THE USE OF NITROPARAFFINS IN THE
PREPARATION OF QUINOLINE DERIVATIVES

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CHAPTER 1

INTRODUCTION AND HISTORY

This paper is the result of an attempt to prepare
quinoline derivatives in this laboratory by the existing
methods reported in the literature. As the yields obtain-
ed by the use of these methods were not satisfactory in
the hands of this investigator, this study making use of
aliphetic nitro compounds now available in commercial
quantities as the oxidizing agents was made. In this
proposed synthesis the excess oxidizing agent would be
soluble in an alkaline solution and would not have to be
removed, while the products formed by the reduction of
these nitroparaffins could be removed from the solution
by boiling.

Many methods for the preparation of quinoline have
been reported. Koenigs[72] reported the preparation of this
compound in 1879 by passing acrylidineaniline over red hot
lead oxide. The following year this author[72] reported the
same product obtained by substituting aniline, glycerine,
and sulfuric acid for the acrylideneaniline. Friedlander[66]
was able to prepare quinoline by heating o-aminobenzalde-
hyde and acetaldehyde with sodium hydroxide on a water bath;
Kulisch[68] reported the same results using glyoxal and o-tolu-

idine in an alkaline solution. Pictet and Fert[67] isolated quinoline as well as other products when methylacetanilide was fused with zinc chloride. By heating aminoazobenzene with glycerine and sulfuric acid Lillmann and Lippert[29] prepared quinoline. Using substituted aminoazobenzene these authors prepared quinoline derivatives.

However, in this paper we shall consider the synthesis of quinoline and its derivatives in which aniline was heated with sulfuric acid, glycerine, and an oxidizing agent. The modifications of this method for preparing quinoline will be discussed at some length now, with the special applications needed to prepare quinoline derivatives discussed in connection with their preparation.

The early articles which were read constantly referred to the violence of the original Skraup method for the synthesis of quinoline. The trend of research then for the most part was an effort to control the reaction and increase the yield of the desired product. The yield of quinoline reported by Walter[69] in repeating Skraup's experiment was 50 per cent theoretical calculated on the basis of the aniline used, but only about 27 per cent in regard to the glycerine.

Knueppel[31] used arsenic acid as the oxidizing agent and reported better yields of quinoline and a reduction in the amount of tarry products. However, if the yield were

to be calculated on the basis of the glycerine used the

yields were poorer then when nitrobenzene was employed for

a large excess of glycerine and sulfuric acid was used in

this modification. Bartow and McCollum[10] working at Kansas

University in 1904, applied this method to other aromatic

amines. While no yields were recorded, they stated that

"the first reaction is quite violent and the flask must be

removed from the bath until the violent reaction has ceased."

A modification in which the amine was converted to the

stannichloride salt and then heated for several hours with

glycerine and concentrated sulfuric acid was reported by

Druce.[28] This was not the first report of this method as

Skraup and Vortmann[28] used the stannichloride salt of

phenylenediamine in the preparation of phenanthroline. The

yield of desired product varied in this work from 25 to 80

per cent of the theoretical. Barnett[71] questioned the vali-

dity of the yields on the grounds that the tin present in

the reaction was not sufficient to oxidize this weight of

addition product to quinoline. Barnett[71] used stannic sul-

fate as the oxidizing agent, but the yields proved to be

less than 30 per cent theoretical.

The addition of ferric sulfate to the reaction solu-

tion of aniline, glycerine, and sulfuric acid produced a

yield of quinoline amounting to 60 per cent of the theore-

tical. Barnett[71] after many experiments in which various

modifications were made reported the following modificstion as giving the best yield.

"A very rapid modification of the above process which gives somewhat better yields, about 60 per cent of the theoretically possible, consists in mixing 50 grams of aniline with 65 grams of glycerine, and 100 grams of calcined ferric oxide, and then adding this mixture as quickly as possible to 150 milliliters of concentrated sulfuric acid in an evaporating basin. A brisk reaction sets in almost at once, and while it lasts the mixture is kept well stirred. When the reaction subsides, the whole is allowed to stand for half-an-hour without heating, and is then poured into water."

The ferrous sulfate modification of the Skraup synthesis as published by Clark and Davis[12] was probably the greatest advance in the enlargement of the yield of quinoline. In this modification 80 grams of powered crystalline ferrous sulfate was added to 218 grams of aniline and the corresponding quantities of the other ingredients including nitrobenzene. The reaction mixture was boiled for five hours. With the addition of this ferrous sulfate it was possible for the first time to use such large quantities of material safely. Yields of 84 to 91 per cent of the theoretical amount based on the aniline taken or 55 to 60 per cent when based on the aniline added plus the nitrobenzene not recovered were reported by this method of

preparation.[2]

Cohn and Gustavson[4] published a report of an extensive investigation on the effect of the yield of quinoline with time of heating, quantity of sulfuric acid added, and the quantity of glycerine used. The authors claimed to "have succeeded in eliminating the occasional violence of the reaction by the addition of acetic acid to the reaction mixture." A yield of thirty-four grams quinoline was obtained when 38 grams of aniline, 24 grams of nitrobenzene, 100 grams of glycerine, 60 milliliters of 85 per cent acetic acid, and 54 milliliters of sulfuric acid (95 per cent) were heated for 28 hours. A twelve hours heating time yielded 28 grams of product. In this paper it was stated that the sudden violence of the Skraup reaction was due to the instantaneous liberation of acrolein by the action of the sulfuric acid on the glycerine. The acetic acid was added to remove some of the glycerine from the reaction sphere by the formation of glycerol mono and diacetates.

By decreasing the quantity of glycerine employed and adding dehydrating and oxidizing catalyst Delaby and Hiron[74] reported better yields of quinoline using nitrobenzene as the oxidizing agent. The following yields were reported when the corresponding catalysts were added. The heating time in all cases was 16 hours.

Catalysts added	Yields
Aluminum oxide	60%
Thorium oxide	70%
Vanadium oxide	82%

The violence of the reaction was avoided in this study by adding the sulfuric acid in stages, controlling the temperature at which the mixture was refluxed, and by stirring the mixture during the reaction.

Cohn[3] reported a modification in 1930 in which 25 grams of boric acid was dissolved in the glycerine before it was added to the other ingredients consisting of 14 grams of ferrous sulfate, 38 grams of aniline, and 29.5 grams of nitrobenzene. A yield of 38 grams was obtained after five hours heating compared to 30 grams by the ferrous sulfate modification and 25 grams by the acetic acid method. When heating was continued for 20 hours, the yield of quinoline was 49 grams. An interesting graph in which the initial rise in temperature was plotted against the time appeared in this paper. The first bubbles escaped from the solution at about the same temperature, 140 $C.$, in each case. However, in the original Skraup method the temperature reached 175 $C.$ within the next minute while in the acetic acid modification of Cohn and Gustavson[4] the temperature never rose above 140 $C.$ In the ferrous sulfate modification[2] the temperature rose 15 $\circ$ in one half minute

after the first bubble appeared. In the case in which
boric acid had been added the slope of the curve was much
more gradual and the refluxing temperature was almost 10°
lower than the ferrous sulfate modification.

An abstract[6] of a Canadian article in which the authors
used an equivalent quantity of acetanilide in place of ani-
line was published this year. The reaction was so smooth
that its inception was difficult to observe. According to
this abstract the yield of quinoline by this method was 67
grams as compared to 47 grams, using the Cohn modification
and 41 grams when the Clarke and Davis modification was used.
No experimental details were included in the review.

La Coste[44] first suggested the use of the acetyl derivative
in 1883 in the preparation of 6-nitro quinoline from p-nitro
aniline or the equivalent amount of p-nitro acetanilide.

An abstract[7] of a Russian article published in 1930
described a method in which quinoline was prepared using
nitrobenzene as the oxidizing agent and ferrous sulfate and
infusorial earth as the catalyst. In this method the pres-
sure was reduced so that water and nitrobenzene would dis-
till until the reaction mixture reached a temperature of
150-4° C. The mixture was kept at that temperature for 4-
5 hours. The yield of quinoline after diazotization re-
presented 85 per cent based on aniline and 42-3 per cent
based on glycerine. This modification was patented.[8]

A yield of 90.6 per cent theoretical was reported[54] when the reduced pressure method was applied to the preparation of 6-methoxy, 8-nitroquinoline using arsenic acid as the oxidizing agent.

Beyer[51] in 1885 wrote the equation for the synthesis of quinoline as follows:

$$C_6H_5N = CH-CH-CH_2 + O \longrightarrow \text{[structure]} + H_2O$$
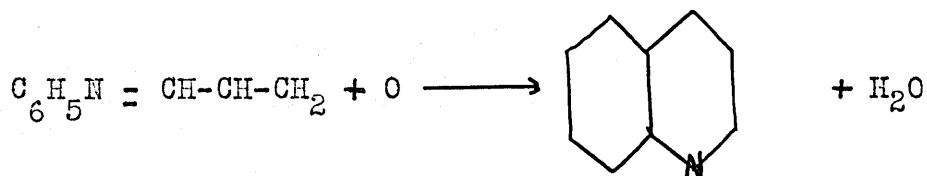
Other authors represented the reaction in the following manner.

$$C_6H_5NH_2 + C_3H_5(OH)_3 \longrightarrow \text{[structure]} + 3H_2O + H_2$$
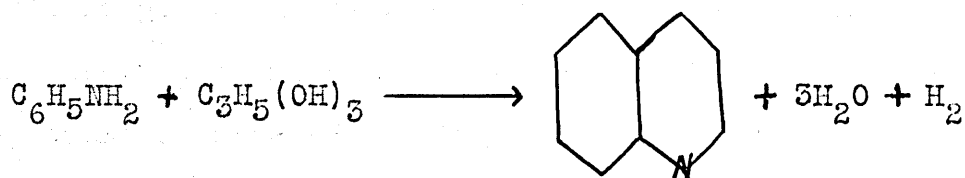
In a paper published in 1904 Barton and McCollum[10] stated, "A quinoline ring is formed by the combining of the aromatic amine and the glycerin with the loss of water and hydrogen". In view of the present day knowledge the probable course of the reaction is as follows:[26]

$$CH_2OH-CHOH-CH_2OH \xrightarrow{H_2SO_4} CH_2 = CH-CHO + 2H_2O.$$
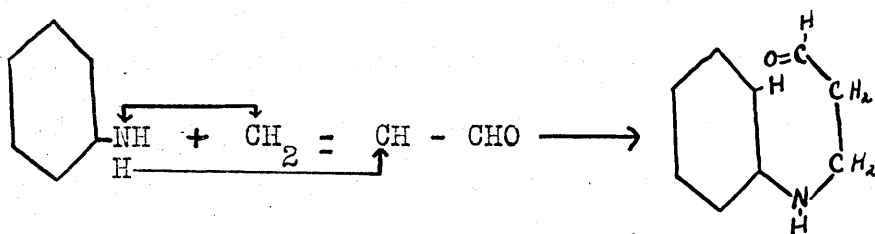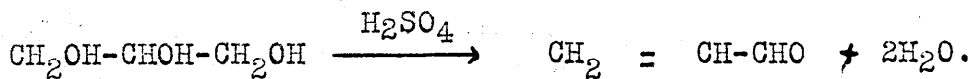
oxygen from

oxidizing agents
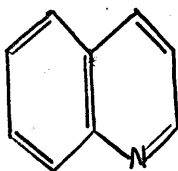
In this paper the numbering system suggested in Chemical Abstracts was used. The number of the positions are represented in the following figure.
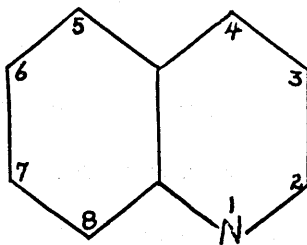
Doebner and Miller[9] first recorded the synthesis of quin-
aldine. This preparation was carried out by heating together
for 3 to 4 hours 80 parts of paraldehyde, 40 parts of aniline,
45 parts of nitrobenzene, and 100 parts of concentrated sul-
-furic acid. In this article[9] these authors postulated the
formation of crotonaldehyde which reacted with the aniline
to form quinaldine. The present structural formula was not
used in this article, but rather the methyl group was on pos-
ition 4. In a later paper[12] these two authors reported a
study on some quinaldine derivatives. In this paper the
method of preparation was modified, substituting aldol for
paraldehyde. The equation for the reaction in this paper
was written as follows:

$$C_6H_7N \;+\; 2C_2H_4O \longrightarrow C_{10}H_9N \;+\; 2H_2O \;+\; H_2$$
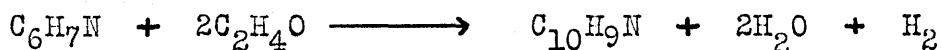
and the structural formula was written with the methyl
group at position 2.

V. Drewson[56] prepared quinaldine by reducing nitro
benzylidene acetone ($NO_2C_6H_4CH = CH - CO - CH_3$) with
zinc chloride, zinc, and hydrochloric acid. Other early
methods of syntheses included Fischer and Kuzel's[57]
method in which nitrocinnamyl acetate was heated with zinc
chloride and Friedlander and Gohring's[58] synthesis from
o-nitrobenzaldehyde, acetone, and sodium hydroxide. Skraup[70]
prepared quinaldine from crotonaldehyde, aniline, nitroben-
zene, and sulfuric acid.

