diphenyloxalimide chloride yielded 5.5 g of crude product containing 3,8-dimethoxyacenaphthenequinone. Since difficulty was encountered in extracting the quinone into aqueous bisulfite, as experienced[2] with another dimethoxyacenaphthenequinone, the crude product was oxidized in a mixture of 22 ml of 95% ethanol, 185 ml of 4 *N* NaOH, 185 ml of 30% H_2O_2, and 256 ml of water. After the reaction mixture had been allowed to stand for 30 min with occasional shaking, the large (3.15 g) dark precipitate which still remained was removed by filtration. The white precipitate obtained by acidification of the alkaline filtrate was recrystallized from ethylene glycol to yield 869 mg (21% from 2,7-dimethoxynaphthalene) of the desired anhydride, mp 346–348° (lit.[18] mp 340–344°).

Reduction of 2,7-Dimethoxy-1,8-naphthalic Anhydride.—Attempted reduction of 58 mg of this anhydride, with twice the normally used ratio of $NaBH_4$ to BF_3, resulted in recovery of 50 mg of starting material. Reduction of 100 mg of the anhydride with $LiAlH_4$ as described for the parent anhydride, except that the mixture was heated for 30 min under reflux, yielded 91 mg of crude product. This material was heated under reflux for 1 hr with 10 ml of 10% methanolic KOH (to saponify any naphthalide present), and the cooled and water-diluted solution was extracted with three portions of ether. The ether extracts yielded 27 mg of oily material, from which no pure product could be isolated. Acidification of the alkaline solution yielded 33 mg of product, which gave after crystallization from methanol 20 mg (21%) of 2,7-dimethoxy-1,8-naphthalide, mp 198–201°. After two additional crystallizations, the analytical sample had mp199–202°; uv (*cf.* Table II); ir ($CHCl_3$) 5.84 μ; nmr τ [*J* (for doublets) = 9 Hz] 2.05 (d, 1, Ar H), 2.23 (d, 1, Ar H), 2.77 (d, 1, Ar H) 2.83 (d, 1, Ar H), 4.31 (s, 2, Ar CH_2O), 5.85 (s, 3, Ar OCH_3), 5.99 (s, 3, Ar OCH_3).

TABLE II

UV ABSORPTION OF 1,8-NAPHTHALIDES[a]

1,8-Naphthalide	λ_{max}, nm[b] ($\epsilon \times 10^{-3}$)			
Parent	c	213 (42.0)	241 (23.1)	314 (7.1)
2,7-Di-OCH_3	218 (32.9)	232 (52.9)	255 (16.4)	344 (11.8)
7	224 (23.1)	254 (40.8)	...	338 (9.45)

[a] Solvent 95% ethanol. [b] λ_{min} in order of listing above: 262 (1.05), 282 (2.7), 279 (1.5). [c] Below range observable in ethanol solvent.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.8; H, 4.95. Found: C, 68.4; H, 5.0.

In a similar reduction, except that twice the ratio of $LiAlH_4$ was used and heating was continued for 3 hr, the saponifiable material (naphthalide) amounted to only 6 mg and the neutral product was 39 mg. Recrystallization from methanol yielded 20 mg (22%) of **4,9-dimethoxy-2,1,3-*peri*-naphthopyran (6)**, mp 130–133°. Two crystallizations from methanol yielded analytical sample: mp 132.5–134°; ir ($CHCl_3$) clear in carbonyl region, aromatic absorption at 6.15 μ.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.6; H, 6.2.

Uv of 1,8-Naphthalides.—Uv absorption of the naphthalides is shifted to longer wavelengths (Table II) by the methoxyl substitution adjacent to the ester function; however, additional methoxyl substitution (7) has little effect on the longest wavelength band, except to broaden it significantly on the low-wavelength side. The spectrum of 7 is also simplified, in that the band to be expected near 275 nm is entirely absent.

Reduction of Anhydride 1.[5]—Attempted reduction of 54 mg of 1 with diborane by the same procedure applied to 1,8-naphthalic anhydride led to recovery of 30 mg of starting material; no homogeneous reaction product could be isolated, even after diverse applications of liquid-phase column chromatography. Reduction, during 30 min, of 100 mg of 1 with $LiAlH_4$ and work-up *via* saponification with methanolic KOH followed the pro-

(12) R. C. Fuson and G. Munn, *J. Amer. Chem. Soc.*, **71**, 1870 (1949).

(13) G. Errera and G. Ajon, *Gazz. Chim. Ital.*, **44** (II), 92 (1914).

(14) P. A. S. Smith and R. O. Kan, *J. Amer. Chem. Soc.*, **82**, 4753 (1960). Details of experimental procedure were adapted from the preparation of homophthalic acid: P. A. S. Smith and R. O. Kan, *Org. Syn.*, **44**, 62 (1964).

(15) Classical combustion analysis tended toward low values for several of the compounds encountered in this investigation; however, this naphthalide gave unacceptably low values (highest C, 77.5%). The correct value was obtained, as for previously reported compounds,[2] by the method depending on combustion in a sealed tube; *cf.* C. W. Koch and E. Jones, *Mikrochem. Acta*, **4**, 734 (1963).

(16) H. Krzikalla, E. Woldan, and O. Dornheim, German Patent 736,024 (1943); *Chem. Abstr.*, **38**, 4620 (1944).

(17) H. Bunzly and H. Decker, *Ber.*, **38**, 3272 (1905).

(18) D. H. R. Barton, P. de Mayo, G. A. Morrison, and H. Raistrick, *Tetrahedron*, **6**, 48 (1959).

cedure described for 2,7-dimethoxy-1,8-naphthalic anhydride. No homogeneous product could be isolated from the base-insoluble fraction. After crystallization of the base-soluble material from methanol–water, there was obtained 17 mg (18%) of lactone 7, mp 112.5–114.5°. This material was combined with the products from two other similar runs, and, in solution in 10 ml of ether–hexane (2:3), was applied to a column of 10.6 g of Woelm alumina (activity III). Elution with ether–hexane, then with ether, while observing band movement in uv light, revealed only a single blue band, which was finally eluted with ether. Crystallization of the eluted product (49 mg) from hexane yielded 43 mg of white crystals, mp 115.0–116.5°; two additional crystallizations gave the analytical sample of 7, mp 115.5–116.5°, ir 5.87 μ (carbonyl), uv (Table II), nmr (Table I).

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.1; H, 5.7. Found: C, 64.0; H, 5.9.

Registry No.—**1**, 6398-92-1; **2**, 518-86-5; **3**, 39050-28-7; **4**, 26495-88-5; **5**, 5657-01-2; **6**, 39050-31-2; **7**, 39050-32-3; $NaBH_4$, 16940-66-2; $LiAlH_4$, 16853-85-3; 1,8-naphthalic anhydride, 81-84-5; diborane, 19287-45-7; 3-methoxy-1,8-naphthalic anhydride, 5289-78-1; 5-methoxy-2,1,3-*peri*-naphthopyran, 39050-34-5; 1,2-naphthalic anhydride, 5343-99-7; 2,7-dimethoxy-1,8-naphthalic anhydride, 32432-09-0; 2,7-dimethoxy-1,8-naphthalide, 39050-37-8.

Notes

Addition of Amide Ion to Isoquinoline and Quinoline in Liquid Ammonia. Nuclear Magnetic Resonance Spectra of Anionic σ Complexes[1]

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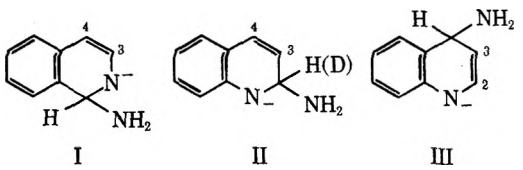
Anionic σ complexes are formed by the addition of nucleophiles to aromatic and heteroaromatic molecules.[2] Recent studies of such complexes, commonly called Meisenheimer-type complexes, have provided new insights into the effects of structure on the addition of nucleophiles to unsaturated carbon centers.

We wish to call attention to a class of anionic σ complexes long postulated[3] but largely uncharacterized. The complexes are formed by the reaction of amide ion with hetarenes.

We now report the first unambiguous evidence in the form of nmr spectra for the existence of anionic σ complexes I–III formed by the addition of amide ion to



I II III

isoquinoline and quinoline. Amide ion adds faster to C-2 than to C-4 of quinoline to give II but the C-4 adduct (III) is more stable; *i.e.*, kinetic and thermodynamic products are formed, respectively.

Complexes I–III have long been postulated to occur in the Chichibabin amination of isoquinoline and quinoline.[4,5] Some appear to have been isolated by Bergstrom in the 1930's, but owing to their instability in the solid state they were characterized only superficially.

Results and Discussion

In the presence of excess KNH_2, reaction with isoquinoline or quinoline is complete and rapid; no hetarene can be detected by nmr when mixtures are examined shortly after preparation. When substrate is present in excess, spectra of both complexed and free heterocycles are observed, and there is no evidence of signal averaging between these two, either in coupling constants or chemical shifts.

A significant change occurs in the pattern of a single multiplet of a complex as the amide ion concentration is varied. The multiplicity decreases as the concentration of KNH_2 increases. This means that amide ion catalyzes proton transfer between the amino group of an adduct and solvent, leading to spin decoupling.[7,8] When the amide ion concentration is low, this exchange is slow and spin coupling is observed. This multiplicity change serves as a useful way to recognize the proton signal of the tetrahedral center of the complex and provides direct evidence for a complex containing an amino group. In the absence of amide ion, isoquinoline and quinoline in NH_3 show no evidence of adduct formation.

Isoquinolines.—The spectrum of the complex between isoquinoline and amide ion at −10° shows a broad multiplet at τ 2.7–3.65, a triplet (J_{HCNH} = 7.0 Hz) at τ 4.66 which collapses to a singlet when amide ion is present in excess and a doublet ($J_{3,4}$ = 5.5 Hz) at τ 5.13. The triplet–singlet change and the lack of further splitting indicates that the adduct is formed by

(1) Presented in part at the Gordon Conference on Heterocyclic Chemistry, New Hampton, N. H., June 26–30, 1972.

(2) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(3) K. Ziegler and H. Zeiser, *Chem. Ber.*, **63**, 1847 (1930).

(4) F. W. Bergstrom, *J. Amer. Chem. Soc.*, **56**, 1748 (1934); *Justus Liebigs Ann. Chem.*, **515**, 34 (1934); *J. Org. Chem.*, **2**, 411 (1937); *ibid.*, **3**, 233, 424 (1938).

(5) Simple ions are written here, but early conductance studies indicate that ion pairing is important in ammonia.[6]

(6) C. A. Kraus, *J. Phys. Chem.*, **58**, 673 (1954), and references cited therein.

(7) R. A. Ogg, Jr., *Discuss. Faraday Soc.*, **No. 17**, 215 (1954).

(8) T. J. Swift, S. B. Marks, and W. G. Sayre, *J. Chem. Phys.*, **44**, 2797 (1966).

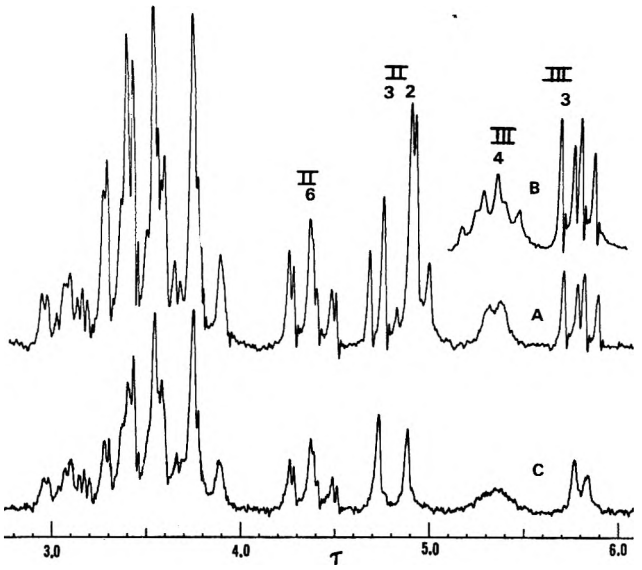
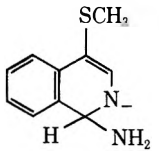


Figure 1.—Nmr spectra of complexes between quinoline and amide ion in ammonia at −45°. Insert B shows H-3 and coupling of the amino group to H-4 of III. Spectra A and C show mixtures of II and III, the former complex being present in larger amount. Quinoline-*2-d* was used to obtain C.

addition of amide ion to C-1. If amide ion had added to any other ring carbon, a more complex multiplet would have resulted.

The doublet at τ 5.13 could be associated with either C-3 or C-4 of the complex. In order to distinguish between these two possibilities a complex between KNH_2 and 4-methylthioisoquinoline was prepared. (A methylthio group has only a small influence on the shift of a proton at an ortho position.[9]) When similar quantities of the aromatic compound and the complex were present at room temperature, a broad multiplet of the adduct at τ 2.83–3.65 and a triplet (J_{HCNH} = 7.2 Hz) at τ 4.93 (CH-1) and an SCH_3 singlet at τ 8.11 were observed. No other signal at τ ~5 was apparent. The anionic σ complex formed in this instance must have structure IV.



IV

The nmr shifts observed for IV allow an unambiguous assignment of the signals of I. The high-field doublet must be associated with C-4. For I and also IV the C-3 signal must lie in the broad multiplet associated with the protons of the carbocyclic ring.

When isoquinoline forms complex I, the signals of C-1 and C-4 shift upfield by 4.1 and ~3 ppm, respectively. Similarly, for 4-methylthioisoquinoline the C-1 and SCH_3 shifts are 4.0 and 0.65 ppm, respectively. Other signals due to ring protons shift by smaller amounts. These shifts[2] provide further strong evidence for the existence of σ complexes I and IV.

Quinoline.—A mixture of quinoline and excess KNH_2 or $NaNH_2$ when examined at −45° shortly after preparation provides a time-dependent spectrum. After the mixture stands for a few minutes or after it is warmed above −45°, the signals at τ 5–6 increase as those at τ 4–5 decrease. Cooling the sample does not reverse the change. This indicates that two complexes are being formed and that one is being converted into another. Figure 1A shows the spectrum of an adduct mixture at −45°; about 75% of II and 25% of III are present. When the amide ion concentration is decreased, coupling of ~7 Hz to an NH_2 in III becomes apparent. This is shown in Figure 1B. Owing to signal overlap, amino coupling in II is less clear and consequently is not shown. The partial spectrum shown in B was obtained when approximately equal concentrations of quinoline, and its complexes were present. The tetrahedral center (H-2) of II shows a signal at τ 4.9 while that (H-4) for III is at τ 5.3.