Using the proportions of 1.5 parts of paraldehyde, 1 part of amine, and 2 parts of sulfuric acid Doebner and Miller[59] prepared several derivatives of quinaldine from substituted anilines. The properties of these quinaldines as well as their salts were reported in this paper. Bartow and McCollum[10] heating "aldehyde" and hydrochloric acid with the sudstituted anilines prepared several chlorine and bromine derivatives of quinaldine in 1904. The preparation of still more substituted quinaldines was contained in a German patent of 1931. The substituted amines were heated with crotonaldehyde or other compounds yielding crotonaldehyde in a sulfuric acid solution in the presence of arsenic acid or nitrobenzene sulfonic acid. The melting and boiling points of many substituted quinaldines were recorded in this abstract[62]. Doebner and Miller[60] applied their method of synthesis to the preparation of other heterocyclic compounds prepared by condensing higher aryl aldehydes with aniline. Another synthesis which must be of some value in the preparation of quinaldine judging from the patents[61] on the process was one in which aniline was mixed with acetylene and passed over hot metallic and metallic salt catalysts including mercury, copper, and zinc salts.

In an article by Mills, Harris, and Lambourne[65] in which a study of the by-products obtained in the quinal-

dine preparation were determined interesting results were obtained. Before this time it had been supposed that the hydrogen formed in the preparation of quinaldine by the Doebner and Miller method was consumed in the production of tetrahydroquinaldine. However, these authors[65] stated that the two volatile by-products isolated were monoethyl aniline which Doebner and Miller[59] had recognized and n-butylaniline. In this study the Doebner and Miller process was modified by substituting commercial acetaldehyde for paraldehyde and adding "a certain amount of zinc chloride, a modification which was found to increase the yield of quinaldine".

Quinaldine contains this active CH_3 group and has been condensed with benzaldehyde and many substituted benzaldehydes. Hoffmann[63] prepared many derivatives of 8-methyl quinaldine by condensing this compound with various aryl aldehydes as well as with benzaldehyde and its derivatives. Recently the condensation products of 6-substituted quinaldines and substituted benzaldehydes have been prepared and used as photographic sensitizers[64].

Throughout the experimental work, thermometers which had been calibrated using standards obtained from the Bureau of Standards were used in determining all melting and boiling points.

Since all of the compounds prepared had been synthesized

previously and their physical constants recorded, few analyses were made. In one case when the melting point of the compound prepared differed 10° from the recorded melting point a halogen analysis was made. The recrystallized solid sample was dried over calcium chloride in a dessicator for several days.

In this analysis a .2 gram sample of the produt was mixed thoroughly with 15 grams of sodium peroxide, 1 gram of potassium nitrate, and .5 gram of cane sugar in a Parr bomb. The bomb was clamped shut and the contents fused by heating with a Bunsen cone. The contents of the cooled bomb was dissolved in hot water. The solution was boiled to remove excess hydrogen peroxide and 50 ml. of saturated solution of hydrazine sulfate added. After the solution was acidified with nitric acid, it was filtered to remove carbon and other foreign matter. The halide was then precipitated with a slight excess of silver nitrate solution. The solution was heated to coagulate the precipitated silver halide, cooled, the precipitate filtered into a prepared Gooch crucible, and dried at 110-115°C. for an hour before weighing.

Most distillations were carried out at reduced pressures to prevent excessive decomposition of the compounds. A Cenco vacuum pump was used to obtain pressures of from 3 to 25 Millimeters.

In all cases the yields reported in this paper were
for the redistilled product collected between the boiling
ranges indicated. The final product was further purified
by this method. In some cases the reaction mixture was
so dark colored that the blue color test on starch-potassium
iodide paper for excess nitrous acid could not easily be
read. In case all the unreacted aniline had not been de-
composed by the nitrous acid it could be detected in the
distillation and the nitrous acid treatment repeated.

The aniline and substituted anilines were purified
before they were used in the experiments. In case of the
liquid anilines the purification was effected by distill-
ing the oil at reduced pressure. If the solid aniline
derivatives did not melt at the recorded temperatures,
the compounds were recrystallized.

EXPERIMENTAL

Preparation of Quinoline.

After a search of the literature it was decided to
use the proportions of chemicals suggested in Williams and
Brewster "Laboratory Manuel of Organic Chemistry". These
quantities were very similar to those used by many invest-
gators and the yield of quinoline obtained was sufficient
to be handled easily. In this procedure 38 grams (.4 gram
mole) of aniline was placed with 24 grams (.2 gram mole)
of nitrobenzene and 10-12 grams of ferrous sulfate in a 1000
milliliter round bottom flask. To this were added with
constant shaking 100 grams of concentrated sulfuric acid
and 120 grams of glycerine. The flask was then heated un-
til the reaction began, the burner was removed until the
reaction had subsided, and then the heating was continued.

Throughout this problem the basic proportions for the
reagents to be added into the flask were 38 grams (.4 gram
mole) of aniline, 120 grams of glycerine, and 60 millilit-
ers of sulfuric acid (specific gravity 1.83). Then by add-
ing the various quantities of oxidizing agents, nitroparaffins,

it was possible to determine their merits in the preparation of quinoline.

After the best oxidizing agent had been found, varying quantities of possible catalysts were added to the formula and the yields of quinoline again measured. Later the concentration and the quantity of the acid were varied as well as the quantity of glycerine used.

After several variations of the general method had been tried, the suggestion noted by Clarke and Davis[2] was given consideration. The glycerine which was being used was U.S.P. glycerine obtained from Proctor and Gamble Company and upon investigation was found to contain about five per cent water which could be removed by heating to 200-225° C. The experiments which had been carried out were repeated, and substantially better yields of quinoline were obtained. Throughout the remainder of the research one hundred and thirty grams of glycerine was placed in an evaporating dish and heated to 200-225° C before being used. Most of the water was driven off between 165-190° C. In this report the yields were for glycerine which had been heated. Throughout the investigation the ingredients were placed in the flask in the following order. To the glycerrine, which was placed in a 1000 milliliter round bottom flask covered with a watch glass while it cooled to 100-

125 $^{\circ}$C. were added the ferrous sulfate, the aniline, and
the nitroparaffin. The flask was then connected to a
water cooled condenser and the sulfuric acid added in five
milliliter portions with constant shaking. In preparing
some of the quinoline derivatives it was found that by drop-
ping the acid into the reaction mixture over a period of
thirty to forty-five minutes slightly better yields were ob-
tained. When this variation was applied to the methods
giving the best yields of quinoline, the yields were not
increased markedly as had been expected. Even when the acid
was added in five milliliter quantities the reaction did not
become violent as when nitrobenzene was used as the oxidiz-
ing agent.

The temperature of the reaction mixture was observed
to be from 130 to 155 $^{\circ}$C depending on the quantity of solids
added to the reaction mixture. The temperature was usually
110 $^{\circ}$C at the beginning of the reaction with the lighter lay-
er of nitroparaffin not soluble in the reaction mixture boil-
ing gently. However, as the reaction proceeded and the so-
luble nitroparaffin was reduced the temperature increased
to the above temperatures. The ferrous sulfate was not
soluble in this mixture but remained suspended, settling
out to the bottom of the flask after the reaction was complete.

The mixture of aniline, glycerine, ferrous sulfate, (when it was used) and the nitroparaffin was usually slightly colored. As the acid was introduced through the condenser, aniline sulfate separated and much heat was generated. Before all of the acid had been added all of the solid aniline sulfate was dissolved. The solution was then cherry red and sometimes exhibited fluorescence. As the solution was heated, the color darkened and usually became almost black after several hours.

When the reaction mixture had been heated for the specified length of time, the mixture was poured into a liter beaker and diluted to 700-800 milliliters. After cooling the mixture a sodium nitrite solution was added slowly until a drop of the solution caused a blue spot on starch-potassium iodide paper. After standing for thirty minutes the solution was heated to 100° C. Upon cooling the solution was made alkaline with a sodium hydroxide solution and subjected to steam distillation until the distillate became clear. The distillate was then extracted with chloroform and dried over solid sodium hydroxide. After removing the chloroform the oil was subjected to vacuum distillation and the light yellow oil collected in a weighed receiver. In most cases this yield of quinoline was the whole portion of the oil extracted from the

steam distillate, no unchanged aniline being detected.

In the flask used for steam distillation a residue was always present after the steam distillation had been completed. When iron was included in the reaction, there were no large pieces of tar present but solid organic material found in the ferrous and ferric hydroxide residue upon filtration. When no iron was used as the oxygen carrier, a large piece of tarry material was left in the flask after the distillation was complete. This dark colored material was soft and pliable but when washed to remove the alkali it became hard and crystalline. It could then be handled without any color wiping off on the hands. When the yield of quinoline was high, the quantity of tar was small; but when the yield was poor, the tarry product was much greater.

During the neutralization of the reaction mixture after diazotization and during the first part of the steam distillation an ammonia-like smell could be noted. This was the aliphatic amine which was produced in the reduction of the aliphatic nitro compound in the oxidation of the glycerine aniline addition product to quinoline. This was collected in two different experiments and its quantity determined by neutralization to phenol red with a standard acid solution.

In the experiments in which ferrous sulfate was used the crystalline salt with seven moles of water of hydration was employed. As was shown by experiment the dehydration of this salt had little or no effect on the yield of quinoline. The sulfuric acid employed was chemically pure acid with a specific gravity of 1.83. The aniline was distilled and kept in a dark place in a glass stoppered bottle. The product distilling 179-182° C was collected and used as aniline.

To make sure that the products obtained by the use of the various oxidizing agents were the same, the product collected from the use of each nitroparaffin was kept in separate bottles. After the product of several preparations had been collected the boiling points of the products were determined and the picrate salt of the products prepared and their melting point determined. The picrate salt was prepared by adding a saturated alcohol solution of picric acid to an alcohol solution of quinoline until no more precipitate was formed. The Canary yellow crystalline powder was filtered from the alcohol and dried on a porous plate. The boiling points of the quinoline products at reduced pressure and the melting points of the picrate salt are listed here.

Oxidizing agent used	Boiling point of product (14mn. pressure)	Melting point of picrate salt
Nitroethane	115-8°C	203-4°C
Nitroethane	115-9°C	202-3°C
1-Nitropropane	114-7°C	203-4°C
2-Nitropropane	114-8°C	203-4°C
Nitrobenzene	115-8°C	202-3°C

A mixed melting point of all of these picrate salts showed no depression in the melting point. Decker[5] reported a melting point of 203°C. for quinoline picrate recrystallized from benzene.

1. <u>Time</u> <u>of</u> <u>Heating</u>.

It was thought that the higher nitroparaffins would prove to be the best oxidizing agents, so the first test was to determine the length of heating time necessary for the completion of the reaction and production of the best yield of quinoline. Three tenths gram mole of 1-nitropropane was added to the reaction mixture of four tenths gram mole of aniline, one hundred and twenty grams of glycerine, and sixty milliliters of sulfuric acid (specific gravity 1.83). After the specified times of heating the mixture was treated as before mentioned and the following yields were obtained; the percentage yields are in parenthesis.

Time of Heating (hours)	Yield (Grams) No Catalyst	Yield (Grams) 10 Gm. $FeSO_4 \cdot 7H_2O$
2	14(27%)	12(23%)
4	22(43%)	24(46%)
6	26(50%)	30(58%)
8	26(50%)	31(60%)
12	27(52%)	31(60%)

As further reactions were carried out it was found that nitroethane gave the best yields of quinoline, so this experiment was repeated using three tenths gram mole of nitroethane instead of 1-nitropropane. The results from this series of experiments are shown in the following table with the yield of quinoline in grams and the percentage yield in parenthesis.

Time of Heating (hours)	Yield (Grams) No Catalyst	Yield (Grams) 10Gm. $FeSO_4 \cdot 7H_2O$
4	24(46%)	25(48%)
6	29(56%)	33(64%)
8	30(58%)	34(66%)
12	30(58%)	34(66%)

From the results obtained here it would seem that from six to eight hours would be sufficient to heat the reaction mixture. Additional heating time does not increase the yield markedly. Almost all of the aniline had reacted after

the mixture was heated from six to eight hours, for in
most cases when the solution was diazotized it was nec-
essary to add less than five milliliters of a twenty per
cent sodium nitrite to get the color test with starch-
potassium iodide paper.

This does not agree with the results of Cohn[3] and
Cohn and Gustafson[4]. In these papers the yield of quin-
oline increased markedly up to twenty hours and reached a
maximum at about thirty hours in the latter case. In the
study by Cohn and Gustafson[4] the general Skraup method had
been modified by the addition of acid to act as a diluent
and so decreased the violence of the reaction. Cohn[3] re-
ported, "For fifteen hours refluxing, the yield of quinoline
was 90% of the theoretical based upon the amount of aniline
originally used". In this work twenty-five grams of boric
acid was added to the glycerine before it was mixed with
the aniline, ferrous sulfate, and nitrobenzene. The acid
was then added and the contents of the flask refluxed for
a period "depending upon the yield desired".

2. Various Oxidizing Agents Used

In this series of experiments the mixture was heated
for eight hours, using various aliphatic nitro compounds.
The nitroparaffins were added in various quantities to the
standard four tenths gram mole aniline mixture. In an

attempt to compare the yields obtained by the nitrobenzene method the same molar quantities of nitrobenzene were used and the excess nitrobenzene was collected by steam distillation from the acid solution. In the case of nitrobenzene the temperature of reaction was 150-160° C. while the reaction temperature in the case of the nitroparaffin was 130-150° C. The following results were obtained when no catalyst was used. The yields of quinoline in grams appears in the table with percentage yields in parenthesis.