Unequivocal identification of II and III results from a consideration of a spectrum of complexes formed from quinoline-*2-d*. Figure 1C shows such a spectrum; again II is present in larger amount than III.

On deuteration the upfield multiplet of II centered at τ 4.8 ($J_{2,3}$ = 4.3 Hz) collapses to a doublet due to H-3 ($J_{2,4}$ = −1 Hz and $J_{3,4}$ = 9.0 Hz). The splitting of H-3 of III at τ 5.8 by H-2 ($J_{2,3}$ = 6.5 Hz) also vanishes, leaving a doublet ($J_{3,4}$ = 4.3 Hz). No four-bond coupling is observable in adduct III. In addition there is a reduction in area by one proton of the multiplet at τ 3–4 and a change in appearance around τ 3.4, owing to the absence of H-2 of III. Note that the signal of the tetrahedral center in the more stable adduct is not lost on deuteration at position 2, clearly showing that this complex is not II but III.

The multiplet at τ 4.4 of II is tentatively assigned to H-6 rather than to H-7 because it is para to the electron-donating nitrogen center. The shielding of this proton and of H-3 of III relative to H-3 of II suggests that more charge is delocalized into the benzene ring in II than in III.

The signal for H-2 shifts to higher field by 3.8 ppm when II is formed; H-4 shifts by about the same amount on forming III. These large shifts provide strong evidence for the formation of anionic σ complexes.[2]

Since quinoline is completely converted into III in the presence of a slight excess of amide ion, it is likely that this complex is formed in an exothermic reaction having a transition state which does not closely resemble the product ion.[10] Hence the structural and solvation factors which influence the energies of the transition and product states need not be similar. It therefore is understandable that, even though III is more stable than II, it need not form faster. The allylic type resonance stabilization possible in III but not in II may account for the greater stability of III over II.

In other experiments some consequences of complex formation on the chemical reactivity of quinoline in NH_3 were demonstrated by examining base-catalyzed deuterium–hydrogen exchange. A competition experiment involving quinoline-*2-d* and naphthalene-d_8 in KNH_2–NH_3 was carried out at room temperature. In the absence of adduct formation quinoline is expected to undergo the hydrogen exchange reaction faster than naphthalene does, just as pyridine is more reactive than benzene.[11] However, the results of the competition

(9) W. E. Stewart and T. H. Siddall, III, *J. Phys. Chem.*, **74**, 2027 (1970); W. Brügel, *Z. Elektrochem.*, **66**, 159 (1962).

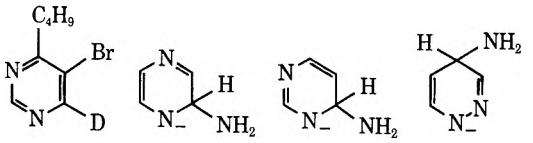
(10) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(11) J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969); I. F. Tupitsyn, N. N. Zatzepina, A. W. Kirowa, and J. M. Kapustin, *Reakts. Sposobnost Org. Soedin.*, **5**, 601 (1968).

experiment showed that naphthalene undergoes more extensive D–H exchange than quinoline. This result is understandable in terms of deactivation due to adduct formation. We suggest that such a competition experiment may serve as a simple chemical method of detecting σ complexes in other heterocyclic systems.

Such deactivation due to σ complex formation probably accounts for the observation that 4-*tert*-butyl-5-bromopyrimidine-6-*d* (V) does not undergo significant exchange in KNH_2–NH_3.[12] In the absence of the addition of amide ion the pyrimidine is expected to be more reactive than deuterated pyridine in an H–D exchange reaction;[11] yet it is less reactive.

The present results along with those given in our earlier report dealing with the formation of complexes VI–VIII from diazines[13] show that σ complex formation between amide ion and hetarenes is extensive. Clearly an area awaits further profitable investigation. It promises to provide a wealth of new information, especially about complexes of simple heteroaromatic compounds which do not react in the more widely employed solvent–base systems.[2]



V VI VII VIII

Experimental Section

Quinoline-2-*d* was prepared by heating equal volumes of quinoline and D_2O at 225° for 2 days in a bomb.[14] Nmr analysis indicated >95% deuteration. Naphthalene-d_8 (>95% D) was obtained from Merck Sharpe and Dohme of Canada.

The general procedure for obtaining nmr spectra of ammonia-amide ion reaction mixtures has been presented.[15] Trimethylamine (τ 7.87) or benzene (τ 2.60) served as a shift standard. A Varian A-60A spectrometer having a V-6040 variable temperature controller was employed.

Competitive Hydrogen–Deuterium Exchange of Quinoline-2-*d* and Naphthalene-d_8 in Ammonia.—Potassium amide (0.3 *M*) was generated by the method indicated above. To a precooled Parr metal bomb, flushed with nitrogen, was added 60 ml of amide solution. This was followed by the addition of 0.0074 *m* of naphthalene-d_8 and 0.0051 *m* of quinoline-2-*d*. The sealed bomb was heated in running tap water for 45 min, cooled in acetone–Dry Ice, and opened; the reaction was quenched by the addition of 3.2 g of NH_4Cl. After evaporation of the solvent, the residue was treated with 50 ml of 18% KOH to remove salts and then dissolved in ether. The aqueous solution was extracted with 2 × 30 ml of ether. The combined ether phases were exposed to 2 × 30 ml of 1 *M* HCl. Evaporation of the ether gave naphthalene which was sublimed. The nmr spectra of a mixture of purified naphthalene and *tert*-butyl alcohol (area standard) indicated that 74% dedeuteration had resulted.

Quinoline was recovered from the HCl following neutralization with Na_2CO_3 and extraction with ether (2 × 25 ml). Nmr analysis of the ether solution showed that 20% dedeuteration had taken place.

Registry No.—II, 38896-70-7; III, 38896-68-3; IV, 38896-69-4; isoquinoline, 119-65-3; quinoline, 91-22-5; 4-methylthioisoquinoline, 38896-71-8; amide ion, 17655-31-1.

(12) H. C. van der Plas, P. Smit, and A. Koudijs, *Tetrahedron Lett.*, 9 (1968).

(13) J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.*, **94**, 682 (1972).

(14) J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3358 (1967); U. Bressel, A. R. Katritzky, and J. R. Lea, *J. Chem. Soc. B*, 4 (1971).

(15) J. A. Zoltewicz and L. S. Helmick, *J. Org. Chem.*, **38**, 658 (1973).

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Covalent Amination of Heteroaromatic Compounds[1]

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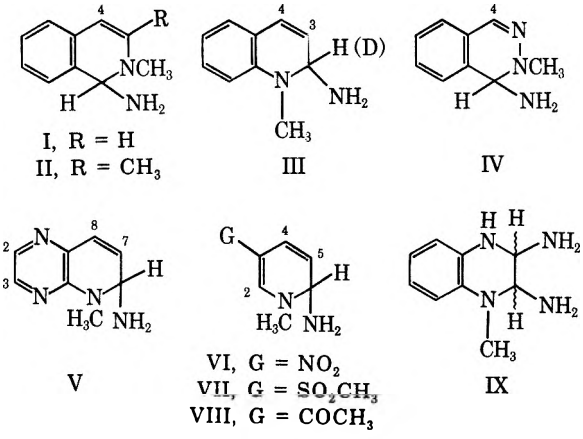
The discovery that heteroaromatic molecules may be transformed into their covalent hydrates in aqueous solution is of great importance. In the hydration process a water molecule or hydroxide ion serving as a nucleophile adds to a ring carbon atom to give a hydroxy derivative. This brings about major changes in the physical and chemical properties of the original substance.[2,3]

We wish to call attention by this report to analogous structural transformations involving heteroaromatic molecules in ammonia solvent. Covalent amination results.[4] Examples reported here include quaternized isoquinoline, quinoline, phthalazine, triazanaphthalene, 3-substituted pyridines and quinoxaline. These cations are converted in liquid ammonia, *free of added amide ion*, into aminodihydro structures I–IX. The amination reactions are remarkable in that they are complete in minutes below 0°. No starting material could be detected by nmr at equilibrium.



I, R = H
II, R = CH_3
III
IV
V
VI, G = NO_2
VII, G = SO_2CH_3
VIII, G = $COCH_3$
IX

The present study complements our other investigations which show that uncharged heteroaromatic molecules such as the diazines, isoquinoline, and quinoline react rapidly and completely with amide ion in am-

(1) Presented in part at the Gordon Conference on Heterocyclic Chemistry, New Hampton, N. H., June 26–30, 1972.

(2) W. L. F. Armarego, *Advan. Heterocycl. Chem.*, **1**, 253 (1963); A. Albert and W. L. F. Armarego, *ibid.*, **4**, 1 (1965); D. D. Perrin, *ibid.*, **4**, 43 (1965); A. Albert, *Angew. Chem., Int. Ed. Engl.*, **6**, 919 (1967); D. Beke, *Advan. Heterocycl. Chem.*, **1**, 167 (1963).

(3) J. W. Bunting and W. G. Meathrel, *Can. J. Chem.*, **50**, 919 (1972).

(4) Amino complexes of the type reported here have been isolated. For example, N-substituted isoquinolinium and quinolinium ions give crystalline solids with piperidine.[5]

(5) F. Krohnke and J. Vogt, *Justus Liebigs Ann. Chem.*, **600**, 211 (1956).

TABLE I

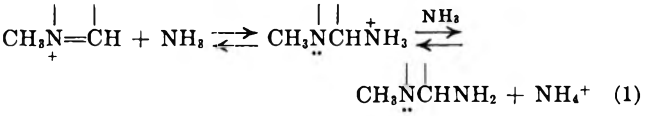
CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS OF AMINODIHYDRO COMPOUNDS[a]

Compd	H-1	H-2	H-3	H-4	Other	J, Hz
I	4.85		3.63	4.55	H-5–H-8, 2.7–3.0	$J_{3,4} = 7$
					NCH_3, 6.90	$J_{1,3} = 1.2$
II	4.97			4.67	H-5–H-8, 2.7–3.0	
					NCH_3, 7.02	
					CCH_3, 8.06	
III		5.21	4.14		H-4–H-8, 2.6–3.4	$J_{3,4} = 9.8$
					NCH_3, 6.97	$J_{2,3} = 5.5$
IV	4.87			2.45	H-5–H-8, 2.4–2.7	
					NCH_3, 6.78	
V		2.17[b]	1.93[b]		H-6, 4.82; H-7, 3.60; H-8, 3.27	$J_{6,7} = 4.5$
					NCH_3, 6.84	$J_{7,8} = 10$
						$J_{2,3} = 3$
VI		1.51		3.15	H-5, 4.62; H-6, 4.94	$J_{5,6} = 4$
					NCH_3, 6.52	$J_{4,5} = 10$
						$J_{2,4} = 2.5$
VII		2.75		3.71	H-5, 4.72; H-6, 5.10	$J_{5,6} = 4.5$
					NCH_3,[b] 6.74	$J_{4,5} = 10$
					SO_2CH_3,[b] 7.03	$J_{2,4} = 2$
VIII		2.38		3.35	H-5, 4.75; H-6, 5.12	$J_{5,6} = 4.5$
					NCH_3, 6.74	$J_{4,5} = 10$
					$COCH_3$, 7.87	$J_{2,4} = 2$
IX		5.93[b]	6.04[b]		H-5–H-8, 3.41	$J_{2,3} = 2.5$
					NCH_3, 7.10	

[a] Nmr spectra of covalent amination products I, III, V, VIII, and IX appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-1949. Remit check for $3.00 for photocopy or $2.00 for microfiche. [b] Assignments may be interchanged.

monia to give anionic covalent amination products.[6] Clearly, aminations must be taken into consideration when dealing with the chemistry of heteroaromatic compounds in ammonia[7] because major changes in physical and chemical properties are expected to result. The amination phenomenon is not limited to heterocyclic compounds.[8]

Structural assignments I–IX are based on the nmr data listed in Table I and on the well-established principle that the nucleophile will add to a carbon center so as to neutralize the charge on the quaternized nitrogen atom. This center generally will be located α or γ to the nitrogen atom. Product signals are at higher fields than those of the precursor cations. For example, reaction of 2-methylisoquinolinium ion[10] with ammonia gives a single product showing up-field shifts for H-1, H-3, and H-4 of about 4.4, 2, and 3 ppm, respectively. Such large shielding factors are similar to those known to result when nucleophiles add to aromatic rings.[11] Chemical shifts and coupling constants are consistent with those of known dihydro structures.[3,12,13] No spin coupling between the amino group and the proton of the newly formed tetrahedral carbon is found and none is expected. The probable stoichiometry of the addition reaction is given in eq 1. The ammonium ion product is expected to catalyze proton exchange between solvent and the amino group, leading to spin decoupling.[15] In agreement with this, the solvent shows a singlet rather than its usual triplet spectrum.



$$CH_3\overset{+}{N}{=}CH + NH_3 \rightleftharpoons CH_3\ddot{N}CH\overset{+}{N}H_3 \overset{NH_3}{\rightleftharpoons} CH_3\ddot{N}CHNH_2 + NH_4^+ \quad (1)$$

It is most likely that 2-methyl- and 2,3-dimethylisoquinolinium ions react with ammonia at C-1 to give aminodihydro compounds I and II. Of all the ring proton signals, that for H-1, easily recognized by the absence of large spin coupling, is found at the highest field (Table I). This is consistent with the formation of a tetrahedral center at C-1 by an addition reaction. Addition to C-3 or to a carbon atom of the carbocyclic ring can be ruled out if it is assumed that the proton at the tetrahedral center will resonate at high field. Such a proton is not expected to show a single, small (1.2 Hz) coupling as is found in the present case. Comparison of the spectra for I and II indicates that this 1.2-Hz coupling is likely to involve H-1 and H-3 of I. Note that the coupling constant involving the vinyl center

(6) J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.*, **94**, 682 (1972); J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King, and P. E. Kandetzki, *J. Org. Chem.*, **38**, 1947 (1973).

(7) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, Part 2, Interscience, New York, N. Y., 1963; H. J. den Hertog and H. C. van der Plas in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 17; T. Kauffmann and R. Wirthwein, *Angew. Chem. Int. Ed. Engl.*, **10**, 20 (1971).