Oxidizing Agent	Quantity of oxidizing agent used			
	.1gm. mole	.2gm.mole	.4gm. mole	.8gm.mole
Nitromethane	12gm.(23%)	18gm(35%)	23gm.(44%)	24gm.(46%)
Nitroethane	14gm.(27%)	20gm(39%)	29gm.(56%)	23gm.(44%)
1-Nitropropane	18gm.(35%)	21gm(41%)	26gm.(50%)	21gm.(41%)
2-Nitropropane	16gm.(31%)	18gm(35%)	22gm.(43%)	19gm.(37%)
Nitrobenzene	28gm.(54%)	40gm(78%)	40gm.(78%)	40gm.(78%)

In the case of nitrobenzene the yields were based on the aniline originally used. In the first two cases no excess nitrobenzene was recovered. When the four tenths gram mole of nitrobenzene was used, fourteen hundredths of a gram mole was recovered. In the case in which eight tenths of a gram mole of nitrobenzene was used five tenths of the mole was recovered by steam distillation of the acid reaction mixture.

In order to study the effect of the addition of ferrous

sulfate on the yield of quinoline, the foregoing ex-
periments which had given the best yields were repeated.
These yields in grams are listed in the following table
with the percentage yields in parenthesis.

Oxidizing Agent	Quantity of oxidizing agent used		
	.2gm. mole	.4gm. mole	.8gm. mole
Nitromethane	20gm.(39%)	28gm.(54%)	25gm.(48%)
Nitropropane	25gm.(48%)	32gm.(62%)	27gm.(52%)
1-Nitropropane	21gm.(41%)	30gm.(58%)	26gm.(50%)
2-Nitropropane	19gm.(37%)	24gm.(46%)	20gm.(39%)

Two aliphatic nitro alcohols were used as the oxidi-
zing agents instead of the nitroparaffins. Forty-eight
grams (.4 gram mole) of 2-nitro, 1-butanol was introduced
into the reaction flask along with ten grams of ferrous
sulfate, aniline, and glycerine. As the acid was added
the mixture became homogoneous. When the product was col-
lected and weighed, there was only 24 grams (46 per cent of
the theoretical yield) of quinoline. A second experiment
gave no better yield- 23 grams (44 per cent of the theore-
tical yield).

When an isomer, 2-nitro, 2-methyl, 1-propanol, was used
as an oxidizing agent the yield of quinoline was even less.
Forty-eight grams (.4 gram mole) of the nitro alcohol was
used, and the yield was 18 grams (35 per cent of the theoret-
ical yield) of quinoline. As the acid was added there was
much charring and the reaction mixture became very dark.

When the flask was emptied, it contained much carbonized material.

The most widely used preparation of quinoline utilizes nitrobenzene as the oxidizing agent and so aniline, the starting product, was obtained as the reduction product. In order to study the relative ease of oxidation of nitroethane and nitrobenzene an experiment using both of these oxidizing agents was performed. Thirty grams (.4 gram mole) of nitroethane and 25 grams (.2 gram mole) of nitrobenzene were added to the reaction mixture containing 10 grams of ferrous sulfate. After heating the solution for eight hours the mixture was diluted with water and subject steam distillation. A total of thirty milliliters of oil was collected in the distillate. After making the distillate alkaline to dissolve the nitroethane twenty milliliters of nitrobenzene remained. Thirty-six grams (70 per cent of the theoretical yield, based on aniline used) of quinoline was obtained from this preparation. From this it would be concluded that the nitroethane was more easily reduced.

A series of experiments were then performed to see whether it would be possible to increase the yield of quinoline by first using the nitrobenzene as the oxidizing agent and then adding nitroethane to oxidize the aniline

produced by the reduction of nitrobenzene. In these
experiments twenty grams of nitrobenzene was used as the
oxidizing agent. In one experiment the mixture was heat-
ed for five hours, cooled, thirty milliliters of nitro-
ethane added, and the heating continued for four hours
more. Only a trace of nitrobenzene was recovered upon
steam distillation. Forty-seven grams (91 per cent of
the theoretical yield, based on aniline used) of quino-
line was obtained by this method. When this experiment was
repeated and the mixture heated for six hours before the
nitroethane was added, the yield of quinoline was 49 grams
(95 per cent,based on aniline used). To check the yield
of quinoline even if no nitroethane had been added but the
mixture heated for the above mentioned times, controls
were run with these experiments. In the case in which the
mixture was heated a total of nine hours the yield of
quinoline was 40 grams (78 per cent, based on the aniline
used) while when the mixture was heated for a total of ten
hours the yield was 42 grams (81 per cent of the theoreti-
cal yield, based on the aniline used).

These yields were rather imposing when calculated on
the basis of the aniline used. However, if the yield were
calculated on the basis of aniline used originally plus the
aniline produced from the nitrobenzene not recovered the

yields were very similar to those obtained from the use

of nitroethane. For example, the yield of 91 per cent

based on aniline used was 65 per cent when the yield was

based on the total aniline present including the reduced

nitrobenzene.

3. Variations in the Oxygen Carriers

The objection that most investigators in this field

have had to the Skraup synthesis of quinoline has been the

violence with which the reaction takes place. Clarke and

Davis[2] state, "By the addition of ferrous sulfate, which

undoubtedly functions as an oxygen arrier, the reaction

is extended over a longer period of time". Several oxygen

carriers were tested to determine their effect on the yield

of quinoline. A series of experiments were tried to de-

termine the most favorable concentration of the agents which

showed the most promise in improving the yield of quinoline.

It was thought that some of the tar left after steam distil-

lation might be converted if the reaction was controlled a

little more.

The first salt added to the reaction mixture to act as

an oxygen carrying agent was manganese dioxide. Three and

one-half grams of manganese dioxide was added to the mix-

ture of four tenths gram mole of aniline, one hundred and

twenty grams of glycerine, four tenths gram mole of nit-

roethane, and sixty milliliters of sulfuric acid (specific gravity 1.83). After heating the mixture for eight hours 28 grams (54 per cent) of quinoline was obtained.

According to the results of Cohn[3] addition of twenty-five grams of boric acid to the mixture containing nitrobenzene and ferrous sulfate, increased the yield of quinoline. After five hours heating Cohn[3] reported a yield of of 38 grams (74 per cent of the theoretical yield) for this boric acid modification compared to 30 grams obtained when ferrous sulfate alone was used. Twenty-five grams of boric acid was added to the glycerine in the usual four tenths gram mole formula using four tenths gram mole of nitroethane as the oxidizing agent. As the sulfuric acid was added more heat than usual was evolved. Considerable tar and charred material were found in the flask after the eight hour heating period. The yield of quinoline was twenty-seven grams (52 per cent). When this experiment was repeated, with ten grams of crystalline ferrous sulfate added to the mixture, the yield of quinoline was thirty grams (58 per cent).

As has already been indicated ferrous sulfate served as a good oxygen carrying agent so various concentrations of iron in both the ferric and ferrous forms were tested

to determine their effect on the yield of quinoline. The
yields of quinoline obtained when varying quantities of
ferric chloride were added to the mixture are listed in
the following table with the percentage yields in parenthesis.

Grams of ferric chloride added to the mixture	Yield of quinoline (grams)
.5 grams	30 (58%)
3.0 grams	32 (62%)
6.0 grams	33, 32, (64, 62%)
12. grams	32, 33, (62, 64%)

The use of ferrous sulfate as an oxygen carrier in this
type of reaction was known to be advantageous so a series of
experiments were made to determine the proper quantity of
ferrous sulfate to add to the reaction mixture. The yield
of quinoline obtained in each case along with the percentage
yield in parenthesis is shown in the following table.

Grams of crystalline ferrous sulfate added to the mixture	Yield of quinoline (grams)
3 grams	29 (56%)
5 grams	33 (64%)
7 grams	35 (68%)
10 grams	34 (68%)
15 grams	34 (66%)
20 grams	34 (66%)

In the experiments in which more than ten grams of ferrous
sulfate was used the quinoline obtained upon the steam dis-

tillation of the alkaline solution was quite yellow in
comparison to the oil collected when less ferrous sulfate
was used. To check the yield on the better preparations
of quinoline, four experiments using ten grams of ferrous
sulfate were compared. The yields from the four experim-
ents were 32, 34, 34, 35 grams (62-68 per cent).

Since the small amount of water in the glycerine made
considerable difference in the yield of quinoline, it was
thought that if water in the crystalline ferrous sulfate
were removed the yield would be increased. The water was
driven out of the salt by heating it in a crucible for
several minutes over a Bunsen burner. Ten grams of the hy-
drated salt was placed in the crucible, heated, and added
to the reaction mixture. The yield from this method was
thirty-three grams (64 per cent). Upon repeating this ex-
periment twice the yields were found to be 32 and 33 grams
respectively. It would be concluded from these results
that dehydration of the crystalline ferrous sulfate had an
effect of decreasing the yield. However, the slightly
less yield was not significant, but the ferrous sulfate
was not dehydrated in the other trial experiments.

4. Variations in the acid.

When data was taken from the various papers published
in this line of research, it was noted that there were con-

siderable differences in the quantity and concentration
of the sulfuric acid employed. In order to study the
effects of varing quantities of acid on the yields of
quinoline a series of experiments were made varying the
quantity of sulfuric acid (specific gravity 1.83) from
twenty milliliters to ninety milliliters. In the follow-
ing table the quantity of acid used and the yield of
quinoline in grams is listed; the percentage yield is in
parenthesis.

Milliliters of sulfuric acid (sp. gr. 1.83) used	Yield of quinoline (grams)
20	8 (15%)
30	20 (39%)
40	26 (50%)
50	29 (56%)
60	34 (66%)
70	33 (64%)
80	10
80	10

In the first two experiments listed in the above table
there was considerable frothing as the solution was heated.
In these cases the quantity of acid added was not enough to
dissolve all of the aniline sulfate formed. In the last two
experiments, 80 and 90 milliliters of acid added, the yields

were less than ten milliliters and so were not collected separately. In these cases the quantity of acid was sufficient to cause considerable charring, and the mixture became black as soon as it was heated.

A stronger acid was prepared by adding fuming sulfuric acid (specific gravity 1.88) to the stock sulfuric acid (specific gravity 1.83). The specific gravity of this acid so prepared was 1.84. When sixty milliliters of this acid was added to the four tenths gram mole aniline solution and the reaction mixture heated for eight hours, the yield of quinoline was 33 grams (64 per cent). In order to compare the yield if more concentrated acid was employed sixty milliliters of the fuming acid (specific gravity 1.88) was added to the mixture and the contents of the flask heated for eight hours. The yield of quinoline was 31 grams (60 per cent). When this fuming acid was dropped on the aniline, glycerine, ferrous sulfate, nitroethane mixture, the heat evolved was more than when the less concentrated acid was employed. In this case there was considerable carbonized material in the flask after the period of heating.

As had been suggested by other investigators it was thought that the acrolein was produced in large quantities at the start of the reaction, and all of it did not react

with the aniline sulfate。 In an effort to overcome this,
the sulfuric acid was added in two portions. In this
series of experiments forty milliliters of acid was added
to the reaction mixture which was then heated for three
hours. After cooling, a second portion of thirty millili-
ters of acid was added and the heating continued for a
total of eight hours. The following table shows the yields
 of quinoline obtained in these experiments by the use of
varying concentrations of acid.

Specific gravity of acid added before heating	Specific gravity of acid added after three hours heating	Yield (Grams)
1.88	1.88	24(46%)
1.83	1.83	25(48%)
1.88	1.83	21(41%)
1.83	1.88	35(68%)

From the data shown here it would be concluded that the
yield of quinoline was markedly affected by both the con-
centration and the quantity of sulfuric acid used.
The yield was not increased enough, if at all by the add-
ition of the acid in smaller portions to justify the in-
creased work in carrying out this experiment.

5. Variation in Glycerine and Aniline.

As has been stated previously it was found that the
U.S.P. glycerine used in this investigation contained
five per cent water. When this water was removed by heat-
ing, the yield of quinoline was increased markedly. Even
though the quantity of glycerine used in the standard pro-
cedure was more than the theoretical quantity needed, two
experiments were carried out to determine the effect on
the yields of quinoline when the quantity of glycerine was
increased. Instead of heating the one hundred and thirty
grams of glycerine before using, a larger quantity of gly-
cerine was heated and used. When one hundred and fifty
grams of heated glycerine was used, thirty grams of quino-
-line (58 per cent of the theoretical yield was obtained.
In the second experiment one hundred and eighty grams of
glycerine was used and the yield was exactly the same.
This experiment was repeated using the larger quantity of
glycerine but instead of sixty milliliters of sulfuric
acid eighty milliliters of the acid (specific gravity 1.83)
was added. The yield of quinoline from this experiment
was only 18 grams (35 per cent).

A trial experiment using less than one hundred and
twenty grams of glycerine was unsuccessful as the foaming
and charring became so bad that the heating was discontinued

and the flask emptied. In order to study the effect of
less glycerine on the reaction, it was decided to increase
the quantity of aniline added. Instead of adding four
tenths gram mole of aniline to the mixture, more aniline
and correspondingly more oxidizing agent, nitroethane,
was used. When five tenths gram mole of aniline was add-
ed and the reaction flask heated for six hours the yield
of quinoline after diazotization and heating was 35 grams
(64 per cent of the theoretical yield). As it was necess-
ary to add considerable sodium nitrite solution before all
of the aniline was diazotized, the reaction mixture con-
taining six tenths gram mole of aniline was heated for a
total of ten hours. The yield of quinoline in this trial
was seventy-four per cent of the theoretical (38 grams).