(8) Polynitrobenzenes also have been reported to react with ammonia to give amino complexes.[9]

(9) R. Foster and R. K. Mackie, *Tetrahedron*, **18**, 161 (1962).

(10) Iodide and perchlorate salts show identical spectra, thus eliminating the possibility that iodide ion rather than ammonia served as the nucleophile.

(11) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(12) R. Bramley and M. D. Johnson, *J. Chem. Soc.*, 1372 (1965); C. J. Cooksey and M. D. Johnson, *J. Chem. Soc. B*, 191 (1968); J. W. Bunting and W. G. Meathrel, *Tetrahedron Lett.*, 133 (1971); H. Albrecht and F. Kröhnke, *Justus Liebigs Ann. Chem.*, **717**, 96 (1968); T. Severin, H. Lerche, and D. Batz, *Chem. Ber.*, **102**, 2163 (1969); **103**, 1 (1970).

(13) Ring-opened structures can easily be eliminated as possibilities. No aldimine signals are found at low fields. Coupling constants, *e.g.*, 2–5 Hz, for products from pyridinium ions are too small to be consistent with such structures.[14]

(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 191 and Chapter 4; R. Kuhn and E. Teller, *Justus Liebigs Ann. Chem.*, **715**, 106 (1968).

(15) R. A. Ogg, Jr., *Discuss Faraday Soc.*, **No. 17**, 215 (1954); D. R. Clutter and T. J. Swift, *J. Amer. Chem. Soc.*, **90**, 601 (1968).

directly bonded to the annular nitrogen atom is 7 Hz. In the case of II a new spectrum is observed at room temperature, corresponding to methylamine and 3-methylisoquinoline.

Although ammonia could add to the C-2 and C-4 positions of 1-methylquinolinium ion to give mixed monoaddition products, varying the temperature from −50 to 25° had no influence on the nature of the spectrum. Hence, only a single structure is detectable. That ammonia added to C-2 and not to C-4 follows from the spectrum of the adduct having deuterium at C-2. The doublet at τ 5.21 which is expected to be associated with the newly formed tetrahedral center disappeared on deuteration, showing that ammonia added to C-2 to give III. The large coupling constant (9.8 Hz) found for the vinyl protons in the nonaromatic ring provides additional evidence for the proposed structure. The C-4 adduct is expected to have a smaller coupling constant.[3,12]

1-Amino-2-methyl-1,2-dihydrophthalazine (IV) results from the amination of 2-methylphthalazinium ion. The chemical shift of the proton at the tetrahedral center (C-1) is nearly the same as those for H-1 of the analogous isoquinoline compounds I and II (Table I).

5-Methyl-1,4,5-triazanaphthalinium ion also readily undergoes amination. Ammonia could add to several positions of this cation. Only one structure was detected by nmr over the temperature range −43 to +30°. A structure may be designated by a consideration of the magnitude (10 Hz) of the coupling constant for the protons of the pyridine ring. The large value indicates that vinyl protons are present and the vinyl center is not bonded directly to nitrogen. Hence, addition takes place α to the quaternized nitrogen atom to give V.

In the case of 1-methyl 3-substituted pyridinium ions, three different amination products are likely, involving addition to positions C-2, C-4, and C-6. Only one isomer was detected between −50 and +30° (−23 and +30° in the case of the nitro compound). This isomer appears to be the same for ions having a nitro, a methylsulfonyl, or an acetyl substituent, as evidenced by similar coupling constants. Structures VI–VIII may be assigned. Amino adducts are formed by addition to C-6. The 10-Hz coupling constant rules out a C-4 adduct and the low-field position of H-2 eliminates a C-2 amination product. At room temperature another reaction occurs. Methylamine and a 3-substituted pyridine are formed; the order of increasing reactivity is acetyl, methylsulfonyl, and nitro substrate. Some 3-acetylpyridine imine forms as well.

It is interesting that 1-methylpyridinium ion, the parent compound, does not react with neutral ammonia to give covalent amination product in amounts detectable by nmr. Clearly, the effect of the 3 substituent is important. In the present cases, the electron-withdrawing effects of the substituents destabilize the precursor pyridinium ions, but the groups stabilize the amino adducts, especially when there is significant conjugation between the annular nitrogen atom and the substituent.

An especially interesting result is obtained with 1-methylquinoxalinium ion. Diaddition product IX is observed over the temperature range −30 to +30°. Evidence for this unusual structure is found in the high-field chemical shifts (τ 5.93 and 6.04) of the two protons bonded to the heterocyclic ring. A monoadduct, would, of course, show one of these protons at considerably lower field. Diaddition to the 1-methylquinoxalinium ion is not unprecedented. Most recently, di- as well as monoadduct formation in water and methanol were demonstrated.[3]

Ammonia and not amide ion formed from the dissociation of ammonia must be the nucleophile. The amide ion concentration resulting from the ionization of pure ammonia is $10^{-13.8}$ (pK = 27.7 at 25°),[16] but in the presence of 1 M NH_4I this is reduced to $10^{-27.7}$. In the case of 2-methylisoquinolinium ion adduct formation was complete in the presence or absence of NH_4I by the time the first spectrum was taken, about 30 min after mixing. If the heterocyclic cation had reacted with amide ion at a diffusion controlled rate, the half-life for the reaction involving NH_4I would be in excess of 10^{10} years.

Finally, a comparison of the extent of covalent amination and hydration reveals that for the cations considered here amination in neutral ammonia is complete but hydration in neutral water[2,3] is insignificant. This marked difference is readily understandable, however. In the reactions under consideration a cationic heterocycle is changed to a polar covalent molecule while a solvated proton is formed. Now, moderately polar ammonia is a better solvent for polar covalent molecules than for ions but the reverse is true for highly polar water.[17] Hence, the covalent adduct is stabilized in ammonia. Moreover, the solvated proton is considerably more stable in ammonia than in water.[18]

On the basis of our survey it seems that covalent amination of heteroaromatic compounds in ammonia is extensive.

Experimental Section

All compounds (perchlorate and/or iodide salts) were available from other studies. A Varian A-60A spectrometer equipped with a V-6040 variable temperature controller was employed. Quinoline-*2-d* was prepared by H–D exchange using D_2O.[19]

General Method of Amination.—Ammonia was added to quaternized compound in an ordinary nmr tube cooled in an acetone–Dry Ice bath. Vapor was passed into the tube through a glass capillary until about 0.5 ml of solvent condensed. Then 2 ml of trimethylamine (τ 7.87) vapor was added through a needle inside the tube in a region cooled by the bath. In a few instances benzene (τ 2.60) was employed as an internal standard. The tube, sealed with a torch, was alternately shaken and cooled so as to induce mixing without unduly warming the contents. The tube then was placed into the cooled (generally −50°) nmr probe. In some instances samples were not sufficiently soluble to give spectra at −50°; the most extreme case was 2-methylphthalazinium iodide which required about 0° to give a suitable spectrum. Substrate concentrations were 0.4 M. In some cases higher concentrations give rise to oil formation. Before spectra are recorded at ambient temperatures, it is wise to check the seal of the nmr tube to avoid damage to the spectrometer. A water bath heated 10–20° above that of the probe was used for this purpose.

(16) L. V. Coulter, J. R. Sinclair, A. G. Cole, and G. C. Roper, *J. Amer. Chem. Soc.*, **81**, 2986 (1959).

(17) J. J. Lagowski, *Pure Appl. Chem.*, **25**, 429 (1971).

(18) W. L. Jolly, *J. Phys. Chem.*, **58**, 250 (1954); P. Kebarle in "Ions and Ion Pairs in Organic Reactions," M. Szwarc, Ed., Wiley-Interscience, New York, N. Y., 1972, Chapter 2.

(19) J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3358 (1967); U. Bressel, A. R. Katritzky, and J. R. Lea, *J. Chem. Soc. B*, 4 (1971).

Registry No.—I, 38896-59-2; II, 38896-60-5; III, 38896-61-6; IV, 38896-62-7; V, 38896-63-8; VI, 38896-64-9; VII, 38896-65-0; VIII, 38896-66-1; IX, 38896-67-2.

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The Oxidation of Benzylamines with Nitrosobenzene

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Aromatic amines react readily with nitrosobenzene to afford azobenzenes,[2] presumably through elimination of water from intermediate *N*-hydroxyhydrazines[3] (**1**, R = Ar). In view of this, we envisioned that the analogous reaction of nitrosobenzene with aliphatic amines might provide a convenient source of phenylazoalkanes (**2**, R = alkyl).[4] In fact, an early report is

$$\mathrm{ArNO} + \mathrm{RNH_2} \longrightarrow \underset{\mathbf{1}}{\mathrm{ArN(OH)NHR}} \longrightarrow \underset{\mathbf{2}}{\mathrm{ArN{=}NR}}$$

available which describes the formation of toluene-α-azobenzene (**2**, R = benzyl) from nitrosobenzene and benzylamine in alcohol solvent.[5] However, a subsequent study of this reaction with a variety of benzylamines reported instead the production of aldehydes or ketones, azoxybenzene, and ammonia with no evidence for azo formation.[6] The mechanism postulated for this reaction involved transfer of an oxygen from a molecule of nitrosobenzene to the benzyl carbon with concurrent loss of ammonia and generation of azoxybenzene.[6]

In order to shed light on the above discrepancies and hopefully to divert the reaction to give phenylazoalkanes, the reaction was reinvestigated in a variety of solvents, including diethyl ether, benzene, and dimethyl sulfoxide (DMSO); the results are presented in Table I. In all cases the product profiles were nearly identical as determined by glpc and consisted of *N*-benzylbenzaldimine (**3**) and azoxybenzene, identified by nmr and mass spectral comparisons with authentic samples. In addition, structure **3** was confirmed by chemical methods (see Experimental Section). Repetition of the exact experimental conditions employed by previous workers[6] using a 2:1 mole ratio of nitrosobenzene to benzylamine in refluxing benzene gave glpc-determined yields of 78% azoxybenzene and 76% **3** in 9 hr (Table I). Conceivably, **3** may arise by condensation of initially produced benzaldehyde with remaining benzylamine. However, in no case was benzaldehyde detected by glpc under conditions where its presence would have been evident.[7] In addition, **3** reacts readily with 2,4-dinitrophenylhydrazine by an amine–imine exchange reaction to liberate benzylamine along with the corresponding 2,4-dinitrophenylhydrazone of benzaldehyde. This latter reaction would account for the identification of carbonyl compounds as primary products.[6] As an alternative, the mechanistic sequence depicted in Scheme I is suggested in which initial attack of benzylamine on nitrosobenzene occurs to furnish the hydroxylhydrazine species **4**. Elimination of phenylhydroxylamine (**5**), possibly *via* a Cope-type elimination (as in **6**),[8] affords benzaldimine[9] (**7**), which gives the observed imine **3** and ammonia upon exchange with benzylamine.[13] The azoxybenzene most probably arises by the well-known condensation of phenylhydroxylamine with nitrosobenzene.[10]

To provide evidence for the production and intermediacy of unsubstituted imines, the reaction of diphenylmethylamine with nitrosobenzene was investigated in hopes of detecting the fairly stable imine **8**[15] before exchange with starting amine. Indeed, in benzene at 70°, **8** was observed to be produced concomitantly with azoxybenzene. The imine **8** further reacted with benzylamine to afford *N*-benzyldiphenylmethyleneimine (**9**), which had been previously observed.[6] The production of various products was monitored by glpc and plotted in Figure 1. Furthermore, benzophenone was observed to be unreactive toward

(1) National Science Foundation Undergraduate Research Participant, 1971.

(2) (a) P. Ruggli and J. Rohner, *Helv. Chim. Acta*, **25**, 1523 (1952); (b) W. Borsche and I. Exss, *Ber.*, **56**, 2353 (1923); see also (c) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, pp 319–321, and references cited therein.

(3) P. Y. Sollenberger and R. B. Martin in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, p 395.

(4) Phenylazoalkanes may be prepared by oxidation of the corresponding hydrazines; see, for example, A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 2788 (1965). The reaction of alkylzinc compounds with diazonium salts gives phenylazoalkanes, but the method is often unreliable; see D. Y. Curtin and J. A. Ursprung, *J. Org. Chem.*, **21**, 1221 (1956). See also ref 2c, p 219, for a review of preparative methods for azo compounds.

(5) P. Gallagher, *Bull. Soc. Chim. Fr.*, **29**, 683 (1921).

(6) (a) K. Suzuki and E. K. Weisburger, *Tetrahedron Lett.*, 5409 (1966); (b) *J. Chem. Soc. C*, 199 (1968).

(7) Benzaldehyde reacts with benzylamine to give the observed product *N*-benzylbenzaldimine under the reaction conditions, but sufficient amounts of benzaldehyde remain to be detectable by glpc. In addition, the reaction of nitrosobenzene with benzylamine at room temperature was followed by nmr (220 MHz). Even under such mild conditions benzaldehyde was not detected, only benzylbenzaldimine.

(8) A. C. Cope and E. R. Trumbull, "Organic Reactions," Vol. XI, Wiley, New York, N. Y., 1960, p 361.

(9) Alternately, the breakdown of the first condensation intermediate **4** could involve an electron transfer to nitrosobenzene to afford an amino nitroxide (i) and nitrosobenzene radical anion; the latter species couple

$$\underset{\mathbf{i}}{\mathrm{ArN(O\cdot)NHCH_2Ar}} \qquad \underset{\mathbf{ii}}{\mathrm{ArNH\cdot}}$$

readily to azoxybenzene (ref 10). The amino nitroxide i may fragment to furnish benzylamino radical ii [in analogy to the behavior of alkoxy nitroxides (ref 11)], which could disproportionate to benzylamine and benzaldimine (**7**) (ref 12). While nitrosobenzene has been documented as an electron acceptor (ref 13, 14), other experiments in our laboratory using such easily oxidized amines as *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine do not indicate this to be the general case in the presence of amines. In addition, the reaction of phenylhydroxylamine and nitrosobenzene generates a small concentration of monophenyl nitroxide as detected by esr. An examination of the reaction of nitrosobenzene with benzylamine demonstrated the same occurrence. The somewhat analogous reaction of benzyl alcohols with nitrosobenzene in the presence of base to yield benzaldehyde and azoxybenzene is also thought to proceed by an ionic mechanism; see J. Hutton and W. A. Waters, *J. Chem. Soc. B*, 191 (1968).