Manske, Leger, and Gallagher[6] reported that by using
the methods of Cohn[3] and Clark and Davis[2] it was possible
to obtain forty-seven and forty-one grams of quinoline
respectively from 53.5 grams of aniline. "When an equiva-
lent amount of acetanilide was used, the yield of quinoline
was 67 grams by using either procedure".[6] According to
this report the acetylated amine reduced the violence of
the reaction so that the start of the reaction was diffi-
cult to observe. To check the yield of quinoline by the
use of such a modification four tenths gram mole of acet-

anilide (54 grams) was placed in the flask along with the glycerine, ferrous sulfate, and nitroethane. As the acid was added to the mixture very little heat was evolved and the mixture did not become hot enough to boil the nitroethane as was usually the case. A yield of 31 grams of quinoline (60 per cent) was obtained from this experiment after the reaction mixture was heated for seven hours. The experiment was repeated without the ferrous sulfate. Twenty-one grams of quinoline (41 per cent of the theoretical yield) was obtained in this trial. More tar was left in the flask after the steam distillation than in any other experiment.

As had been noted previously in the experiments in which the mixture was heated for six to eight hours with an excess of oxidizing agent, it was necessary to add only a very small quantity of sodium nitrite to obtain the blue color on starch-potassium iodide paper. Two experiments were made in which the mixture was not diazotized but the reaction mixture made alkaline and steam distilled after the eight hour heating period. The product collected by this steam distillation appeared to be all quinoline when it was distilled. However, this product was taken up in dilute acid and the sodium nitrite solution added. Less than five milliliters of this twenty per cent solution was

needed to give the blue color on starch-potassium iodide
paper. After a second steam distillation the quinoline
was again collected and distilled under vacuum. The loss
of product in one case was two grams while in the second
case the loss was four grams. However there was a very
good chance that part of this loss was due to losses in
manipulation and the oil remaining in the distilling
system.

In order to determine whether the diazotization was
necessary a series of duplicate experiments were made in
which one of the mixtures was diazotized, heated to $100^{\circ}C$,
cooled, made alkaline, and steam distilled while the other
flask was made alkaline and steam distilled without diazo-
tization. The total oil was collected by vacuum distilla-
tion and weighed. These results are listed in the follow-
ing table.

Time of Heating (Hours)	Grams of Product No. Diazotization	Grams of Product Diazotization
4	30	24
6	34	35
	32	32
	34	33
8	34	35
	33	33
	34	33

The results in this table showed that it was unnecessary
to diazotize the reaction mixture, for very little or no

unchanged aniline remained in the reaction mixture after the six hour period of heating. In many of the experiments in which this period of heating was used the solution was not diazotized. However, if any oil was collected below 100°C. upon vacuum distillation the total yield of that experiment was dissolved in excess acid, diazotized, and repurified.

An attempt was made to mix the two layers of the reaction mixture and thus to get more intimate contact between the oxidizing agent and the remaining reaction mixture. To accomplish this a three neck two liter round bottom flask was equipped with a stirrer, reflux condenser, and thermometer. The mixture was stirred while the acid was added and throughout the eight hours of heating. The temperature remained below 125°C. during the whole heating period. After diazotization thirty-two grams of quinoline (62 per cent of the theoretical yield) was obtained. This experiment was repeated several times, but this was the best yield obtained.

It appeared that if the system could be put under a small amount of pressure to raise the temperature of the reaction mixture the yields might be improved. It has been noted elsewhere in this paper that the refluxing temperature of the mixture containing nitrobenzene was

slightly higher than the temperature at which the mixture containing nitroparaffins as the oxidizing agent boiled. However, it should be remembered that there was published[7] and patented[8] by a group of Russian scientists a method for the preparation of quinoline in which the pressure was reduced so that the water formed would leave the reaction chamber and condenser but all other refluxing material would be retained. In this work the temperature of the reaction mixture was 150-154 C., and the oxidizing agent was nitrobenzene. The yield of quinoline was reported in this paper as being 85 per cent, but the basis for this calculation was not stated.

6. Addition of Some Salts.

If potassium acid sulfate and other dehydrating agents are heated with fats or glycerine acroelin is produced. Although no mention of such methods was found in the literature, potassium acid sulfate and sodium sulfate were added to the reaction mixture to determine their effect on the yield of quinoline. The results of this series of experiments was not too encouraging, but something along this line might be used to improve the yield of quinoline.

In the first experiments the sodium sulfate was added in place of the ferrous sulfate. In the trial in which

ten grams of the chemically pure salt was added the yield
of quinoline after heating for eight hours was twenty-three
grams (44 per cent yield). When the amount of sodium sul-
fate was doubled, the yield was increased to 52 per cent of
the theoretical yield, twenty-seven grams. Upon repeating
the first trial using ten grams of sodium sulfate and add-
ing ten grams of ferrous sulfate the yield was increased
to 30 grams (58 per cent of the theoretical yield).

The addition of potassium acid sulfate to the react-
ion mixture proved less successful. When ten grams of this
salt was added to the mixture, the yield of quinoline was
twenty-four grams (46 per cent). Doubling the quantity of
the salt reduced the yield to seventeen grams (33 per cent).
Upon cooling the reaction flask in this experiment the black
tarry mass solidified and was very hard to remove from the
flask. A large amount of tar and charred material was left
in the flask after steam distillation. When ten grams of
ferrous sulfate was added along with the ten grams of potass-
ium acid sulfate and the mixture heated for seven hours, the
yield of quinoline was thirty-one grams,(60 per cent).

7. <u>Utilization of the Oxidizing Agent.</u>

It was noticed that when the reaction mixture was
allowed to cool after heating for eight hours a layer of
the unreacted nitroparaffin could be detected above the
heavier black mixture in the flask. An experiment was
performed to determine how much of the nitroethane was
reduced to ethyl amine. After heating for eight hours
the reaction mixture was transferred to a larger flask,
diluted, and made alkaline by introducing the alkali
through a dropping funnel with the flask connected to a
condenser for steam distillation. The distillate and vapor
was collected in a beaker partially filled with distilled
water. A total of 1750 milliliters of distillate was col-
lected. The water was decanted from the heavier quinoline
layer and aliquot portions of this solution titrated to
phenol red neutrality with standard acid. It was neces-
sary to add 30.6, 31.0, and 31.0 milliliters of, .108 nor-
mal acid to three 25 milliliter portions of this solution.
From this it was calculated that there were .15 grams of
ethyl amine in this portion of the solution and 10.5 grams
in the total volume of solution. This corresponded to .23
gram mole of ethyl amine while the yield of quinoline ob-
tained in this experiment, thirty-two grams (62 per cent
of the theoretical yield) represented .25 gram mole of

quinoline.

This was rather strange, for according to the equation for this reaction only one atom of oxygen was needed to oxidize the addition product of aniline and glycerine to quinoline. Therefore, the experiment was repeated with the heating time shortened to five hours in an attempt to minimize the oxidation of any other products in the reaction mixture. In this trial a total of 2250 Milliliters of distillate was collected. It required 21, 21.5, and 21.5 milliliters of the same acid to neutralize three 25 milliliter portions of this solution. Calculation from this data showed that there were .104 grams of ethyl amine in each portion and 9.5 grams in the total distillate. The oil collected in this steam distillation was dissolved in acid, diazotized, and again steam distilled. The quinoline, 29 grams (56 per cent of the theoretical yield), corresponded to .22 gram mole while the ethyl amine represented .21 gram mole. This was a very good check on the first experiment but did not help to explain the high ethyl amine production.

8. Student Laboratory Trial of This Method.

As the time necessary to prepare quinoline in the laboratory by the usual method--use of nitrobenzene as an ox-

idizing agent — was rather long, it was thought that this preparation using nitroethane might be substituted.

This would shorten the preparation time considerably since only one steam distillation was necessary and the diazotization could be omitted when the heating time was from six to eight hours. The following instruction sheet was given to the twenty-one students enrolled in the second course in Organic Chemistry. These students had had considerable laboratory experience in general organic preparations.

A Modification in the Skraup Synthesis of Quinoline.

Weigh 130 to 135 grams of glycerine into a number four evaporating dish and heat it to 210-220°C. After this has cooled to 100-125°C. it is placed in a flask along with 38 grams of aniline, 10 grams of powdered crystalline ferrous sulfate, and 25 grams of nitroethane. After connecting the flask with a reflux water-cooled condenser, add cautiously and with shaking 100 grams of concentrated sulfuric acid in 5 to 10 cc portions. After adding the acid shake the flask until all the solid has dissolved and then heat slowly to boiling. Have a pan of water handy in case the reaction becomes too violent. The mixture should then be heated to refluxing for a total of 6 to 8 hours. It is a good idea to agitate the flask occasionally during this heating period. The flask is then cooled, 500-600 cc of water added, the mixture made distinctly alkaline with concentrated sodium hydroxide while cooled under the tap, and the alkaline solution subjected to steam distillation. It is usually necessary to collect from 800 to 1500 cc. of distillate. Notice the smell of amonia. When all of the oil has been distilled, extract the quinoline from the water with several 25 cc of ether. Dry the ether solution over solid sodium hydroxide. Decant the solution from the drying agent, evaporate the ether at the steam bath, and distill the quinoline through an air condenser. The boiling point of quinoline is 237°C. It is a pale yellow liquid with a disagreeable odor.

Notes.

This is part of a research project on this preparation. It is a somewhat shorter method than the one suggested in the laboratory manual, page 192. We solicit your cooperation by following directions and using the quantities of material suggested. Write all equations for this reaction and record yields in your notebooks.

None of the students reported that it was necessary to use the cooling pan at the outset of the reaction as was usually necessary when nitrobenzene was employed as the oxidizing agent. These students used commercial sulfuric acid rather than the chemically pure acid in the experiment in the laboratory. The specific gravity of the acid in several of the desks was checked and found to be about 1.82.

Twenty of the students reported yields on this experiment; the other person spilled the quinoline before it could be weighed. The poorest yield reported by any student was ten grams (20 per cent), while two students reported yields of 32 grams of quinoline (62 per cent). Eighteen of the twenty students reporting yields obtained more than seventeen grams of quinoline (33 per cent of the theoretical yield). One half of the students (ten) reported more than a forty-eight per cent yield while three students obtained yields of over thirty grams (58 per cent yield).

While the yields in grams obtained by the students in

this laboratory trial of the method were not so high as
when nitrobenzene was used as the oxidizing agent, this
preparation had some advantages. If the calculation of
the percentage yield of quinoline was based on the aniline
--originally added and the aniline formed from the nitro-
benzene not recovered, the percentage yields of the two
methods were not far different. The yields obtained from
the longer method ranged from 30 to 40 grams. These re-
sults represent a 58 to 78 per cent yield when based on
the aniline originally added, but the percentage yield
was reduced to 47-62 if calculated on the basis of five
tenths gram mole of aniline in the reaction mixture.
Many questions were asked concerning the "ammonia" smell
noticed at the beginning of the steam distillation.
This probably helped the students to realize that a re-
duction had taken place during the reaction. The equat-
ions for the reaction explained the "ammonia" noted dur-
ing the steam distillation.

9. Variations in the Order of Adding Ingredients

As the first concentrated sulfuric acid was dropped into the reaction mixture, aniline sulfate was formed and the heat of neutralization was sufficient to heat the entire mixture. It was thought that if the salt was was formed previously and this "local heating" avoided, the yield of quinoline might be improved. The aniline sulfate was prepared by dropping cold sulfuric acid (specific gravity 1.83) on aniline chilled in an ice bath. The salt so formed was collected on a filter and dried.

Duplicate trials were made. In one reaction flask 10 grams of ferrous sulfate was included while in the other this was omitted. Seventy-six grams (.4 gram mole) of aniline sulfate, 30 milliliters of nitroethane, 40 milliliters of sulfuric acid (specific gravity 1.83), and the ferrous sulfate were placed in a one liter round bottom flask. In order to bring all the salt into solution the mixture was heated to 80°C. before the glycerine which had been heated to remove all of the water was added through the water condenser. The temperature of the mixture did not rise as had been expected but was lowered by the addition of the cool glycerine. When all the glycerine had been added, the solution was light orange and exhibited fluorescence.

During the eight hour heating period the solution became darker gradually. Thirty-five grams (68 per cent of the theoretical yield) of quinoline was obtained after diazotization.

In the duplicate trial in which the ferrous sulfate was omitted the yield was 33 grams (64 per cent yield). Time did not allow further investigation into this modification of the method but the above yield (no ferrous sulfate) was the best obtained during the problem. This modification seemed to give as smooth a reaction as when acetanilide was used.

Preparation of Quinoline Derivatives

1. Quinaldines

As these nitroparaffins had proved to be of some value as oxidizing agents in the preparation of quinoline, it was thought that these compounds might be used in the preparation of quinoline derivatives. Quinaldine, 2-methyl quinoline, was one of the first derivatives thought of since in its preparation from acetaldehyde and aniline it was necessary to lose one mole of hydrogen. In one of the early papers Doebner and Miller[12] suggested that nitrobenzene be used as the oxidizing agent. This suggestion was carried out in a later paper[9], but the yield of quinaldine was not recorded in either paper so the effect of the oxidizing agent could not be determined.

Since the nitroparaffin would react with the acetaldehyde, it was decided to mix the other ingredients in the flask, heat the reaction mixture on the water-bath for an hour, add the nitroparaffin, and heat the flask for another hour on the water bath. The proportions of the ingredients were obtained from the paper by Doebner and Miller[9]. In the first trial one part of aniline, 20 grams, and two parts of acetaldehyde, 40 grams, were placed in the small round bottom flask. Forty-five grams of sulfuric acid was added after connecting the flask to the condenser.

Considerable heat was evolved during this addition.
The mixture was heated for an hour on the water-bath
after which 20 grams of nitroethane was added to the
reaction flask and the heating continued for another
hour. After diluting the mixture, enough solution
of sodium nitrite was added to react with the unchanged
aniline. The solution was then heated, made alka-
line, and steam distilled. Very little oil--less than
five milliliters--was collected in a liter of distill-
ate. The quinaldine was reported to boil at 238-9°C.
and distill with steam.[9] Nevertheless, the cooled re-
sidue left after steam distillation was extracted sev-
eral times with chloroform. After the removal of the
chloroform the residue was subjected to vacuum distill-
ation, but no product was obtained when the residue was
heated to 250°C.

This large amount of tar suggested that the re-
action mixture was too concentrated so another trial
was made adding twenty-five milliliters of water to
the ingredients. The yield was no better in this case.
An attempt to use hydrochloric acid with a total heat-
ing time of four hours instead of sulfuric acid was no
more successful. In all cases the aniline had reacted
in some manner, for only a few milliliters of sodium
nitrite were required to diazotize the unreacted aniline.

Since some polymer of acetaldehyde must form in this reaction to yield quinaldine two of the polymers of acetaldehyde, paraldehyde and aldol, were substituted for the acetaldehyde. These gave no better yields. When a trial was made omitting the oxidizing agent, the yield of the oil was little better. The total yield obtained from all these trials was less than twenty milliliters.

As such small amounts of oil were difficult to handle, it was decided to use some aniline derivative which would yield a solid quinaldine for further study along this line. It was found that 6-chloro 2-methyl quinoline, 6- chloroquialdine, was a solid compound and had been prepared by Bartow and McCollum[10] here at Kansas University in 1904.

It was thought that the method for the preparation of this halogen derivative of quinaldine as outlined by Bartow and McCollum[10] would be satisfactory as few methods could be found in the literature. No yields were reported in the original article, but Cocker and Turner[11] reported that from nineteen grams of p-anisidine ten grams of 6-methoxyquinaldine, melting point 64-5°C, was obtained by the use of the method of Bartow and McCollum[10]. This quantity represented 38 per cent of the theoretical yield.

In this method "fifteen grams p-chloraniline,
24 grams of aldehyde, and 10 grams of concentrated
hydrochloric acid were heated on the water-bath for
four hours."[10]   The first trial with the p-chloran-
iline was made using 24 grams of aldol. As the con-
centrated acid was added, the mixture frothed and it
was necessary to cool the reaction flask. Before all
of the acid had been added the mixture became very black
and some tar-like material separated from the solution.
The mixture was then heated for two hours on the water-
bath, fifteen milliliters of nitroethane added, and the
heating continued for a total of four hours. After the
reaction mixture had stood at room temperature overnight,
it was diluted, diazotized, made alkaline and subjected
to steam distillation. A small quantity of oil was
collected which solidified when the distillate was chill-
ed in salt and ice. The melting point of this crude pro-
duct was 91-2°C.

The above reaction was repeated using dilute sul-
furic acid instead of the concentrated hydrochloric acid.
This dilute acid was prepared by adding 12 milliliters of
acid (specific gravity 1.83) to 10 milliliters of water.
In this trial when the acid was added the heat evolved was
sufficient to cause the water in the reaction flask to
boil. After diazotization a few grams

of oil was separated by steam distillation. This dark
yellow oil solidified when cooled. The melting point
of this product was 91-3°C.

As the yields obtained from the use of the aldol
had been only two or three grams in each of the experi-
ments, paraldehyde was substituted for the aldol in two
experiments. In these experiments the acid was added to
the p-chloraniline, the flask cooled and then twenty grams
of paraldehyde added slowly through the condenser. The
reaction mixture was allowed to stand for an hour before
heating during which time the temperature in the flask
rose to about 80°C. After the heating period of four
hours during which the nitroethane was added the mixture
was diazotized, made alkaline, and subjected to steam dis-
tillation. The product solidified in the condenser during
this steam distillation. Four grams of product was obtain-
ed, melting point 91-2°C. A second trial was attempted
using fifteen milliliters of sulfuric acid undiluted.
Then the paraldehyde was added, the solution became
black and frothed over the top of the condenser even
though the reaction flask was in an ice and water bath.
However, when the dilute sulfuric acid (10 ml. of water
and 12 ml. of acid) was used the reaction was not so
violent and the product obtained again solidified in

the condenser during steam distillation. The yield of 6-chloroquinaldine was less in this trial than in the trial in which hydrochloric acid was used.

It was impossible to detect the odor of ehtyl amine during the steam distillation so the nitroethane was not being reduced. It was thought that if 2-nitropropane were substituted for nitroethane the reaction between the nitro-paraffin and the acetaldehyde polymer would be lessened. A trial was made using hydrochloric acid and fifteen milli-liters of 2-nitropropane. The product, five grams, obtain-ed on steam distillation solidified in the condenser and melt-ed at 90-2°C.

Since the polymers of acetaldehyde had not proved to yield satisfactory results in this preparation, it was decided to use the low boiling acetaldehyde itself in an attempt to improve the yields. To the cooled solution of the chloraniline hydrochloride was added with constant shaking twenty grams of acetaldehyde (Niacet). Unless the reaction flask was cooled in an ice and water bath the heat evolved was enough to boil the acetaldehyde out of the top of the water condenser. After all of the aldehyde had been added the flask was allowed to come to room temp-erature after which it was heated in a water bath for two hours, the 2-nitropropane added, and the heating continued for two more hours.

The yields from three such experiments were five, five,
and six grams of dried product respectively. In all cases
the oil solidified in the condenser when steam distilled
and melted at 90-2°C.

The results of this work were rather disappointing.
When the experiment reported by Bartow and McCollum[10] was
repeated omitting the oxidizing agent, the yield of 6-ch-
loroquinaldine was eight grams which represented 37 per
cent of the theoretical yield. This yield was very simi-
lar to the yield of 6-methoxy quinaldine obtained by Cock-
er and Turner[11]. The best yield obtained in any of the
experiments in which nitro-paraffins were added was six
grams of the dry product (28 per cent of the theoretical
yield). From this it would be concluded that the yields
of quinaldines were not improved by the addition of
these nitroparaffin oxidizing agents. If some oxygen
carrier could be found, the yields might be increased.

No excess nitroparaffin could be detected in the
reaction mixture after the heating period. In an effort
to determine any reaction that might have taken place
between 2-nitropropane and paraldehyde ten milliliters
of 2-nitropropane was placed in a beaker with five milli-
liters of concentrated hydrochloric acid and ten grams
of paraldehyde. When the paraldehyde was added the mix-
ture became cool. No noticeable reaction could be det-
ected for twelve hours after which the mixture darkened

and a black gummy mass settled to the bottom of the
beaker. Several attempts to isolate any solid mater-
ial from this viscid black oil were unsuccessful.

The solid obtained from these experiments was deep
orange and sometimes red, though Barton and McCollum[18]
described no such color and reported difficulty in solid-
ifying the oil obtained. After two recrystallizations
from ligroin with treatment by charcoal almost colorless
needles melting at 97-8°C were obtained. In this paper[10]
the melting point was rocorded as being 91°C and the ana-
lysis of 19.95 per cent chlorine (calculated 19.80).
The analysis of the product melting at 97-8°C was made and
is listed here:

	Trial 1	Trial 2
Weight of sample	.1556 gm.	.3145 gm.
Weight of precipitate	.1256 gm.	.2531 gm.
Factor	.2474	.2474
Per cent of Chlorine found	19.96%	19.96%
Per cent of Chlorine calculated	20.04%	19.91%

## 2. Quinolines from Substituted Anilines

Since the use of nitroparaffins had proved to be of little or no value in the synthesis of quinaldines, attempts to use these oxidizing agents in other similar syntheses were forgotten and their use in the preparation of substituted quinolines from substituted anilines was given consideration. All of the quinoline derivatives prepared in this study had been reported previously in the literature, so it was only necessary to prepare the compounds using nitroparaffins as the oxidizing agent and determine the yield in each preparation. In this paper all previous preparations of the compounds are listed at the close of the discussion of the experiment involved.

As nitroethane was found to be the best oxidizing agent in the preparation of quinoline, this nitroparaffin was employed in the preparation of these derivatives. In the cases in which the substituted quinoline could be separated from the reaction mixture by steam distillation, ten grams of crystalline ferrous sulfate was added to the reaction. Two preparations of the substituted quinolines which would distill with steam were carried out at the same time with one reaction mixture including crystalline ferrous sulfate and the other omitting this salt.

The comparison of the yields from these two methods are listed in each preparation. When the substituted quinoline was an oil but would not distill with steam, it was necessary to extract the alkaline solution after diazotization with chloroform, recover the chloroform and purify the product by vacuum distillation. If the product of the synthesis was a solid and would not distill with steam, the solution was diluted after diazotization, cooled in salt and ice, and made alkaline with a cooled sodium hydroxide solution, dried and recrystallized from various solvents. In these cases in which the products were not steam distilled, the ferrous sulfate was omitted from the reaction mix; for it was very difficult to separate the substituted quinoline from the ferrous and ferric hydroxides.

Preparation of 6-chloroquinoline

Reaction.--

$+ C_3H_5(OH)_3$ $\dfrac{H_2 SO_4}{C_2 H_5 NO_2}$
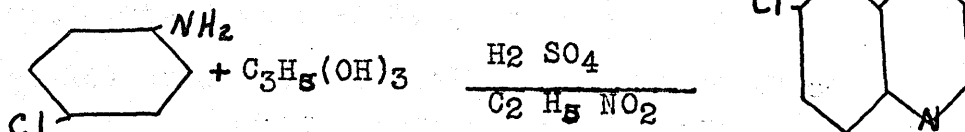
Procedure.--Fifty-one grams of p-chloraniline (.4 gram mole) was placed in a one liter round bottom flask along with 120 grams of glycerine which had been heated to above $200^\circ C$, ten grams of crystalline ferrous sulfate, and thirty grams of nitroethane. After the flask had been connected to a water condenser 60 ml. of sulfuric acid (sp. gr. 1.83) was dropped into the reaction flask.

After all the acid had been added the mixture was heated
for nine hours. Upon cooling the contents of the flask
was emptied into a liter beaker, diluted, cooled, and
diazotized. Approximately ten milliliters of the twenty
per cent sodium nitrite solution was added to react with
the excess amine. The beaker was then placed on the sand
bath overnight. After cooling the solution was diluted,
made alkaline, and subjected to distillation with steam.
A total of two liters of distillate was collected before
the distillate became clear.

The oil was extracted from the distillate with choloro-
form and after removing the chloroform the residue was sub-
jected to vacuum distillation. The light yellow oil collect-
ed 148-151°C at 22 millimeter pressure was chilled in an
ice-bath. The oil solidified and was found to melt at
40-1°C. A total of thirty grams (49 per cent yield) of
this product was obtained in this experiment.

The duplicate experiment in which the oxygen carrier
was omitted yielded 30 grams (46 per cent of the theoretical
yield) of 6-chloroquinoline. Previous trials of this ex-
periment, both with and without the ferrous sulfate but
with shorter periods of heating, had yielded less product-
27 grams (41 per cent yield) and 24 grams (37 per cent
yield) respectively. In an earlier experiment four tenths
gram mole of -p-chloraniline was heated for four hours with

two tenths gram mole of p-nitro chlorobenzene after
which fifteen grams of nitroethane were added and the
heating continued for another four hours. No excess
p-nitro chlorobenzene could be isolated by steam dis-
tilling the acid solution. After diazotization the
yield of 6-chloroquinoline was 55 grams. This re-
presented an 84 per cent yield when based on the original
amine used but 55 per cent on the basis of the total am-
ine present in the reaction. When the acid was added at the
beginning of this reaction it was necessary to use the cool-
ing pan.

The product obtained from these experiments was placed
in one bottle and later a portion of it recrystallized from
ether. The melting point of the colorless needles was
41°C. This 6-chloroquinoline was first prepared by Claus
and Scheller[14] by the method of La Coste[15] in which the
halogenoamine was treated with glycerine and sulfuric
acid using the corresponding halogeno nitro compound as
the oxidizing agent. No yield of the product was record-
ed by Claus and Scheller[14]; they described the product
as "farblosen, glasglanzenden, langen Nadeln" melting at
40-1°C. and boiling at 261-2°C./740 mm. Braun, Grabowski,
and Rawiez[16] prepared this same compound by this method in
order to study its tetrahydroquinoline derivatives. They[16]
report a yield of 260 grams of the product from 300 grams
of p-chloraniline which represented a 70 per cent yield on
the basis of the amine originally used.