(10) G. A. Russell, E. J. Geels, F. T. Smentowski, K. Chang, J. Reynolds, and G. Kaup, *J. Amer. Chem. Soc.*, **89**, 3821 (1967).

(11) D. J. Cowley and L. H. Sutcliffe, *J. Chem. Soc. B*, 569 (1970).

(12) J. R. Roberts and K. U. Ingold, *J. Amer. Chem. Soc.*, **93**, 6686 (1971); M. A. Ratcliff, Jr., and J. K. Kochi, *J. Org. Chem.*, **37**, 3268, 3275 (1972).

(13) H. Schecter, S. Rowalay, and M. Tubis, *J. Amer. Chem. Soc.*, **86**, 1701 (1934).

(14) F. T. Smentowski, *ibid.*, **85**, 3036 (1963).

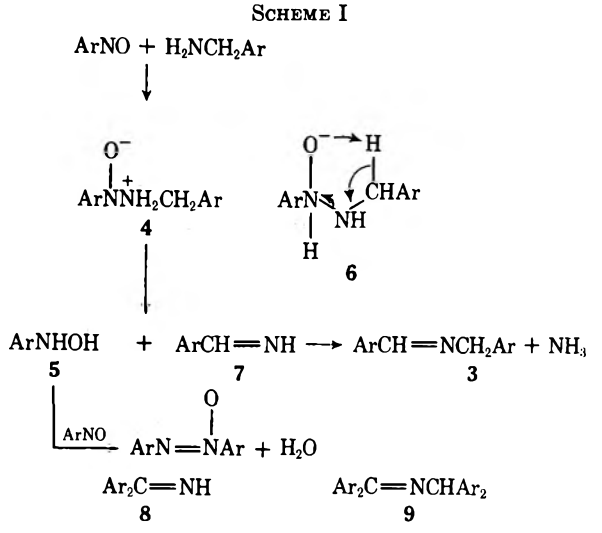
(15) P. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).

TABLE I
REACTION OF NITROSOBENZENE WITH BENZYLAMINES

Benzylamine	Ratio nitroso-benzene: benzyl-amine	Solvent	Temp, °C	Reaction time, hr	Products, % yield[a] Imine (isolated)	Azoxybenzene (isolated)
Benzylamine	1.0	DMSO	25	48	77 (56)[b]	87 (44)
	2.0	Benzene	78	9	76[b]	78
	1.0	Benzene	25	72	75[b]	70
	1.0	Diethyl ether	25	72	44[b]	51
p-Methoxybenzylamine	2.0	Benzene	78	4.5	65[c]	82
Diphenylmethylamine	2.0	Benzene	70	0.5	56,[d] 3[e]	62
				1.0	57,[d] 11[e]	73
				1.5	68,[d] 15[e]	80
				2.7	52,[d] 34[e]	81
				3.2	48,[d] 37[e]	78
				19.5	35,[d] 57[e]	73

[a] Yields of products were determined by glpc using internal standards and detector response factors. [b] *N*-Benzylbenzaldimine. [c] *N*-(*p*-Methoxybenzyl)-*p*-methoxybenzaldimine. [d] Diphenylmethyleneimine. [e] *N*-Benzyldiphenylmethyleneimine.

SCHEME I



diphenylmethylamine in benzene, indicating that **9** does not arise by this route. On the other hand, **8**[15] reacted smoothly with diphenylamine to afford **9** and ammonia.

In conclusion, the primary products from the reaction of benzylamines with nitrosobenzene appear to be azoxybenzene and imines resulting from oxidation of the starting amines. This is followed by amine exchange to give substituted imines.

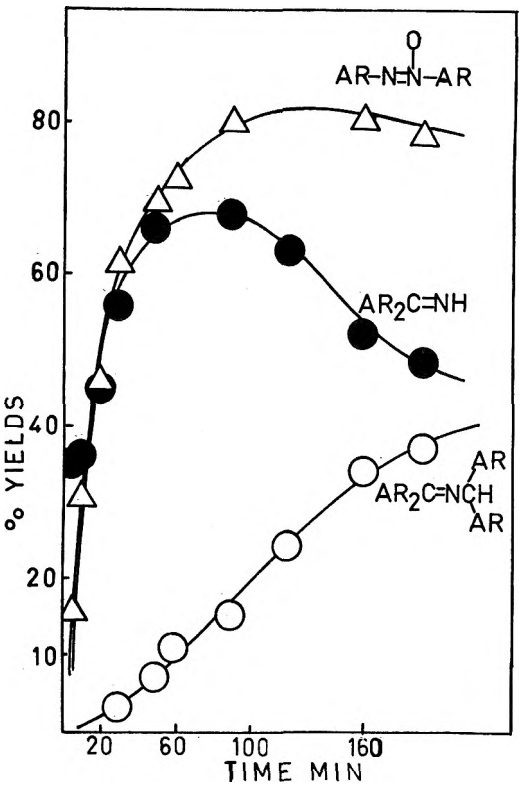


Figure 1.—Reaction of diphenylmethylamine with nitrosobenzene in benzene at 70°. The yields were determined by glpc (OV-1 column) using an internal standard and corrected for detector response.

Experimental Section

Melting points and boiling points are uncorrected. Gas-liquid chromatographic separations were accomplished using either a 6 ft × 0.125 in. 3% OV-17 on 80/100 Chromosorb W (column A) or a 6 ft × 0.125 in. 10% OV-1 on 80/100 Chromosorb W column (column B). Nmr data were obtained on either a Varian A-60 or HR-220 instrument. Nitrosobenzene was sublimed prior to use. Benzylamine, *p*-methoxybenzylamine, and diphenylmethylamine were commercial materials, distilled before use. Authentic samples of products were either obtained commercially or prepared by standard procedures.

Reaction of Nitrosobenzene with Benzylamine. General Procedure.—Benzylamine (214 mg, 2 mmol) and nitrosobenzene (214 mg, 2 mmol, or 428 mg, 4 mmol; see Table I) were dissolved in 5 ml of the appropriate solvent, bibenzyl (184 mg, 1 mmol) was added as an internal standard, and the solution was kept at the appropriate temperature for the intervals listed in Table I. Analysis of the reaction mixtures was accomplished using column A and predetermined detector response factors for the products. As a typical procedure, a preparative reaction in DMSO is given. Nitrosobenzene (2.0 g, 18.7 mmol) and benzylamine (2.0 g, 18.7 mmol) in 50 ml of DMSO were kept at room temperature for 2 days, during which time the color gradually changed from green to orange. The mixture was diluted with water and extracted with ether; the ether solution was dried ($MgSO_4$) and concentrated on a rotary evaporator. Distillation of the residue afforded an orange oil (1.5 g), bp 85–100° (0.07 mm), consisting of *ca.* 44% azoxybenzene and 56% *N*-benzylbenzaldimine. The products were separated by glpc (3% OV-17 on 80/100 Chromosorb W) and identified by nmr and mass spectral comparisons with authentic samples. Further characterization of **3** was obtained by degradation and preparation of benzylamine picrate, mp 201–202° (lit.[16] mp 204–205°), and benzaldehyde phenylhydrazone, mp 156–157° (lit.[8] mp 156°).

Reaction of Diphenylmethylamine with Nitrosobenzene.—A solution of diphenylmethylamine (458 mg, 2.5 mmol), nitroso-

(16) M. Pesez and J. Bartos, *Bull. Soc. Chim. Fr.*, 1122 (1963).

benzene (536 mg, 5.0 mmol), and *n*-tridecane (460.9 mg, 2.5 mmol, internal standard) in 5.5 ml of dry benzene was stirred under nitrogen at 70°. At appropriate intervals (Table I and Figure 1), the reaction solution was analyzed by glpc (column B) using predetermined detector response factors for the products which were identified by glpc retention times and, in the case of **8**, by preparative glpc and comparison with an authentic sample (see below).

Preparation of Imine 8.—The procedure described by Pickard and Tolbert[15] afforded **8** (66%), bp 127–129° (1.75 mm) [lit.[15] bp 127° (3.5 mm)].

Reaction of 8 with Diphenylmethylamine. Preparation of Imine 9.—A solution of **8** (1.83 g, 0.01 mol) and diphenylmethylamine (1.81 g, 0.01 mol) in 20 ml of dry benzene was refluxed for 30 hr. Removal of solvent on a rotary evaporator and recrystallization of the resulting white solid from ethanol gave 2.8 g (81%) of **9** as white flakes, mp 149–150° (lit.[6b] mp 153). An attempted preparation of **9** by refluxing benzophenone and diphenylmethylamine in benzene for 48 hr with azeotropic distillation of any water formed resulted in recovery of starting materials with no evidence of **9** detected by glpc.

Registry No.—**8** (Ar = Ph), 1013-88-3; **9** (Ar = Ph), 5350-59-4; nitrosobenzene, 586-96-9; benzylamine, 100-46-9; *p*-methoxybenzylamine, 2393-23-9; diphenylmethylamine, 91-00-9.

Dimerization of Phospholium Ions[1]

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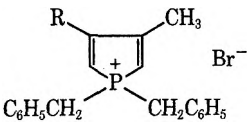
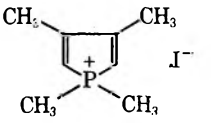
Received November 13, 1972

Quaternary salts have been prepared for many of the phospholes synthesized since the recognition of the existence of this ring system in 1959. In every case,[2] the salts have been assigned monocyclic structures with alkylation at phosphorus, although spectral changes in solutions of the benzyl bromide salt of 1-methylphosphole were suggestive of dimerization.[3] On the other hand, dimerization of phosphole 1-oxides can be quite rapid, and in some instances only the dimer can be isolated.[2] This behavior is consistent with the 4-π-electron system of the phosphole oxides and indeed might be expected for the phospholium salts as well. In characterizing some phospholes prepared in a recent study,[4] salts have been isolated which do indeed exhibit dimeric structure. They are described in this paper.

When monomeric structure is present in a salt, it is easily recognized from the simplicity of the proton nmr spectrum. Some examples are given in Table I. Furthermore, monomer character is also revealed by the presence of only one ^{31}P nmr signal; for a D_2O solution of **3**, for example, the signal appeared at −34.4 ppm.[5]

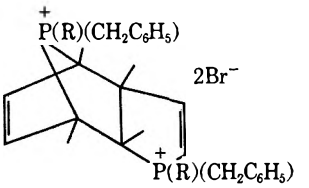


1, R = CH_3
2, R = H



3

The benzyl bromide salt (**4**) of 1-benzylphosphole, as well as the benzyl bromide salt (**5**) of 1-(2-phenylethyl)phosphole, had much more complex nmr spectra. They were incompatible with monomeric structure, but were suggestive of the molecular framework demonstrated[6] for phosphole oxide dimers. In particular, the presence of signals attributable to protons on saturated ring carbons (3.2–4.1 ppm) and the complexity of the *P*-benzyl signal point in this direction. Dimer structure imposes different character on the benzyl groups of each phosphorus atom; in **4**, all four benzyls are in structurally different environments, and in **5** stereoisomeric forms may be present. The *P*-benzyl absorption in both structures would then be a complex composite, rather than a doublet as observed in the monomer. The ^{31}P nmr spectrum for one salt (**4**) provided confirmation of the dimeric structure; two signals were observed (−51.6 and −53.1 ppm in $CDCl_3$), indicating that two structurally different phosphorus atoms were present. Furthermore, the signals were present in equal intensity.



4, R = $CH_2C_6H_5$
5, R = $CH_2CH_2C_6H_5$

It is of significance that we have encountered dimeric salts only for phospholes without a C substituent;[7] 3,4-dimethylphospholium ions (**1** and **3**) remain monomeric, probably through steric crowding encountered in the construction of the bicyclic structure. 3,4-Dimethyl substitution in phosphole oxides has been noted to reduce the east of dimerization in this family

(1) Taken in part from the Ph.D. Dissertations of S. G. B. (1972) and J. F. E. (1971). Supported by Public Health Service Research Grant CA-05507 from The National Cancer Institute. The Bruker nmr system was purchased in part with funds from the National Science Foundation (Grant No. 10301).

(2) The earlier work has been reviewed: A. N. Hughes and C. Srivanavit, *J. Heterocycl. Chem.*, **7**, 1 (1970). See also ref 7, and F. Mathey and R. Mankowski-Favelier, *Org. Magn. Resonance*, **4**, 171 (1972).

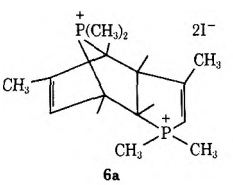
(3) L. D. Quin, J. G. Bryson, and C. G. Moreland, *J. Amer. Chem. Soc.*, **91**, 3308 (1969).

(4) L. D. Quin, S. G. Borleske, and J. F. Engel, *J. Org. Chem.*, **38**, 1858 (1973).

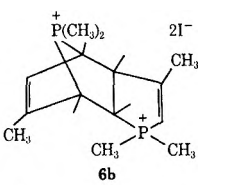
(5) All ^{31}P measurements in this study were performed under conditions of proton decoupling; this gives a sharp singlet and eliminates overlapping of two ^{31}P signals of similar chemical shift, as seen in the phosphole dimers. Spectra were determined at 36.4 MHz on a Bruker HFX-10 spectrometer.

(6) Y. H. Chiu and W. Lipscomb, *J. Amer. Chem. Soc.*, **91**, 4150 (1969).

(7) Two phosphole salts with one C substituent have been prepared that also appear to be dimeric from their ^{31}P nmr spectra. The methiodide (**6**) of 1,3-dimethylphosphole had 1:1 signals at −55.3 and −56.4 ppm (D_2O solution), and the methiodide of 1,2-dimethylphosphole had signals at −58.4 and −59.4 ppm (CF_3COOH solution), also 1:1 in intensity. The C substituent introduces the possibility of positional isomerism in the dimers (*e.g.*, **6a** and **6b** for **6**) and the exact structures of these salts remains unknown at this time.



6a



6b

TABLE I
PROTON NMR SPECTRA[a] OF SALTS OF PHOSPHOLES

Salt	Solvent	—PCH— δ	—PCH— $^2J_{PH}$, Hz	—PCH$_2$C$_6$H$_5$ δ	—PCH$_2$C$_6$H$_5$ $^2J_{PH}$, Hz	—C=CH— δ	—C=CH— $^2J_{PH}$, Hz	C$_6$CH, δ	CCH$_3$, δ
				A. Monomers					
1	CF$_3$COOH[b]			3.99	15.4	6.43	32.4		2.00
2	CDCl$_3$[c]			4.94	16.8	6.2–7.84[d]			1.85
3	CDCl$_3$[b]	3.05	15			7.53	33		2.81[e]
				B. Dimers					
4	CDCl$_3$[b]			5.3–5.7		5.9–6.3, 7.1–7.2[f]		3.8–4.1	
5	CDCl$_3$[c]			4.5–4.8		5.72–7.60[d]		3.2–3.4[g]	

[a] Taken with a Varian A-60 spectrometer. [b] External TMS as standard. [c] Internal TMS as standard. [d] Overlapped by C$_6$H$_5$ signals. [e] J_{PH} = 3 Hz. [f] Complex multiplet. [g] Overlapped by phenethyl CH$_2$ signals.

as well.[8] The nature of the P substituents may also play a role in preventing dimerization of phospholium ions; thus, the *P,P*-dimethyl derivative of the 3-methylphospholium ion appears to be dimeric[7] while the *P,P*-dibenzyl derivative (2) remains monomeric. It would seem to be necessary to consider carefully the structure assigned to a new phosphole salt in view of these results.

The two ^{31}P signals of the dimers are due to the presence of 3-phospholenium and 2-phospholenium moieties. In the dimers examined, the signals are separated by only 1–1.5 ppm. Normally, isomeric 3-phospholenium and 2-phospholenium ions have a greater spread in their ^{31}P shifts (*e.g.*, for the 1,1,3-trimethyl ions, −47.1 and −54.5 ppm, respectively). However, in the dimeric salts, the 3-phospholenium and 2-phospholenium moieties have differences in the substitution at saturated carbons. Thus, as seen in structures **4** and **5**, the 3-phospholenium moiety has carbon substituents at the two α positions, whereas the 2-phospholeniun moiety is substituted at one α and one β position. An analysis of substitution effects on ^{31}P shifts in several families of acyclic phosphorus compounds has shown the shifts to be dependent on the number of carbons in positions β and γ to the phosphorus atom.[9] As in ^{13}C nmr spectra, deshielding is associated with β carbons and shielding (a relatively weaker effect) with γ carbons. The leveling of the ^{31}P shifts for the two components of the phospholium ion dimers is a result of the different substitution patterns in the components. In particular, phosphorus in the 2-phospholenium moiety is deshielded by only one β carbon, and in the 3-phospholenium by two.

Experimental Section[10]

1,1,3-Trimethyl-2-phospholenium Iodide.—To 0.4 g of 1,3-dimethyl-2-phospholene[11] in pentane was added 1 g of methyl iodide. The salt that had precipitated after 1 day at room temperature was recrystallized from a mixture of 2-propanol and ether, mp 135–137°, $\delta_{^{31}P}$ (CDCl$_3$) −54.5 ppm.

Anal. Calcd for C$_7$H$_{14}$IP: C, 32.83; H, 5.51; P, 12.09. Found: C, 32.70; H, 5.52; P, 12.23.

1,1,3-Trimethyl-3-phospholenium Iodide.—This salt was prepared similarly from 1,3-dimethyl-3-phospholene;[12] it had mp 133–135° and $\delta_{^{31}P}$ (CDCl$_3$) −47.1 ppm.

Anal. Calcd for C$_7$H$_{14}$IP: C, 32.83; H, 5.51; P, 12.09. Found: C, 32.73; H, 5.45; P, 12.08.

Registry No.—**1**, 38864-31-2; **2**, 38857-58-8; **3**, 37737-13-6; **4**, 38863-80-8; **5**, 38863-82-0; 1,1,3-trimethyl-2-phospholenium iodide, 38857-60-2; 1,1,3-trimethyl-3-phospholenium iodide, 38857-61-3.

(8) F. B. Clarke, III, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **93**, 4541 (1971).

(9) L. D. Quin and J. J. Breen, *Org. Magn. Resonance*, in press.

(10) All phosphole salts were available from another study.[4] Proton nmr spectra are recorded in Table I, and phosphorus spectra for **3** and **4** are in the text.

(11) D. K. Myers and L. D. Quin, *J. Org. Chem.*, **36**, 1285 (1971).

(12) L. D. Quin and D. A. Mathewes, *ibid.*, **29**, 836 (1964).

1*H*-Imidazo[1,2-*a*]imidazoles. II. The Chemistry of 1,6-Dimethyl-1*H*-imidazo[1,2-*a*]imidazole

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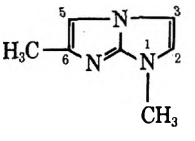
Received December 4, 1972

In a previous paper[2] we described the preparation of a series of 1*H*-imidazo[1,2-*a*]imidazoles which were intended as anthelmintic agents. As part of this project, the chemistry of one member of the series, 1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole (**1**), was investigated. At



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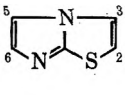


imidazo[2,1-*b*]thiazole

the time the synthetic work was carried out no unsaturated imidazo[1,2-*a*]imidazoles were reported in the literature; however, the reactions of the closely related imidazo[2,1-*b*]thiazole ring system had been studied. The investigations of Paolini[3] and Pyl[4] had revealed that in this ring system the 5 position was the most susceptible to electrophilic attack. It was, therefore, not unexpected to find similar results for the reactions of **1**.

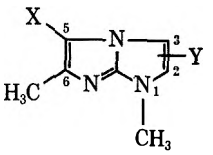
(1) The chemical portion of this work was carried out at the Hess and Clark Division of Richardson-Merrell Inc., Ashland, Ohio, now a division of Rhodia, Inc.

(2) L. F. Miller and R. E. Bambury, *J. Med. Chem.*, **15**, 415 (1972).

(3) J. P. Paolini and L. J. Lendvay, *J. Med. Chem.*, **12**, 1031 (1969).

(4) T. Pyl, R. Giebelmann, and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 145 (1961).

TABLE I
NMR SPECTRAL DATA (δ)



Compd	X	Y	Solvent	1 CH_3	6 CH_3	2 and/or 3 H[a]
1	H	H	$CDCl_3$	3.57	2.32	6.78 (m), 6.55 (d) (J = 2 Hz)
2[b]	Br	H	DMSO-d_6	3.89	2.35	7.74 (s, 2)
3	$C_5H_{10}N$	H	$CDCl_3$	3.40	2.28	6.83 (d), 6.52 (d) (J = 2 Hz)
4	CHO	H	$CDCl_3$	3.77	2.58	7.55 (d), 6.85 (d) (J = 2 Hz)
5	NO_2	H	DMSO-d_6	3.73	2.60	7.65 (d), 7.42 (d) (J = 2 Hz)
6	NHAc	H	$CDCl_3$	3.54	2.18	6.69 (d), 6.55 (d) (J = 2 Hz)
7	NAc_2	H	$CDCl_3$	3.67	2.18	6.73 (s, 1)
8	NO_2	NO_2	DMSO-d_6	3.85	2.60	8.85 (s, 1)

[a] Other significant nmr peaks: 1, 5 H, δ 6.78; 2 (as HBr salt), δ 5.5 (br s, exch); 3, δ 2.98 (m, 4), 1.58 (m, 6); 4, δ 9.68 (s, 1); 6, δ 2.25 (s, 3), 9.25 (br s); 7, 2.32 (s, 6). [b] HBr salt.

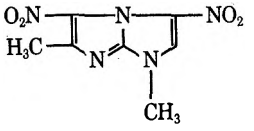
Treatment of **1** in chloroform with bromine gave 5-bromo-1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole hydrobromide monohydrate (**2**). In most instances substitution at the 5 position was readily confirmed by the nmr spectrum which showed the 2,3 protons appearing as two doublets (Table I). However, in the case of **2** the 2,3-proton signal appeared as an apparent singlet, and it was not immediately clear where the substitution had occurred. Reaction of **2** with piperidine afforded the piperidino derivative (**3**). The nmr spectrum of this compound showed the expected pair of doublets, confirming the 5-position substitution of both **2** and **3**. Compound **2** was found to be unstable as the free base. Attempts to dibrominate **1** were unsuccessful giving only resinous material. Formylation of **1** under Vilsmeier conditions yielded the 5-formyl compound (**4**).

Nitrations of **1** were tried by a variety of standard methods which in most instances gave no isolable product, the ring system being quite sensitive to nitric acid. However, by dissolving **1** in cold concentrated H_2SO_4 and carefully adding *ca.* 1 equiv of nitric acid a small quantity of a mononitrated product, 1,6-dimethyl-5-nitro-1*H*-imidazo[1,2-*a*]imidazole (**5**), was obtained. These results led us to investigate several organic and inorganic nitrates as nitronium ion sources. The best yield of **5** (66%) was obtained by chilling **1** in sulfuric acid and carefully adding an equivalent amount of ethyl nitrate. Reduction of **5** in the presence of acetic anhydride gave a mixture of two products: 5-acetamido-1,6-dimethyl-1*H*-imidazo[1,2-*a*]-imidazole (**6**), whose structure was determined by its nmr spectrum, and 5-diacetylamino-1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole (**7**).

By carefully treating **1** with 2 equiv of ethyl nitrate, a dinitrated product (**8**) was obtained. Since **8** could also be obtained by nitration of **5**, one of the $-NO_2$ groups was known to be in the 5 position; however, the location of the other group was not readily discernible. Attempts were made to determine the structure spectrally, by comparing the nmr spectrum of **8** with spectra of 1-methylnitroimidazoles of known structure, and by attempted measurement of a possible nuclear Overhauser effect (NOE). All such attempts were without success.

Reduction of **8** in the presence of acetic anhydride gave a complex mixture of products. In light of the isolation of **6** and **7** from the reduction of **5**, the mixture was probably composed of various mono- and diacetylated diamines; however, no effort was made to identify the components. The complexity of the mixture also precluded the use of the components as intermediates for structure identification.

In order to obtain at least an indication of the probable location of the second $-NO_2$ group in **8** a series of Hückel molecular orbital (HMO) calculations was made. The method of computation and parameters are discussed in the Experimental Section. Since the nitrations were electrophilic attacks carried out in strongly acidic media, the HMO derived quantities chosen for comparison were the electrophilic superdelocalizability (S^E) and the effective charge. Calculations were first made on **1** and indicated the 5 position as the favored site for electrophilic substitution, in agreement with the experimental results. Similar calculations were carried out on **5**. The S^E values calculated for the 2 and 3 positions of **5** (triprotonated model) were 1.175 and 1.234, respectively, indicating the 3 position as the favored site for electrophilic substitution.[5] We therefore feel that the most likely structure for **8** is 1,6-dimethyl-3,5-dinitro-1*H*-imidazo-[1,2-*a*]imidazole.



8

Experimental Section

Melting points were taken in open capillary tubes with a calibrated thermometer using a Thomas-Hoover melting point apparatus. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. The nmr spectra were recorded on a Varian A-60 spectrometer by the Analytical Department of Merrell-National Laboratories. The NOE measurement was attempted on a Bruker HFX-90 spectrometer at the University of Cincinnati. HMO calculations were performed on an IBM S360/40 computer by the Biomedical Engineering

(5) A table of the calculated S^E and effective charge values will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-1955. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Department of Merrell-National Laboratories. The program used was previously described by Allen, *et al.*[6] Parameters chosen were those suggested by Streitwieser.[7]

5-Bromo-1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole Hydrobromide Monohydrate (2).—A solution of Br_2 (1.2 g, 0.0074 mol) in $CHCl_3$ (5 ml) was slowly added to 1 (1 g, 0.0074 mol) in $CHCl_3$ (15 ml) maintained at 5°. The solution was stirred for 5 min and evaporated and the crude solid crystallized from $MeNO_2$ to give 2 (1.5 g), mp 132–133° dec. *Anal.* Calcd for $C_7H_{11}Br_2N_3O$: C, 26.86; H, 3.54; N, 13.42. Found: C, 27.07; H, 3.36; N, 13.64.

Reaction of 2 with Piperidine.—A mixture of 2 (3.1 g, 0.01 mol) and piperidine (2.5 g, 0.03 mol) in C_6H_6 (50 ml) was refluxed for 4 hr and cooled. The solution was extracted with H_2O (discarded), and the organic phase was dried ($MgSO_4$) and evaporated. The residue (1.6 g) was not readily purified either as the free base or as a salt; however, the nmr spectrum of the crude material confirmed the structure as 1,6-dimethyl-5-piperidino-1*H*-imidazo[1,2-*a*]imidazole (3).

1,6-Dimethyl-5-formyl-1*H*-imidazo[1,2-*a*]imidazole (4).—1 (50 g, 0.37 mol) in DMF (100 ml) was slowly added to a formylation complex prepared as described by James, *et al.*,[8] from DMF (250 ml) and $POCl_3$ (80 g, 0.52 mol). The solution was stirred 1 hr at 25°, chilled for 16 hr, and then treated with H_2O (300 ml) and sufficient $NaHCO_3$ to bring the pH to 8. The solution was heated to reflux, cooled, and extracted with $CHCl_3$. The organic phase was extracted with 10% HCl which was then basified with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ was evaporated to give a crude solid (50 g) which was crystallized from petroleum ether (bp 90–100°) yielding 4 (29 g), mp 130–135° (oxime mp 280° dec). *Anal.* Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.82; H, 5.54; N, 25.79.

1,6-Dimethyl-5-nitro-1*H*-imidazo[1,2-*a*]imidazole (5).—To concentrated H_2SO_4 (5 ml) chilled to −10° was slowly added 1 (1.3 g, 0.01 mol). The temperature was lowered to −20° and ethyl nitrate (0.9 g, 0.01 mol) was added dropwise. After stirring 5–10 min, the acid solution was poured on crushed ice and the pH adjusted to 4–5 with aqueous NaOH. The aqueous phase was extracted with $CHCl_3$ which was evaporated to give crude 5 (1.2 g). Crystallization from C_6H_6 gave pure 5, mp 181–184°. *Anal.* Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.47; N, 31.10. Found: C, 46.81; H, 4.44; N, 31.19.