Preparation of 8-chloroquinoline

Reaction.--
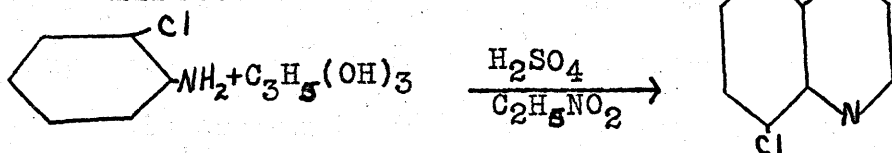
Procedure.--Fifty-one grams of o-chloraniline (.4 gram mole) was placed in the liter flask along with the other ingredients as outlined on page 58. When the acid was dropped into the flask, more heat than usual was evolved. Therefore the acid was added at a slower rate. After heating the mixture for ten hours it was diluted and diazotized. More sodium nitrite than usual was needed to react with the excess amine. Considerable solid material, which on heating formed a tar-like substance, gathered on top of the solution. The alkaline mixture was subjected to steam distillation. Since this oil distilled so slowly, the water layer of the distillate was returned to the flask. After over five liters of water had been collected the distillate became clear. Twenty grams(34 per cent of the theoretical yield) of the 8-chloroquinoline boiling $165-170^{\circ}C/16$ mm. was obtained in this trial.

The duplicate trial containing no ferrous sulfate was diluted after diazotization, made alkaline, and extracted with chloroform. The yield in this trial was

30 grams (46 per cent). In both trials the oil was straw color when freshly distilled but darkened quickly in the air and after a few days on the shelf in a glass stoppered bottle it became brown.

This compound was first prepared by Claus and Scholler.[17] In this report sixteen grams of the thick yellow oil was obtained from twenty-five grams of o-chloraniline. Nitrobenzene was used as the oxidizing agent with the quinoline obtained as a by-product separated by fractional distillation. The boiling point reported in this paper was 288°C with attempts to solidify the oil proving unsuccessful. The reported yield of 16 grams was 49 per cent of the theoretical yield. In an abstract of a Russian paper it was noted that 8-hydroxy quinoline was prepared from 8-chloroquinoline using copper oxide as a catalyst. In this paper it is stated that the chlorine atom in position 8 was more reactive than when in position 6 of the quinoline or in the benzene nucleus.

Preparation of 5,8-dichloroquinoline

Reaction.--
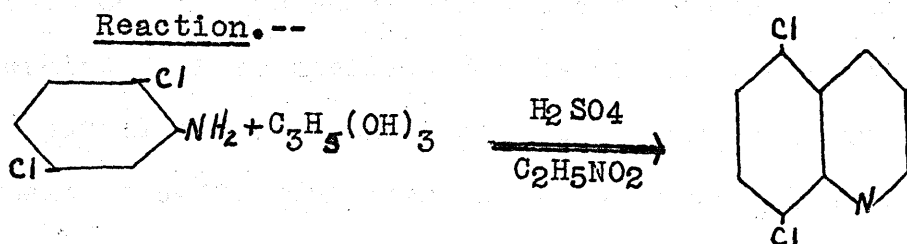
Procedure.--Sixty-five grams (.4 grams mole) of
3,6-dichloraniline was placed in the flask along with
the other ingredients listed on page 58. The mixture
was heated for eight hours. Steam distillation of the
alkaline solution yielded 34 grams (43 per cent yield)
of the solid 5,8-dichloroquinoline which was filtered
from the distillate. The melting point of this crude
solid was 92-3°C. This solid was dissolved in hot
ligroin, treated with charcoal, and filtered from the
chilled solution. Subsequent recrystallization from
ethyl alcohol did not raise the melting point. These
large colorless needles melted at 93-4°C. The duplicate
trial in which no oxygen carrier was used yielded on
steam distillation 27 grams (34 per cent) of the slight-
ly colored solid melting point 92-3°C.

La Coste[15] prepared this compound by heating 3,6-di-
chloraniline with nitrobenzene, glycerine, and sulfuric
acid. No yield was reported but the melting point of the
5, 8-dichloroquinoline was given as 92-3°C after recrystal-
ization from alcohol. Claus and Scholler[17] prepared a
dichloroquinoline by the Sandmeyer reaction from an amino
chloroquinoline whose structure they were trying to det-
ermine. After purification by steam distillation and re-
crystallization from alcohol this compound was found to
melt at 94°C. The crystals were described here[17] as
being colorless, glassy, large needles.

Preparation of 6-bromoquinoline

Reaction.--

$$Br-C_6H_3(NH_2) + C_3H_5(OH)_3 \xrightarrow[C_2H_5NO_2]{H_2SO_4} Br-C_9H_5N$$
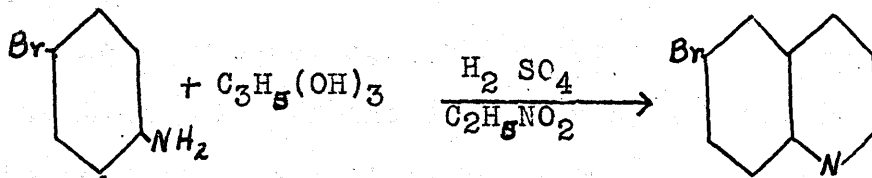
Procedure.--Sixty-nine grams (.4 gram mole) of p-bromaniline was heated for eight hours along with the other ingredients used in this series of experiments. After diazotization the alkaline solution was subjected to steam distillation and the oil which collected rather slowly was extracted from the water as it was returned to the distillation flask. Thirty-nine grams (47 per cent of the theoretical yield) of the pale yellow oil boiling $170\text{-}175^\circ C/15mm$ was collected. The oil solidified upon cooling melted below room temperature. In the duplicate trial in which ferrous sulfate was omitted the alkaline solution was extracted with several portions of chloroform and 32 grams (39 per cent) of 6-bromoquinoline boiling $169\text{-}175^\circ C/15$ mm was collected.

La Coste[15] first prepared 6-bromoquinoline and described its properties. In this paper 86 grams of bromaniline was heated with a corresponding quantity of glycerine, sulfuric acid, and nitrobenzene. The product was purified by steam distillation and fractional distillation. Seventy grams (67 per cent yield) of this

monobromoquinoline boiling at 276-8°C was obtained by
this method. In a later article in which La Coste and
Sorger[18] reported an attempt to synthesize 6-phenyl-
quinoline from 6-bromoquinoline, bromobenzene and sodium,
the melting point of the 6-bromoquinoline was reported
to be 24°C and the boiling point 284°C. Claus and Tor-
nier[19] listed the properties of many salts of this com-
pound but did not record the method of preparation for
the parent compound, 6-bromoquinoline.

Preparation of 8-hydroxy quinoline, quinlinol

Reaction.--
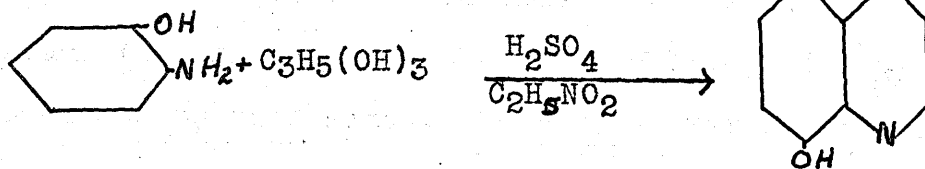
Preparation.--Four tenths gram mole (44 grams) of
o-aminophenol was mixed with the corresponding quant-
ities of glycerine, ferrous sulfate and nitroethane.
As the acid was dropped into the reaction flask the sol-
ution was heated this color changed to black. After a
heating period of eight hours the mixture was diluted
and diazotized. Ten milliliters of the sodium nitrite
solution was added and the beaker was heated to decompose
the diazonium salt. The solution frothed and foamed so
much that it was necessary to transfer the solution to
a larger beaker. Upon cooling the solution was made just

alkaline with sodium hydroxide and then sodium carbonate. To insure neutrality a few milliliters of acetic acid was then added to the solution. Twenty-three grams (40 per cent of the theoretical yield) of the solid was filtered from the distillate. The transfer of the product was rather slow and the solid clogged the condenser repeatedly.

When the ferrous sulfate was omitted from the ingredients the solution did not become purple upon the addition of the sulfuric acid. However, after only a few minutes heating the solution became black. The foaming of the diluted solution after diazotization and during steam distillation was observed in this trial also. Twenty-six grams (45 per cent) of the solid melting 73-5°C. was obtained by this mehod. Recrystallization of the product from alcohol yielded colorless crystals melting at 75-6°C.

This compound, 8-hydroxy quinoline, which is so widely used today was first prepared by Skraup[20]. The original articles could not be read but the melting point was reported to be 73-4°C. Fischer[21] reported the melting point to be 75-6°C. and pointed out that the pure product was white not "rotlich" as had been reported by Skraup[21]. Two years previous to this paper Bedall and Fischer[22] reported a hydroxy quinoline melting 75-6°C. They[22] had obtained this product by

heating the calcium slat of a sulfonate derivative of
quinoline prepared and described by Lubervin [23]. This
must have been 8-hydroxy quinoline prepared from the
corresponding sulfonate derivative. Recently an abstract
appeared in which this method for the preparation of this
compound was said to be used commercially.[24] No yields
were reported. A group of Russian scientists[25] report
good yields of 8-hydroxy quinoline from 8-chloroquinoline
by the action varying concentrations of alkali in the
presence of a copper oxide catalyst[25]. Many papers
and books have been written on this quinoline derivative
but few authors have reported the yields of product ob-
tained in its preparation. Wagner and Simons[26] publish-
ed a method in which the hydrochloride salt of o-amino
phenol was added to glycerine and sulfuric acid with o-
nitro phenol acting as the oxidizing agent. The yields
reported by this method, a proposed student laboratory method,
varied from 50 to 66 per cent based on the o-aminophenol
taken.

Preparation of 6-methoxyquinoline

Reaction.--

$$\text{(p-anisidine)} + C_3H_5(OH)_3 \xrightarrow[C_2H_5NO_2]{H_2SO_4} \text{(6-methoxyquinoline)}$$
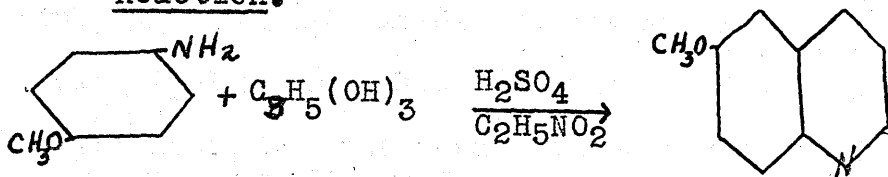
Procedure.--Forty-nine grams of p-anisidine was
treated with glycerine, sulfuric acid, and nitroethane.

After heating the mixture for 9 hours the solution was diluted, diazotized, and heated to decompose the diazonium salt. The alkaline solution was extracted with several portions of chloroform. After recovering the chlorofrom, twenty-eight grams (44 per cent of the theoretical yield) was collected between 175-80°C/25mm. As the boiling point of 6-methoxyquinoline was over 300°C it was found that product distilled very slowly with steam. Therefore, only one trial was made. In this trial no ferrous sulfate was employed.

Skraup[49] first prepared this methoxy derivative by treating 6-hydroxyquinoline with methyl iodide. In two papers the boiling point of this oil was recorded as being 304-5°C/740mm. (193°C./50 mm.). Dobbie and Fox[49] prepared this compound by the same method and found that "the viscous oil obtained when distilled under diminished pressure came over a faintly yellow liquid, which turned dark, not only in contact with the air, but also when kept in closed vessels." The reported boiling point in this paper[49] was 186°C./35 mm. Skraup[49] also prepared this compound from p-anisidine, 4-nitro anisole, glycerine, and sulfuric acid. Decker and Engler[33] used 6- methoxyquinoline in a study of the nitration of quinoline derivatives, but the method of preparation of the starting compound was not given.

Preparation of 6-ethoxyquinoline

Reaction.--
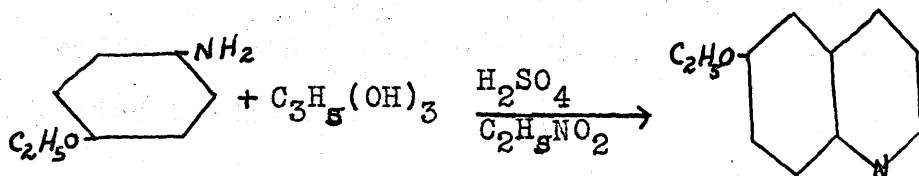
Procedure.--Fifty-five grams (.4 gram mole) of p-phenetidine was mixed with the other ingredients omitting the ferrous sulfate. The mixture was heated for nine hours. When the mixture was diluted a slight odor of ethyl alcohol could be detected. This was unexplainalbe since the starting amine had been distilled before it was used. When the solution was neutralized considerable tar separated from the solution. Sixteen grams (23 per cent of the theoretical yield) of yellow oil boiling $170-5^{\circ}C./20$ mm. was collected. In order to check the yield a second trial was made in which the yield corresponded to 22 per cent of the theoretical yield.

Grimaux[38] reported that the product 6-ethoxyquinoline or quinanisole, obtained by treating p-phenetidine with glycerine and sulfuric acid according to the method of Skraup was a yellow oil boiling with decomposition at $290-2^{\circ}C.$ No yield was reported for the method. This quinoline derivative was prepared by Sonn and Benirschke[52] from p-phenetidine, glycerine, and sulfuric acid. In this report the yield of the 8-ethoxyquinoline was 20 per cent

of the theoretical yield when arsenic acid was used to compare to 53 per cent when nitrobenzene was added to the reaction mixture. The melting point of the hydrochloride of both these products was the same as that reported by Grimaux[38].