Reduction of 5 in Acetic Anhydride Solution.—A solution of 5 (4 g, 0.02 mol) in Ac_2O (50 ml) was reduced under 1.5 atm of H_2 pressure for 16 hr in the presence of Raney nickel catalyst.[9] The catalyst was filtered off, the Ac_2O was evaporated, and the residue was taken up in $CHCl_3$. After stirring vigorously for several hours with aqueous $NaHCO_3$, the $CHCl_3$ was separated and evaporated to an oil (3.8 g) which crystallized on standing. A tlc showed two components, one predominant. By careful crystallization from EtOAc a small amount of the minor constituent was obtained, mp 133–137°. It was unsuitable for elemental analysis, but was shown by its nmr spectrum to be principally 5-acetamido-1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole (6). The mother liquors were evaporated and carefully treated with *i*-PrOH–Et_2O to give a white solid, mp 124–127°, which was shown by its elemental analysis and nmr spectrum to be 5-diacetylamino-1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole (7). *Anal.* Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.91. Found: C, 56.02; H, 6.10; N, 24.09.

1,6-Dimethyl-2(or 3),5-dinitro-1*H*-imidazo[1,2-*a*]imidazole (8).—In a manner similar to the preparation of 5, 1 (16.2 g, 0.12 mol) in H_2SO_4 (150 ml) was treated with 1 equiv of ethyl nitrate (10.9 g, 0.12 mol) at −20°. After addition was complete the temperature was adjusted to −15° and a second equivalent of ethyl nitrate was added. The acid solution was stirred at −5° for 20 min and poured on crushed ice. The resulting solution was extracted with $CHCl_3$ which on evaporation gave crude 8. Recrystallization from H_2O gave pure 8 (3.2 g), mp 190–192°. *Anal.* Calcd for $C_7H_7N_5O_4$: C, 37.34; H, 3.14; N, 31.11. Found: C, 37.41; H, 3.10; N, 31.24.

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(7) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961.

(8) P. N. James and H. R. Snyder in "Organic Synthesis," Collect. Vol. IV, Norman Rabjohn, Ed., Wiley, New York, N. Y., 1963, pp 539–541.

(9) Raney nickel was obtained from Pfaltz and Bauer, Inc., New York, N. Y.

Registry No.—1, 38739-75-2; 2, 38739-94-5; 3, 38739-95-6; 4, 38739-96-7; 5, 38739-97-8; 6, 38739-98-9; 7, 38739-99-0; 8, 38740-00-0; piperidine, 110-89-4.

Acknowledgments.—The authors wish to thank Drs. Fred Kaplan and David Lankin of the University of Cincinnati for attempting the NOE determination. We also wish to express our thanks to Dr. Michael Randall for supervising the HMO calculations and Dr. Michael Edwards for his invaluable suggestions and assistance.

Internal Strain in Benzylic Radical Formation. The Effect of Ring Size in the Reaction of Trichloromethyl Radicals with Benzocycloalkenes

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The degree of importance of steric factors in the formation of organic free radicals has not received full elucidation. Part of this is due to the complexity of the situation and the need to assess both intramolecular and intermolecular effects. The former can qualitatively be considered in terms of I strain as originally proposed by Brown.[1] Overberger, in describing the extension of this generalized approach to radical-forming reactions, has equated changes in activation energy with strain changes in cyclic systems.[2] Intermolecular interactions between attacking radicals and substrates can also greatly influence the course and extent of reaction. Such bulky species as the dialkylamino radical cation[3] and the trichloromethyl radical[4] show unexpectedly increased selectivity in hydrogen-abstraction processes because of this form of steric control.

The relation of internal strain to radical formation has been studied by several groups of workers. Relative rates of hydrogen atom abstraction from cycloalkanes in both the liquid and vapor phases have been obtained using chlorine atom,[5] bromine atom,[6] methyl radical,[7] trichloromethyl radical,[8] and trichloromethylsulfonyl radical,[5] among others. It was noted that ring size did, indeed, affect the relative rates of reaction. With few exceptions the order of reactivity was cyclobutane ≪ cyclopentane < cyclohexane < cycloheptane < cyclooctane. This order clearly shows that the ground-state strain of the cycloalkane cannot be the cause of the effect.

(1) (a) H. C. Brown and M. Gerstein, *J. Amer. Chem. Soc.*, **72**, 2926 (1950); (b) H. C. Brown and R. B. Johannessen, *ibid.*, **73**, 212 (1951).

(2) C. G. Overberger, H. Biletch, A. B. Finestone, J. Lilker, and J. Herbert, *ibid.*, **75**, 2078 (1953).

(3) R. Bernardi, R. Galli, and F. Minischi, *J. Chem. Soc. B*, 324 (1968).

(4) (a) G. J. Gleicher, *J. Org. Chem.*, **33**, 332 (1968); (b) W. D. Totherow and G. J. Gleicher, *J. Amer. Chem. Soc.*, **91**, 7150 (1969).

(5) G. A. Russell, *ibid.*, **80**, 4997 (1958).

(6) K. C. Ferguson and E. Whittle, *Trans. Faraday Soc.*, **67**, 2618 (1971).

(7) W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Amer. Chem. Soc.*, **94**, 1632 (1972).

(8) (a) E. S. Huyser, E. Schimcke, and R. L. Burham, *J. Org. Chem.*, **28**, 2141 (1963); (b) F. B. Wampler and R. K. Kuntz, *Int. J. Chem. Kinet.*, **3**, 283 (1971).

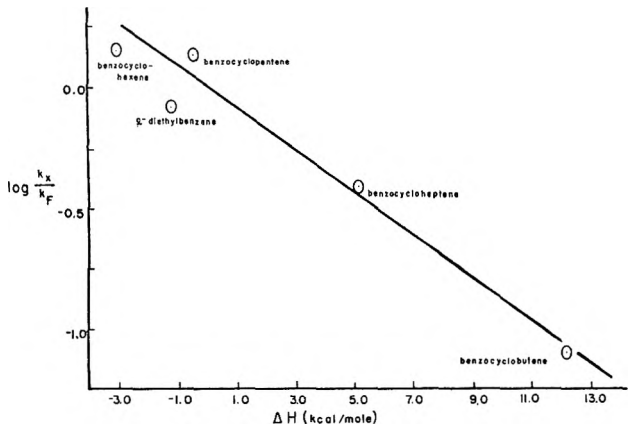


Figure 1.—Correlations of relative reactivities with calculated strain energy changes.

Prior success has been obtained in correlating the reactivity of polycyclic systems with calculated changes in strain energy for both carbonium ion[9] and radical[10] reactions. In hope of extending this approach to the study of the effect of ring size on the ease of hydrogen atom abstraction, a series of benzocycloalkenes was treated with the trichloromethyl radical generated photolytically from bromotrichloromethane at 70°. The trichloromethyl radical was chosen both for its high selectivity and the convenience of operating in a homogeneous medium. The benzannelated cycloalkanes were chosen over their monocyclic counterparts for the following reasons. The annelation of the benzene ring imparts a high degree of rigidity to the hydrocarbon. The effective number of conformers is thereby greatly reduced, thus simplifying all calculations. The presence of the aromatic ring will also cause reaction to take place exclusively in the benzylic position. Table I shows the relative reactivities of

TABLE I

RELATIVE REACTIVITIES OF SOME BENZOCYCLOALKENES TOWARD THE TRICHLOROMETHYL RADICAL AT 70°[a]

Registry no.	System	Relative rate	Average deviation	Number of runs
4026-23-7	Benzocyclobutene	0.076	0.004	5
95-13-6	Benzocyclopentene	1.39	0.08	5
91-20-3	Benzocyclohexene	1.41	0.08	7
264-06-2	Benzocycloheptene	0.42	0.03	5
135-01-3	*o*-Diethylbenzene	0.84	0.06	9

[a] All results given relative to fluorene.

this series of benzocycloalkenes and the electronically equivalent *o*-diethylbenzene. These rates were obtained relative to hydrogen abstraction from fluorene using nmr spectroscopy as the analytical device. It had been originally planned to utilize glc in this capacity; however, the facile dehydrobromination of many of the benzylic halides on the column precluded this approach. The decrease in the nmr signal for benzylic protons was taken as defining the extent of reaction for both the benzocycloalkene and fluorene. These signals are easily separable, being located in distinct areas of the spectrum. All areas were found relative to that of the aliphatic protons in *tert*-butylbenzene. This last compound is suitable as an internal standard owing to its unreactivity under the present conditions.[11]

The strain energies for all species were determined using standard techniques and parameters.[9,10,12] Certain assumptions were of necessity made for the strain associated with the transition states. These structures were assumed to strongly resemble the intermediate radicals.[13] Although cyclic radicals may assume pyramidal structure to relieve potential angle strain,[14-16] it was felt that in the product systems planarity would be maintained in order to maximize the favorable resonance interaction. In Table II are

TABLE II

CALCULATED STRAIN ENERGIES[a]

System	Ground state	Radical	Difference
Benzocyclobutene	116.547	128.637	12.110
Benzocyclopentene	24.797	24.328	−0.469
Benzocyclohexene	17.238	14.195	−3.043
Benzocycloheptene	21.941	27.037	5.096
o-Diethylbenzene	22.627	21.341	−1.286

[a] All results in kcal/mol.

shown the calculated strain energy differences for the present systems. While absolute strain energies, particularly for the cyclobutane derivatives, are strongly exaggerated, the energy differences appear reasonable.

The changes in strain energy may be caused by several factors. In the case of benzocyclobutene the large, unfavorable change in angle strain is the principal factor. This is true to a much lesser extent in benzocyclopentene and is offset by favorable changes in torsional and nonbonded interactions. In benzocyclohexene a favorable change in angle strain is calculated, while in benzocycloheptene changes in angle and torsional strain are both unfavorable. Effects in *o*-diethylbenzene are nearly equivalent in both ground state and radical.

Figure 1 shows a graph of the logarithms of the relative rates plotted against the calculated strain energy changes. Good linearity is obtained. A slope of −0.082 is found with a correlation coefficient of −0.974. This slope is appreciably smaller than the corresponding values of −0.327 and −0.537 found for formation of aliphatic tertiary and secondary radicals.[10] The present small dependence upon strain factors is not, however, surprising in view of the high stability and concomitant ease of formation of benzylic radicals. It is also of interest that *o*-diethylbenzene falls far below the correlation. It is felt that this is due to an intermolecular effect in which one of the ethyl groups may hinder the approach of the large trichloromethyl radical to the benzylic position of the second group. This is much less likely to occur in the more rigid benzocycloalkenes.

(9) G. J. Gleicher and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).
(10) V. R. Koch and G. J. Gleicher, *ibid.*, **93**, 1657 (1971).
(11) E. S. Huyser, *ibid.*, **83**, 391 (1960).
(12) G. J. Gleicher, *Tetrahedron*, **23**, 4257 (1967).
(13) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(14) J. Jacobus and D. Pensak, *J. Chem. Soc. D*, 400 (1969).
(15) M. J. S. Dewar and J. M. Harris, *J. Amer. Chem. Soc.*, **91**, 3652 (1969).
(16) P. Bakuzes, J. K. Kochi, and P. J. Krusic, *ibid.*, **92**, 1434 (1970).

Experimental Section

Materials.—Bromotrichloromethane, benzocyclohexene, benzocyclopentene, and *tert*-butylbenzene were obtained from commercial sources. Benzocyclobutene was kindly donated by Professor Phillip Radlick. Benzocycloheptene was prepared from the Wolff–Kishner reduction of 1-benzosuberone. All materials were purified before use. Purities greater than 99% were determined by glc.

Product Studies.—A mixture of 4.232 g (32.186 mmol) of benzocyclohexene and 36.60 g (184.64 mmol) of bromotrichloromethane were treated under nitrogen for 18 hr at 70° with irradiation by our standard source. After reaction and removal of excess bromotrichloromethane, the reaction mixture was analyzed by gas–liquid chromatography on a 5% SE-30 column. It was shown that about 40% of the tetralin had reacted and one product with a slightly longer retention time than tetralin was formed. The compounds were collected as they eluted from the glc column. An nmr spectrum identified the product as 1,2-dihydronaphthalene. This was formed by probable dehydrohalogenation of the initially formed bromide. The unreacted starting material amounted to 19.311 mmol (2.51 g) and the product to 1.49 g (11.620 mmol). The material balance thus found is 96.1%. Although no attempt was made to isolate the initial bromide, its presence could be readily detected in the reaction mixture by nmr spectroscopy. No elimination product could be detected in the reaction mixture before passage through the SE-30 column.

Kinetic Studies.—Solutions of fluorene, a cycloalkene, bromotrichloromethane, and *tert*-butylbenzene were prepared in the approximate molar ratio of 2:4:20:1. Approximately 0.75 ml of the solution was placed in each of the several ampoules. The ampoules were cooled to Dry Ice–isopropyl alcohol temperature until the solutions solidified. The ampoules were evacuated at 0.5–1.0 mm and flushed with nitrogen several times with three intermediate thawings. The ampoules were sealed under vacuum and one was reserved for the analysis of the unreacted starting materials. The remainder were placed horizontally just below the surface of a mineral oil constant-temperature bath maintained at 70.0 ± 0.5°. The solution was irradiated with ultraviolet light provided by a Sylvania 275-W sun lamp placed 20 cm above the surface of the oil. Reaction times varied from 20 to 40 hr, by which time 30–70% of the total hydrocarbons had reacted. The ampoules were then cooled and opened. Analysis of the mixtures, both before and after the reaction, was carried out *via* nmr spectroscopy. All determinations were run in replicate.

Registry No.—Trichloromethyl radical, 3170-80-7.

Acknowledgments.—We wish to thank the Computer Center of Oregon State University for supplying the requisite funds for these calculations. Deepest gratitude is also expressed to Professor Phillip Radlick of the University of California, Riverside, who generously supplied us with a sample of benzocyclobutene.

Communications

See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

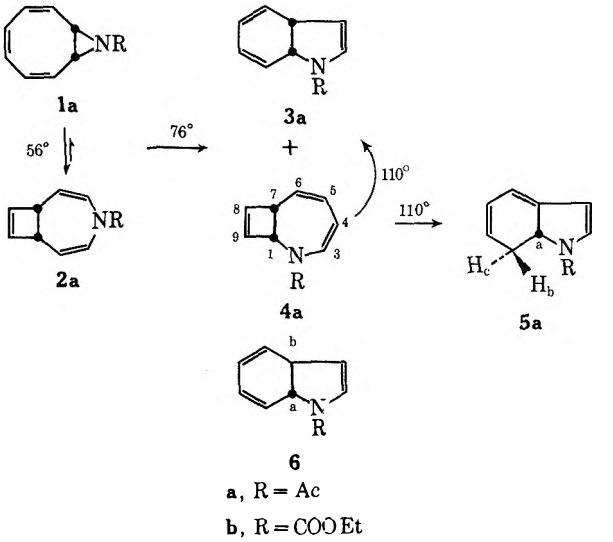
Thermal Reorganization of Select Azabicyclo[*m.n.*0] nonatrienes. Generation of a *cis,cis,trans,cis*-Azonine

Summary: Mild thermal exploration of the C_8H_8NAc energy surface resulted in the discovery of a variety of mechanistically revealing transformations and the detection of a *cis,cis,trans,cis*-azonine.