Preparation of 8-ethoxy quinoline

Reaction.--
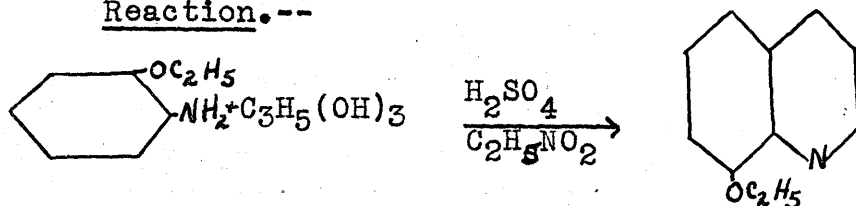
Procedure.-- Two trials in which four tenths gram mole (53 grams) of o-phenetidine were heated for eight hours with nitroethane, glycerine, and sulfuric acid were made. In one trial ferrous sulfate was added while in the other it was omitted. In these preparations as in the previous experiment ethyl alcohol was detected in the mixture after the heating period. Following diazotization and heating the alkaline solution was distilled with steam. Only a small quantity of oil was collected in the distillate. The product from both trials was combined to purify by vacuum distillation. A total of 20 grams (15 per cent of the theoretical yield) of oil was collected between 165 and 170°C. at a pressure of 15 millimeters.

No record could be found in which this compound had been prepared by the Skraup synthesis or any of its

modifications. 8-ethoxyquinoline was first prepared by
Vix[50] by heating the corresponding 8-hydroxy quinoline
with ethyl bromide in ethyl alcohol. The boiling point
reported here[50] was 282-6°C. Fischer[16,39] reported the
preparation of 80 grams of 8-ethoxyquinoline from 100
grams of 8-hydroxy quinoline, alkali, and ethyl bromide.
The heavy yellow oil was found to distill with steam and
boil at 282-6°C./718 mm.

Preparation of 6-phenoxyquinoline

Reaction.--

$$+ C_3H_5(OH)_3 \quad \xrightarrow[C_2H_5NO_2]{H_2SO_4}$$
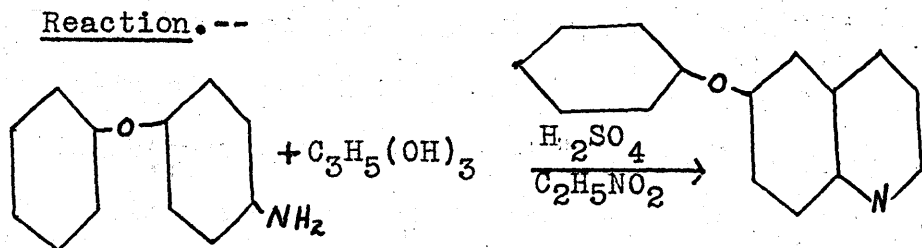
Procedure.--Seventy-four grams (.4 gram mole) of 4-amino diphenyl ether was placed in a one liter round bottom flask with 30 grams of nitroethane and 120 grams of glycerine which had been heated to drive off the water. To this was added dropwise through the water condenser 60 milliliters of sulfuric acid (specific gravity 1.83). The mixture which became dark brown when the acid was added was heated for 8 hours. After cooling, the diluted solution was then made alkaline and extracted several times with chloroform. The chloroform was collected and the residue subjected to vacuum distillation. Twenty-four grams (27 per cent of the theoretical yield) of 6-phenoxyquinoline, a light yellow oil which darkened on standing, was collected. The boiling point of the substance collected was 180-188°C. at 20 millimeter pressure.

An attmept was made to prepare this compound using arsenic acid as the oxidizing agent. Sixty-five grams (35 gram mole) of 4-amino diphenhl ether was heated with 55 grams of 85 per cent arsenic acid, 85 ml.

of glycerine and 60 ml. of sulfuric acid (sp. gr. 1.83).
The mixture was refluxed for 6 hours after which the
very black gummy mixture was filtered by suction. The
tarry residue in the filter was extracted several times
with dilute sulfuric acid and the extractions added to
the filtrate. The total filtrate was made alkaline and
extracted several times with chloroform. After the
chloroform had been recovered the residue was subjected
to vacuum distillation. The fraction 175-185°C./18 mm.
was collected as the desired product. Seventeen grams
(23 per cent of the theoretical yield) of the yellow oil
was collected. This experiment was repeated and the
reaction mixture stirred during the heating period. The
yield of 6-phenoxyquinoline was little better--20 grams
(26 per cent). An attmept to steam distill a small por-
tion of this quinoline proved unsuccessful.

It was thought that this compound could be prepared
by the standard Ullman method[54] from 6-chloroquinoline
and sodium phenolate. In this synthesis 33 grams of
phenol (35 gram mole) and 20 grams of potassium hydro-
xide were heated to 160°C. After cooling the salt, 50
grams (.3 gram mole) of 6-chloroquinoline and one gram
of copper catalyst was added and the mixture heated to
170-5°C. for six hours. The reaction mixture was treated
with alkali to react with any excess phenol and then sub-
jected to steam distillation in order to recover the

unreacted chloroquinoline. Forty-seven grams of
6-chloroquinoline was recovered from the distillate.
This experiment was repeated with the heating temper-
ature raised to 195-200°C. Again almost all of the
6-chloroquinoline was recovered.

La Coste[15] found in studying the reactions of 6-
bromoquinoline that the bromine was not easily removed.
When this compound was heated with sodium ethylate in
an alcohol solution on a water bath no reaction took
place. When the temperature was raised to 160-170°C.
a reaction was noted but the product isolated was not
the 6-ethoxyquinoline but quinoline, indentified by
its double salt with platinum. The equation written
to explain the reaction in that paper was as follows:

$$C_9H_6NBr + C_2H_5ONa \longrightarrow NaBr + C_9H_7N + C_2H_4O.$$
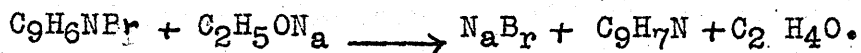
In a more recent abstract[25] the statement was made that
the chlorine atom at position 8 was far more reactive
than when in position 6 of the quinoline or the benzene
nucleus.

The only record of this compound's having been pre-
pared previously was an abstract[27] of a German patent in
which it was listed as one of "the new reagents used."
The only fact stated in this abstract was that of the
boiling point; it was, 170°C./15 mm.

Preparation of 6-methylquinoline

Reaction.--
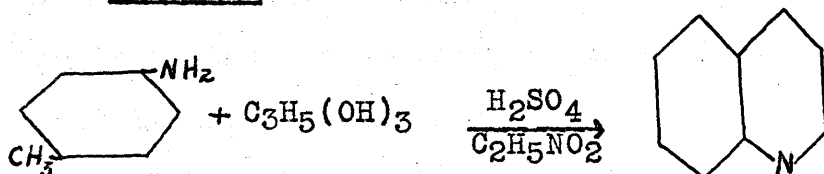
Procedure.-- Forty-three grams (.4 gram mole) of
p-toluidine was heated in a liter flask with the cor-
responding quantities of glycerine, nitroethane, ferr-
ous sulfate and sulfuric acid. The mixture was heat-
ed for 9 hours. Three liters of distillate was collect-
ed before all of the oil had been transferred from the
alkaline solution. Twenty-nine grams (51 per cent of
the theoretical yield) of 6-methylquinoline, a pale
yellow oil, was obtained in this trial. The duplicate
experiment in which the ferrous sulfate was omitted
yielded 27 grams (47 per cent). The fraction collect-
ed as the 6-methylquinoline boiled 138-142°C./12 mm.

In a previous experiment 53 grams of this same
product had been obtained. In this trial four tenths
gram mole (43 grams) of the toluidine was heated with
2. gram mole (275 grams) of p-nitrotoluene for four
hours. The temperature of the reaction mixture was
140-150°C. After cooling the solution, fifteen grams
of nitroethane was added and the mixture heated for
four more hours. No excess nitrotoluene could be

isolated from the final mixture. This yield represented 93 per cent of the theoretical yield on the basis of the p-toluidine originally added or 62 per cent on the basis of the six tenths gram mole of amine actually present in the reaction mixture.

Although the original article was not available, reference by other authors showed that Skraup first prepared 6-methylquinoline and reported its boiling point to be 257.4-258.6°C/745 mm. Baumberger and Wilz[30] reported that "our p-tolylquinoline boiled at 256°C. (715 mm.)." Lellmann and Lippert[29] heated 5 grams of p-toluidine for two hours with 30 grams of glycerine and an equal quantity of sulfuric acid and purified the oil by steam distillation. Many salts of this methylquinoline were prepared but no yields were recorded. Bartow and McCollum[10] extended the use of arsenic oxide as an oxidizing agent to this preparation but recorded no yield of the oil which boiled at 258°C. Druce[28] applied his modification of the use of the stannichloride salts of the amines to the preparation of 6-methylquinoline. He reported a yield of 6.3 grams (70 per cent) of the quinoline from eighteen grams of p-toluidine stannichloride. The boiling point recorded in this paper[28] was 255-7°C.

Preparation of 8-methylquinoline

Reaction.--

$$\text{CH}_3\text{...}\text{NH}_2 + C_3H_5(OH)_3 \xrightarrow[C_2H_5NO_2]{H_2SO_4}$$
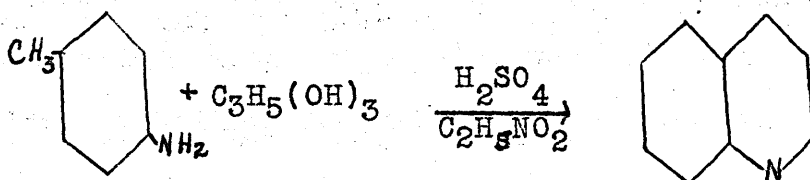
Procedure.--In this set of duplicate experiments 43 grams (.4 gram mole) of o-toluidine was heated with the other ingredients as outlined on 5%. The period of heating was 9 hours. Very little--less than 5 ml--sodium nitrite solution was added to react with the free amine. After steam distillation 33 grams (58 per cent of the theoretical yield), of straw colored oil, 8-methylquinoline, collected at 138-140°C at 8 mm. pressure. In the other trial which included ferrous sulfate the yield was 34 grams (60 per cent). This product as well as most of the other liquid quinoline derivatives became dark after standing on the shelf for a few days.

Knueppel's[31] preparation of 8-methylquinoline was the earliest record available. Skraup[32] prepared this compound by heating o-toluidine, glycerine, and sulfuric acid with o-nitrotoluine as the oxidizing agent. In Knueppel's preparation 50 grams of o-toluidine was treated with 66.5 grams of arsenic acid, 130 grams of sulfuric acid and 140 grams of glycerine. Although no properties of the product were recorded a yield of 65 per cent was claimed.

By using the stannichloride salt of the amine Druce reported a yield of 3 grams (30 per cent), "of a pale yellow oil which had the odor of quinoline, and slowly darkened on keeping for some weeks." One author[32] reported a boiling point of 143 °C./34 mm. for this compound.

Preparation of 7,8-benzoquinoline

Reaction.--

$$+ C_3H_5(OH)_3 \quad \xrightarrow{\frac{H_2SO_4}{C_2H_5NO_2}}$$
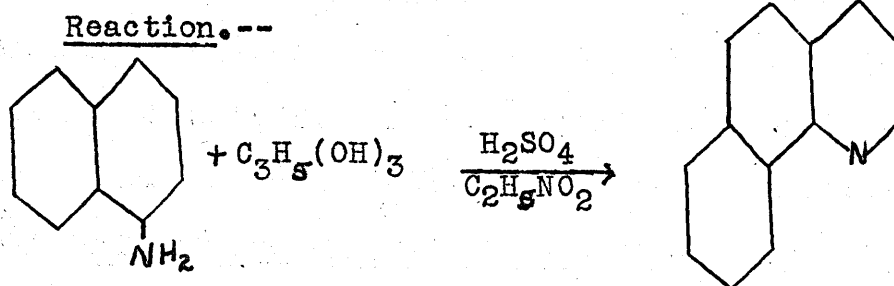
Procedure.--Sixty milliliters of sulfuric acid (specific gravity 1.83) was dropped into the reaction flask containing 57 grams (.4 gram mole) of α-naphyhylamine, 120 grams of glycerine which had been heated, and 30 grams of nitroethane. After heating the mixture for 8 hours the diluted solution was diazotized. The solution was very black and contained considerable black tarry material. When made alkaline and chilled, lavender crystals separated from the solution along with much black tarry material. The melting point of this product was 30-35°C.

Because of this material's low melting point it was very hard to dry. All attempts to purify the impure product by recrystallization proved unsuccessful, so the tarry mass was dissolved in chloroform and subjected to

vacuum distillation. Twenty-three grams (32 per cent
of the theoretical yield) of heavy yellow oil, 7,8,-
benzoquinoline, was collected 195-205°C./15 mm. This
oil solidified when cooled and was found to melt 48-50°C.

In one of the first papers published on quinoline
and its derivatives Skraup[41] reported the preparation of
7,8-benzoquinoline by heating ∝-naphthylamine with sul-
furic acid, glycerine and nitrobenzene. The boiling
point of the product was reported to be 251°C./747 mm.,
Melting point 50°C. Baumberger and Steltenheimer[42] used
the method outlined by Skraup for the preparation of
this compound and reported that upon heating the mix-
ture for five hours the yield from 100 grams of ∝-na-
phthylamine was 25 grams (21 per cent). This product
was reported to have been collected as the distillate
at 330°C. The yellow crystals of this distillate be-
came dark in a few days. Claus and Imhoff[40] heated
∝-naphthylamine with arsenic acid with excess gly-
cerine and sulfuric acid in an oil bath at 150-155°C
for several hours. The yield was not recorded but
the product boiled at 338° (uncorrected) and melted
at 51°C. The authors[40] suggest that the boiling point
reported by Skraup (251°C) must have been a misprint
and should read 351°C. (corrected). Haid[43] repeated
the preparation as recorded by Skraup extending the
heating time to 6-7 hours. The reported yield of

product from 100 grans of α-naphthylamine was 30 grams
(25 per cent of the theoretical yield) which was the
yield recorded by Skraup[41] in the first preparation of
this compound.

Preparation of 5,6-benzoquinoline

Reaction.--


$$+ C_3H_5(OH)_3 \xrightarrow[C_2H_5NO_2]{H_2SO_4}$$
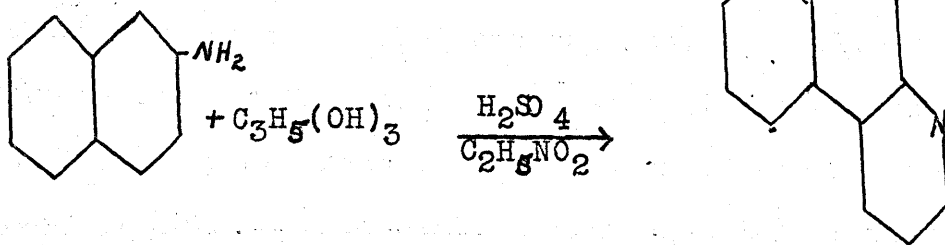
Procedure.--Fifty-seven grams (.4 gram mole) of
β-naphthylamine was heated for eight hours in a liter
round bottom flask with glycerine, sulfuric acid and
nitroethane. After diazotizing, and heating the sol-
ution was cooled and the solid black tar which separa-
ted from the solution was filtered from the solution.
The dark grey solid 5,6-benzoquinoline was collected
by filtering the alkaline solution and dried by the
use of the air blower. The ethyl amine could be de-
tected in the crude precipitate which was light grey
when dry. Fifty-five grams (76 per cent of the the-
oretical yield) of the product melting at 80-5°C was
obtained in this trial.

Ten grams of this material was dissolved in li-
groin and treated with animal charcoal. Nine grams
of slightly pink colored, very fine, needles was

obtained when the orange ligroin solution was cooled. The melting point of these micro crystals of 5,6-benzoquinoline was 92-3°C.

Knueppel[31] reported that he obtained a seventy-five per cent yield of this benzoquinoline by heating 100 grams of β-naphylamine with 215 grams of glycerine, 200 grams of sulfuric acid and 100 grams of arsenic oxide on an oil bath for four hours. He recrystallized the product from ethyl alcohol and reported the melting point of the pure crystals to be 93.5°C. An abstract[53] of a Russian paper reported a yield of 23 parts of 5,6-benzoquinoline from 25 parts of β-naphthylamine using 25 parts of arsenic acid and heating with constant stirring for three hours. This yield represented 72 per cent of the theoretical but no properties of the compound was recorded in the abstract.

Preparation of 6-nitroquinoline

Reaction.--

$$NO_2-\text{(ring)}-NH_2 \quad C_3H_5(OH)_3 \quad \xrightarrow[C_2H_5NO_2]{H_2SO_4} \quad NO_2-\text{(ring)}-N$$
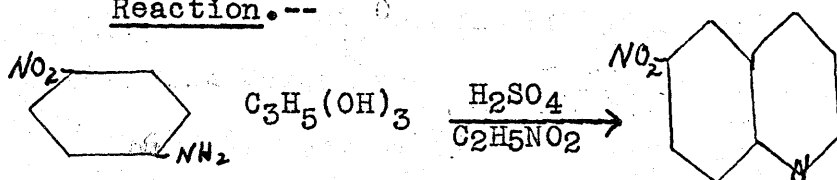
Procedure.--Fifty-five grams (.4 gram mole) of p-nitroaniline, 120 grams of glycerine previously heated to 225°C., and 30 grams of nitroethane were placed in a liter round bottom flask. Sixty milliliters of sulfuric acid (specific gravity 1.83) was dropped onto the reaction mixture through a water condenser. After 8 hours of heating the mixture was diluted, dizaotized, heated to decompose the diazonium salt, and made alkaline. The total mass of solid consisting of 6-nitroquinoline, a black tarry material and some inorganic salts was filtered and dried. The melting point of this crude bulky precipitate was 110-120°C.

To separate the desired product, 6-nitroquinoline, from the undesired products this precipitate was dissoved in hot ethyl alcohol, filtered and reprecipitated by adding water and ice to the alcohol. The light tan thick suspension was filtered. The filtrate so obtained remained cloudy but this material when finally precipitated proved to be a semisolid waxy material melting below 60°C so was discarded. Forty-two grams (60 per cent of the theoretical yield) of the light tan precipitate melting at 245-8°C., was obtained in this experiment. Light orange needles of 6-nitroquinoline

melting 152-3°C., were recovered on a subsequent

recrystallization from hot ligroin.

La Coste[44] recorded no yield of 6-nitroquinoline

in the discussion of its preparation using nitro-

benzene as the oxidizing agent. The colorless fine

crystals obtained from alcohol after boiling with

charcoal melted at 149-50°C. Ninety-eight grams (69

per cent of the theoretical yield) of the product was

obtained from 112 grams of p-nitroaniline by Knueppel[31].

In this experiment arsenic acid was used as the oxidi-

zing agent with an excess of glycerine and sulfuric acid

but no report of any properties of the compound so ob-

tained was recorded.

Preparation of 7-nitroquinoline

Reaction.--

$$O_2N-C_6H_4-NH_2 + C_3H_5(OH)_3 \xrightarrow[C_2H_5NO_2]{H_2SO_4}$$
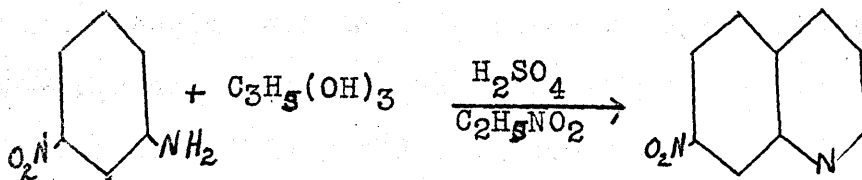
Procedure.--Since para and ortho nitro aniline

had given such good yields of nitroquinolines it was

decided to try m-nitro aniline, though the literature

reported a mixture of compounds was obtained when meta

substituted anilines were employed in the Skraup

synthesis.

Four tenths gram mole (55 grams) of m-nitro aniline was heated for eight hours with 120 grams of glycerine, 30 grams of nitroethane, and 60 milliliters of sulfuric acid (specific gravity 1.83). The solution was diazotized, heated and made alkaline. The alkaline solution was filtered cold collecting a large quantity of black solid material,. This material softened to a semi-solid mass at 40-50°C., melted 100-110°C. and decomposed if heated to 125°C. This material was very hard to dry because of its low softening point. Several extractions of the material with hot ligroin yielded canary yellow needles which melted 105-110°C. After two recrystallizations from ligroin the melting point of these large almost colorless needles of 7-nitroquinoline was 126-8°C. All attempts to use alcohol as a recrystallizing agent failed. Twenty grams of this product was obtained. Much material was lost in these recrystallizations and a large amount of tar was left after the ligroin extractions. This yield corresponded to 29 per cent.

Claus and Stiebel[45] obtained one gram (ten per cent of the theoretical yield) of 7-nitroquinoline upon heating 10 grams of m-nitro aniline with 2.6 grams of sulfuric acid. The product separated "in langen, dunnen, farblosen Nadeln" from ethyl alcohol and melted at

131.5°C. A modification of this method[46] made it possible to obtain better yields and the compound was studied further. It was found that 7-nitroquinoline could be separated from the phenanthroline produced in this reaction by the use of petroleum ether. The melting point recorded in this paper[46] after crystallization of the product from several solvents was 132-4°C. No yield was reported by Knueppel[31] in the preparation of this nitro derivative using arsenic acid as the oxidizing agent. It was stated that it was necessary to separate the phenanthroline, which was also prepared from 7-aminoquinoline, from 7-nitroquinoline by their differences in solubility in petroleum ether.

Decker[47] synthesized this compound by both of the aforementioned methods and purified the 7-nitroquinoline by placing the product in a Soxhlet apparatus and extracting the unused m-nitro aniline and the phenanthroline by-product from the desired product. In this article no physical constants for any of the extraction products were recorded.

Preparation of 8-nitroquinoline

Reaction.--
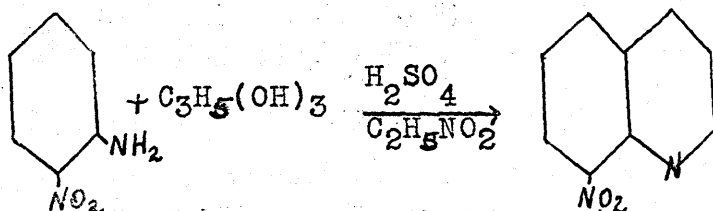
Procedure.--Fifty-five grams (.4 gram mole) of o-nitro aniline was placed in a one liter round bottom flask with 30 grams of nitro ethane and 120 grams of previously heated glycerine. The mixture was then heated for ten hours. The solution was diluted, diazotized, and heated. After cooling, the solid tar which appeared on the top of the solution was discarded and the solution made alkaline with sodium hydroxide. The dark brown precipitate which separated from the alkaline solution was collected at the suction pump. This dried material melted 65-70°C. When this brown material was dissolved in ligroin, treated with charcoal and the ligroin solution chilled light yellow needles separated from the solution. These needles melted 90-1°C. Fifty-four grams (79 per cent of the theoretical yield), of 8- nitroquinoline was obtained in this experiment.

Another synthesis in the paper by La Coste[44] was 8-nitroquinoline from o-nitro aniline, glycerine, sulfuric acid and nitrobenzene. The yield was not reported

but the melting point of the compound obtained was

89°C. Using arsenic oxide as the oxidizing agent,
Knueppel[31] reported an 85 per cent yield of this pro-

duct which he recrystallized from alcohol. Again, no

other physical properties were recorded. Friedlaender[48]

reported this compound when recrystallized from alcohol

melted at 91-2°C.

CHAPTER III

SUMMARY

1. It has been found that the use of nitro-paraffins, now available commercially, as the oxidizing agent in the Skraup synthesis of quinoline produced yields very similar to those obtained by the use of aromatic nitro compounds. In this proposed method the excess nitroparaffin was soluble in an alkaline solution and the product of the reduction, aryl amine, was easily removed by boiling. No violence at the start of the reaction was noted. Laboratory trials of this method were encouraging as one half of the students obtained yields of 48 per cent or better and the time necessary to perform this experiment was shorter than when nitrobenzene was used as the oxidizing agent.

2. The use of these nitroparaffins as oxidizing agents in the synthesis of quinaldines by the general method of Doebner and Miller was not successful. The nitroparaffins reacted with the acetaldehyde, or its polymer, and were not reduced in this reaction.

3. This substitution of nitroparaffins as the oxidizing agent in the Skraup synthesis was applied to several substituted anilines and the yields obtained in most cases were not far different from those reported by other investigators using other oxidizing agents.

This method should prove useful in cases in which the starting products are hard to obtain--the nitro-paraffin could be used as the oxidizing agent.

4. The following table shows the yields of substituted quinolines obtained in this investigation along with the yields reported in the literature. It should be remembered in comparing these yields that the yields reported in the literature are often based on the amine used, not the total amine present in the reaction mixture. The heating periods reported in some cases were longer than used in this study. It was found that the substituted anilines did not react so fast as aniline itself in this reaction.

Derivative of Quinoline	Yield by This Modification	Yield Reported in the Literature	Modification Used to Obtain This Yield
6-chloro	49%* 46%	70%	A [16]
8-chloro	34%* 46%	49%	A [17]
5,8-dichloro	43%* 34%	N. Y. R.	
6-bromo	47%* 39%	67%	A [15]
8-hydroxy	40%* 45%	50%	B [26]
6-methoxy	44%	N. Y. R.	
6-ethoxy	23%	20% 53%	C [52] B [52]
8-ethoxy	15%	N. Y. R.	
6-phenoxy	27%	26%	D
6-methyl	47%* 51%	70%	E [28]
8-methyl	60%* 58%	65%	C [31]
7,8-benzo	32%	21%	A [42]
5,6-benzo	76%	72%	C [53]
6-nitro	60%	69%	C [31]
7-nitro	29%	10%	B [45]
8-nitro	79%	85%	C [31]

A--Nitrobenzene used as the oxidizing agent.
B--Corresponding nitro compound used as oxidizing agent.
C--Arsenic acid used as the oxidizing agent.
D--Reported in this paper using arsenic acid as the oxidizing agent.
E--Obtained by treatment of amine stannichloride with glycerine and sulfuric acid.
*--Crystalline ferrous sulfate used as the oxygen carrier.
N. Y. R.--No yield reported.

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