Sir: Recently, we described the thermal behavior of various *N*-methoxycarbonylazabicyclo[*m.n.*0]nonatrienes.[1] We now report on the thermolysis of the acetamide analogs in terms of (i) product distribution and (ii) cycloadditive trapping.

When warmed to 56° in deaerated (N_2) benzene, **2a**[2] produces a two-component equilibrium consisting (nmr) of ~95% **2a** and 5% **1a** (Scheme I). In turn, when exposed to a higher temperature (76°) this pair undergoes rapid ($t_{1/2}$ ~80 min) and irreversible thermolysis to **3a** and **4a** in the ratio of 1.2:1, respectively (nmr). The thermolysate was separated into its individual components by chromatography at −15° and **3a** was characterized on direct comparison (nmr, ir) with an authentic sample[3] while **4a** was formulated on the basis of its spectra: ν_{CO}^{neat} 1675 cm^{-1}; *m/e* 161 (P^+, 13%);

SCHEME I



$\lambda_{max}^{C_6H_{14}}$ 282 nm (ε 4300), 214 (6000); nmr (100 MHz, benzene-d_6, ~60°) τ 3.92 (1 H, dd, J = 2.6, 1.0 Hz, H_8 or H_9), 4.02 (1 H, d, J = 8.5 Hz, H_3), 4.1 (1 H, br d, J ~ 5 Hz, H_1), 4.30 (1 H, dd, J = 11.5, 6.0 Hz, H_6), 4.48 (1 H, dd, J = 2.6, 0.7 Hz, H_8 or H_9), 4.51 (1 H, dd, J = 11.5, 5.7 Hz, H_5), 4.89 (1 H, dd, J = 8.5, 5.7 Hz, H_4), 6.58 (1 H, dd, J = 6.0, 4.8 Hz, H_7), 8.28 (3 H, s, methyl).[4] While isomers **3a** and **4a** do not intercon-

(1) A. G. Anastassiou, R. L. Elliott, and A. Lichtenfeld, *Tetrahedron Lett.*, 4569 (1972).

(2) A. G. Anastassiou, S. W. Eachus, R. L. Elliott, and E. Yakali, *J. Chem. Soc., Chem. Commun.*, 531 (1972).

(3) A. G. Anastassiou, S. W. Eachus, R. P. Cellura and J. H. Gebrian, *Chem. Commun.*, 1133 (1970).

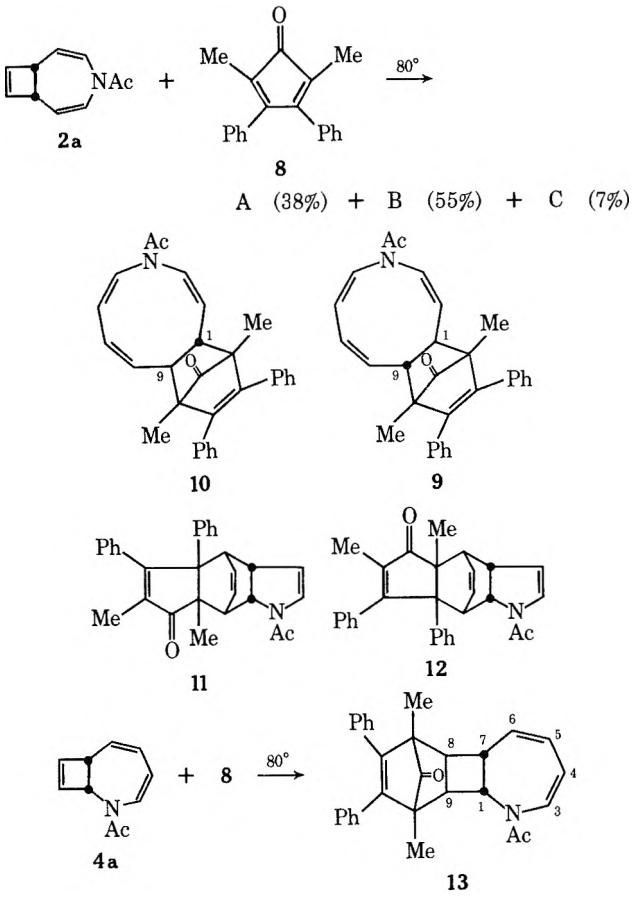
(4) Spectral analysis required extensive decoupling procedures.

vert under the reaction conditions they do differ in their sensitivity to more demanding thermal treatment. Thus, whereas **3a** remains unaffected on brief (~9 min) passage through a vpc column at 150°, **4a** readily thermolyzes at 110° to yield a mixture consisting (nmr) of ~35% **3a** and 65% **5a**.[5] Compounds **3a** (nmr) and **5a** [ν_{CO}^{neat} 1665 cm^{-1}; *m/e* 161 (P$^+$, 34%); $\lambda_{max}^{C_6H_{14}}$ 228 nm (ϵ 12,500), 345 (9500);[6] nmr (100 MHz, benzene-d_6, 10°) τ 3.96 (1 H, d, J = 4 Hz), 3.9–4.1 (1 H, m), 4.3–4.6 (2 H, m), 4.67 (1 H, d, J = 4.0 Hz), 5.54 (1 H, dd, J = 20.5 Hz, 8.5 Hz, H_a), 6.51 (1 H, qd, J = 17.0, 8.5, 6.0 Hz, H_b), 7.93 (1 H, dd, J = 20.5, 17.0 Hz, H_c), 8.49 (3 H, s, methyl)] were obtained pure on chromatography of the thermolysate at about −15°. The presence of a [4.3.0] skeleton in **5a** was securely established on catalytic hydrogenation (Rh/C) of this substance to *N*-acetyl-*cis*-8,9-octahydroindole (ir).[7,8]

Analysis of Scheme I by the method of orbital symmetry establishes the cis-fused dihydroindole (**3a**) as the sole "disallowed" valence tautomer.

To search for intermediates in Scheme I, **2a** was exposed to an equimolar quantity of 2,5-dimethyl-3,4-diphenyl-cyclopenta-2,4-dienone (**8**)[11] in boiling benzene for 24 hr. The product mixture consisted almost exclusively (~93% by nmr) of two 1:1 adducts[12] (Scheme II): A [~38%, white powder, mp 141–142°, $\nu_{(ketonic\ CO)}^{KBr}$ 1775 cm^{-1}, *m/e* 421 (P$^+$, 9%), J_{19} = 4.5 Hz[13]] and B [~55%, white crystals, mp 187.5–188.5°, $\nu_{(ketonic\ CO)}^{KBr}$ 1775 cm^{-1}, *m/e* 421 (P$^+$, 7%), J_{19} = 4.5 Hz[13]]. Of these, B was unambiguously characterized as **10** on the basis of single-crystal X-ray diffraction analysis (Figure 1).[14] Moreover, this information and the close spectral similarity of the two adducts, necessitates the formulation of A as **9**, *i.e.*, the diastereomer of **10**.

SCHEME II



Finally, the minor product (~7%) of cycloaddition between **2a** and **8** was isolated by column chromatography and was shown to be **11** (or **12**) by direct spectral (nmr, ir) comparison with a synthetic sample (mp 254.5–255.5°) prepared on treatment of **3a** with **8** in boiling benzene.

The structural features of **9** and **10** require that these substances form through symmetry controlled [$_\pi 2_s + {}_\pi 4_s$] cycloaddition of **8** onto *N*-acetylazonine incorporating a remote trans double bond, *i.e.*, one not directly linked to nitrogen. Since both possible rotamers of such an azonine, *i.e.*, the cis,cis,trans,cis and cis,-trans,cis,cis variants shown in **14** and **15**, respectively,[15] can in principle react with **8** to produce **9** and **10**, and, since rotamer **15** is formally relatable to **4a** (a major thermal product of **2a** at 76°) through symmetry-allowed conrotation of the cross-link, it was necessary to assess the thermal response of **4a** in the presence of **8**. Prolonged exposure (~48 hr) of **4a** to an equimolar proportion of **8** in boiling benzene produced a mixture containing (nmr) only minor quantities of **9** and (possibly) **10**. Column chromatography of this product mixture led to the isolation of **13** [$\nu_{(ketonic\ CO)}^{KBr}$ 1770 cm^{-1}; *m/e* 421 (P$^+$, 5%); nmr (100 MHz, $CDCl_3$, 90°) τ 2.8–3.2 (10 H, m), 3.59 (1 H, d, J_{34} = 8.5 Hz, H_3), 3.89 (1 H, dd, J_{65} = 11.5, J_{67} = 7.0 Hz, H_6), 4.22 (1 H, dd, J_{56} = 11.5 Hz, J_{54} = 6.0 Hz, H_5), 4.45 (1 H, dd, J_{43} = 8.5 Hz, J_{45} = 6.0 Hz, H_4), 4.75 (1 H, dd, J_{17} =

(5) While reasonably inert at 110°, **5** rapidly isomerizes to two pyrrole-containing substances (nmr, uv, ir, mass spectra) when exposed to 150°.

(6) Band intensities are necessarily approximate owing to serious difficulties encountered in handling this substance which readily resinifies when neat.

(7) Significantly, catalytic hydrogenation of a hydrocarbon analog of **5** also leads to a cis-fused perhydro skeleton: S. W. Staley and T. J. Henry, *J. Amer. Chem. Soc.*, **91**, 1239 (1969).

(8) Interestingly, the thermal behavior of the **1a–2a** equilibrium pair, summarized in Scheme I, differs from that of its methoxycarbonyl analog which, as we noted recently,[1] reorganizes chiefly to a trans-fused dihydroindole when heated at 76°. Fully as anticipated and in obvious contradiction of a recent claim by Masamune, *et al.*,[9] we find urethane **2b** also to yield a trans-fused dihydroindole (**6b**) as the major product (~68% of thermolysate based on the combined amount of **5b** and **6b** isolated) of reorganization at 76°. An earlier report by Masamune, *et al.*,[10] to the effect that thermolysis of **1b** leads to **2b**, is also incomplete. In brief, we discovered that thermal treatment of a deaerated benzene solution of **1b** at 56° leads rapidly ($t_{1/2}$ ~ 75 min) to a product mixture consisting (chromatography at −15°) of ~71% **2b** (nmr), 23% **6b** [ν_{CO}^{neat} 1720 cm^{-1}; *m/e* 191 (P$^+$, 38%); $\lambda_{max}^{C_6H_{14}}$ 229 (ϵ 15,500);[6] nmr (60 MHz, benzene-d_6) τ 2.8 (1 H, br d, J ~ 10 Hz), 3.28 (1 H, dd, J = 4.5, 3.0 Hz), 3.7–4.3 (3 H, m), 5.05 (1 H, dd, J = 4.5, 1.5 Hz), 6.05 (2 H, q), 6.07 (1 H, d, J_{ab} = 24 Hz), 6.78 (1 H, d, J_{ab} = 24 Hz), 9.05 (3 H, t)] and 6% **3c** (nmr, ir). In contrast, prolonged exposure (~8 hr) of **2b** at 56° does not effect rearrangement to **6b** but merely generates a mixture of ~95% **2b** and 5% **1b** (nmr). It follows that *the [6.1.0] skeleton,* **1b**, *rather than its [5.2.0] counterpart* **2b**, *is the major source of* **6b** *at* **56°**.

(9) S. Masamune and N. Darby, *Accounts Chem. Res.*, **5**, 272 (1972).

(10) S. Masamune and N. T. Castellucci, *Angew. Chem.* **76**, 569 (1964).

(11) C. F. H. Allen and J. A. Van Allan, *J. Amer. Chem. Soc.*, **64**, 1260 (1942); **72**, 5165 (1950).

(12) The adducts are stable to prolonged heating at the reaction temperature.

(13) The determination of this value necessitated triple irradiation with a frequency extending over the entire 6 H olefinic region.

(14) The X-ray analysis will be fully detailed in our complete account of the work. Full-matrix least-squares refinement with anisotropic temperature factors for all nonhydrogen atoms converted to the present minimum of 0.12 for the conventional discrepancy index. All bond distances and angles agree well with generally accepted values and there are no abnormally short intermolecular contacts.

(15) The convention adopted here for the sequential differentiation between rotamers **14** and **15** places the NAc function (CH_2 function for the hydrocarbon counterparts) at the origin and the system is then labeled along such a direction as is necessary for encountering the trans double bond from the side of its "outer" proton.

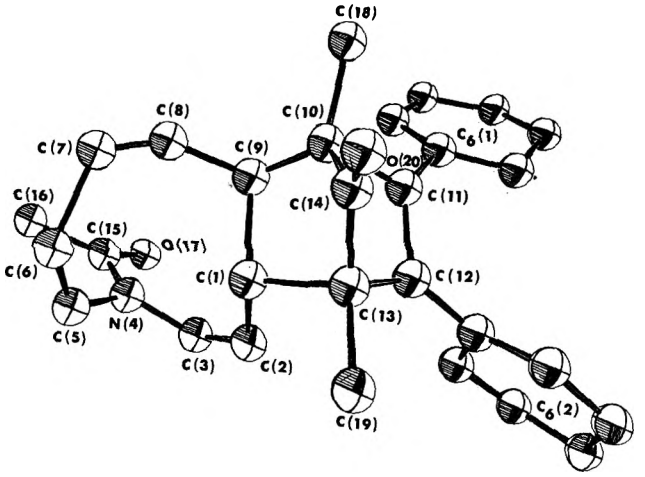
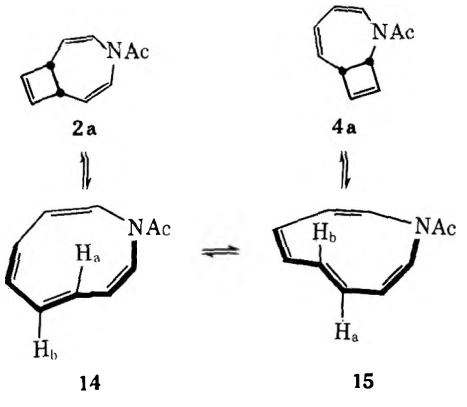


Figure 1.—A structural view of 10 as determined by X-ray analysis depicting conformation.

5.0 Hz, J_{19} = 10.0 Hz, H_1), 7.25 (2 H, m, H_7 + H_9), 7.60 (1 H, dd, J_{87} = 10.0 Hz, J_{89} = 4.5 Hz, H_8), 7.90 (3 H, s), 8.79 (3 H, s), 8.82 (3 H, s)],[4] *i.e.*, the product of symmetry-controlled [$_\pi 2_s$ + $_\pi 4_s$] cycloaddition of **8** onto the cyclobutene double bond of **4a** as a major constituent. It follows that the mono-*trans*-azonine responsible for the formation of cycloadducts **9** and **10** in the trapping of thermally activated **2a** with **8** is derived directly from **2a**, *i.e.*, without prior isomerization of this substance to **4a**. The question of whether the initially generated *trans*-azonine is trapped prior to its rotational conversion to **15** cannot be answered at present. Nonetheless, the absence of **13** among the cycloadducts of thermally activated **1a** could be interpreted to mean that any participation of **15** in the formation of **9** and/or **10** is minor.

The thermal rearrangement of **2a** can be dissected into symmetry-allowed (k_a) and forbidden (k_f) components; it is instructive to contrast the thermal reactions of **2a** in the presence and absence of **8** in terms of the ratio of k_a/k_f. Comparison of past[1] and present findings reveals that this ratio increases from (**4a**)/(**3a**) ~ 0.8 in the absence of trapping agent to (**9** + **10**)/(**11** or **12**) ~ 13 in the presence of **8**. Clearly then, the use of isomer product ratios grossly underestimates the control imposed on the various steps by orbital symmetry. Undoubtedly, this misrepresentation is chiefly due to the reversibility of various symmetry-allowed steps that generate fleeting intermediates, *e.g.*, Scheme III, providing for eventual drain through less accessible but irreversible symmetry-disallowed channels. This rationale also accounts for the thermolytic behavior of the carbocyclic members of the family. It is readily seen for example that the k_a/k_f ratio associated with the thermal response of *cis*-bicyclo[6.1.0]nona-2,4,6-triene at 80° increases in magnitude from ~0.1 in the absence of trapping agent[16] to ~3 in the presence of **8**.[17]

SCHEME III



Acknowledgment—The Syracuse University group thanks the National Science Foundation (GP-26347) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial assistance. The Iowa State University group thanks the Ames Laboratory of the U. S. Atomic Energy Commission for support.

(16) E. Vogel, *Angew. Chem.*, **73**, 548 (1961); **74**, 829 (1962).
(17) A. G. Anastassiou and R. C. Griffith, *J. Amer. Chem. Soc.*, **93**, 3083 (1971).
(18) NDEA Graduate Fellow, 1971–1974.
(19) Camille and Henry Dreyfus Foundation Teacher–Scholar Grant Awards, 1972–1977.

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RECEIVED FEBRUARY 9, 1973

Selective Demethylation of Quaternary Salts with Lithium *n*-Propylpercaptide in Hexamethylphosphoramide[1]

Summary: Lithium *n*-propylmercaptide in hexamethylphosphoramide provides a mild, rapid, and convenient system for dealkylation of quaternary ammonium salts in excellent yield with high propensity for methyl group removal.

Sir: The perennial problem of dealkylating quaternary ammonium salts has received considerable attention and led to the development of several reagent systems for effecting such transformations. The most successful of these include alkyl displacement using lithium aluminum hydride,[2a] sodium in ammonia,[2b] ethanolamine,[2c] thiophenoxide anion,[2d] lithium iodide,[2e] or acetate anion.[2f]

The recent disclosure of the exceptional nucleophilic displacement ability of lithium *n*-propylmercaptide in hexamethylphosphoramide (HMPA)[3] prompts this report of the utility of this reagent system as an effective, mild, and rapid method for dealkylation of aromatic and aliphatic quaternary ammonium salts with superior selectivity for displacement of methyl

(1) Presented in part of the 7th Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1972.
(2) (a) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. Meisinger, *J. Amer. Chem. Soc.*, **82**, 4651 (1962); (b) E. Grovenstein, Jr., S. Chandra, C. Collum, and W. Davis, Jr., *ibid.*, **88**, 1275 (1966); (c) S. Hunig and W. Baron, *Chem. Ber.*, **90**, 395 (1957); (d) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966); (e) H. O. House, H. Muller, C. Pitt, and P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); (f) N. D. V. Wilson and J. A. Joule, *Tetrahedron*, **24**, 5493 (1968). In addition, 1,4-diazabicyclo[2.2.2]octane in DMF or HMPA has recently been shown to effectively dealkylate quaternary salts; see T. L. Ho, *Synthesis*, 702 (1972).
(3) P. A. Bartlet and W. S. Johnson, *Tetrahedron Lett.*, 4659 (1970).

groups. The procedure for the selective demethylation of phenyldimethylethylammonium iodide is illustrative. A solution of the ammonium salt (376 mg, 2.5 mmol) and *n*-tridecane (235 mg, 1.25 mmol, internal standard) in 5 ml of HMPA (distilled from CaH_2) was cooled to 0–5° and lithium hydride (159 mg, 20 mmol) was added, followed by freshly distilled *n*-propylmercaptan (630 mg, 8.3 mmol, 0.75 ml). The solution was stirred under nitrogen at 0° for 30 min, then diluted with water, and extracted with cyclohexane. Analysis of the cyclohexane solution by glpc indicated a 97% yield of phenylmethylethylamine (1) and <0.5% deethylated product, phenyldimethylamine (2). A

$$C_6H_5\overset{+}{N}(CH_3)_2(C_2H_5)I^- \xrightarrow[\text{HMPA, 0°, 30 min}]{C_3H_7S^-Li^+} \underset{\mathbf{1},\ 97\%}{C_6H_5NCH_3(C_2H_5)} + \underset{\mathbf{2},\ \sim 0}{C_6H_5N(CH_3)_2}$$

$$C_6H_5\overset{+}{N}(CH_3)_2(C_2H_5)I^- \xrightarrow[85°,\ 5\ min]{} \underset{94\%}{\quad} \quad \underset{4\%}{\quad}$$

similar reaction conducted at 85° gave a 94% yield of 1 and 4% 2. With completely aliphatic salts, slightly more vigorous conditions (50°, 2–3 hr) were required to effect demethylation as expected since the departing amines are stronger bases. The results for a variety of quaternary salts are presented in Table I. As evident from the table, the reagent system offers several advantages including excellent yields of tertiary amines (93–99%), relatively short reaction times, and mild conditions. Furthermore, the method shows exceptional selectivity for methyl group removal, especially at lower temperatures, and appears to surpass other procedures[2,4] in this regard. Coupled with recent improved procedures for quaternary salt formation,[5] the method offers a convenient method for preparing unsymmetrical tertiary amines *via* alkylation of methylamines and demethylation with *n*-propylmercaptide.

The high nucleophilicity of the reagent system limits the procedure to compounds devoid of ester groups, which are readily cleaved, at least at higher temperatures.[3] In addition, primary and secondary alkyl halides afford substitution and/or elimination products and aromatic nitro groups may be displaced[6] or give undefined, highly colored products. Most other functional groups such as cyano, amido, carboxylic acid, and carbonyls should be tolerable. We are currently further exploring the scope and limitations of the reagent system.

TABLE I

DEALKYLATIONS OF QUATERNARY AMMONIUM SALTS WITH LITHIUM *n*-PROPYLMERCAPTIDE IN HEXAMETHYLPHOSPHORAMIDE

Quaternary salts	Temp, °C	Time, min	% yields[a] Demethylated product	% yields[a] Dealkylated product	Selectivity ratio
$C_6H_5N(CH_3)_3I$	25	15	96		
	85	5	95		
$C_6H_4N(CH_3)_2C_7H_5I$	0	30	97	~0	
	85	5	94	4	24:1
$C_6H_5N(CH_3)_2CH(CH_3)_2I$	0	30	93	~0	
$CH_3(CH_2)_{11}N(CH_3)_2C_2H_5I$	50	120	94	<3	>31:1
	85	15	92	4	23:1
$CH_3(CH_2)_{11}N(CH_3)_2CH(CH_3)_2I$	50	180	99	~0	~100:1
	85	15	94	4	24:1
$CH_3(CH_2)_{11}N(CH_3)_2(CH_2)_3CH_3I$	50	180	99	~0	~100:1

[a] Yields were determined by glpc using internal standards and predetermined detector response factors. The percentages are averages of four–six samples.

(4) For instance, the most selective reagent system previously developed appears to be thiophenoxide anion in refluxing (80°) 2-butanone which afforded a 3.5:1 ratio of demethylated to deethylated product with methyltriethylammonium halides in 19 hr[2d] while ethanolamine gave only a 1.6:1 ratio of the same products at 172° for 5 hr.[2c]

(5) H. Z. Sommer, H. I. Lipp, and L. J. Jackson, *J. Org. Chem.*, **36**, 824 (1971).

(6) J. B. Bauman, *ibid.*, **36**, 396 (1971).

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ROBERT O. HUTCHINS*
FRANK J. DUX

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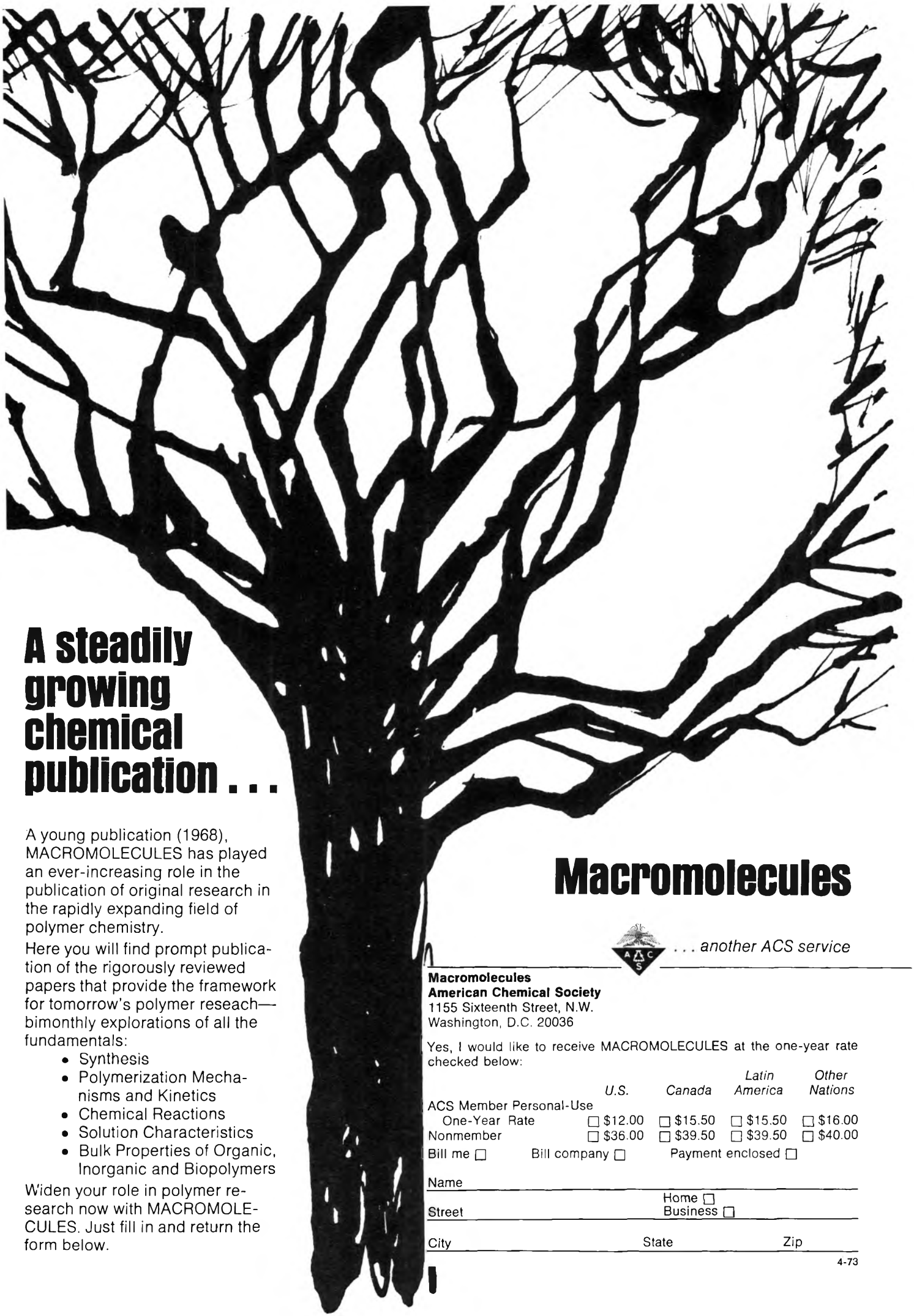

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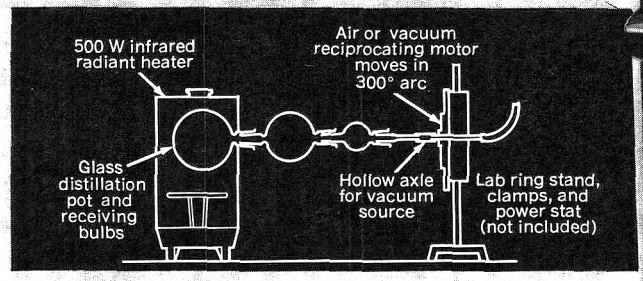

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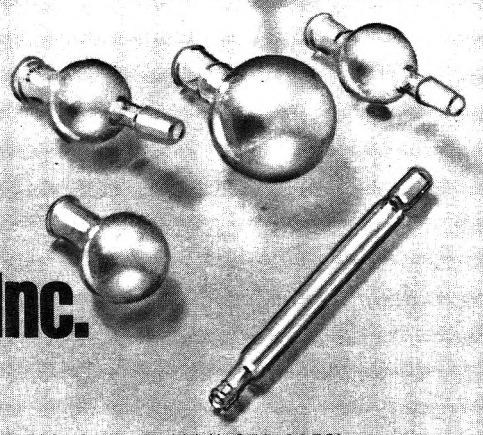

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