

PART I

THE OPENING OF PYRIDINE RINGS BY USE OF SODIUM BISULFITE

PART II

THE APPLICATION OF THE BUCHERER REACTION TO 5-AMINO AND  
5-HYDROXY QUINOLINES

By

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School of the University of Maryland in  
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ments for the degree of Doctor  
of Philosophy

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### PART II

#### THE APPLICATION OF THE BUCHERER REACTION TO 5-AMINO AND 5-HYDHOXY QUINOLINES

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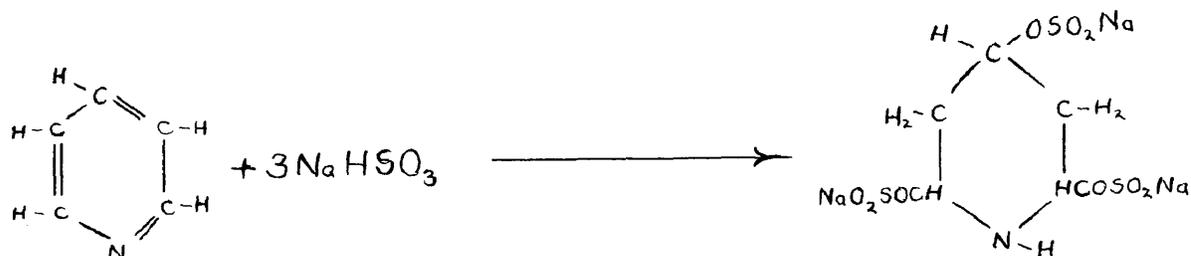
## PART I

### THE OPENING OF PYRIDINE RINGS BY USE OF SODIUM BISULFITE

#### INTRODUCTION

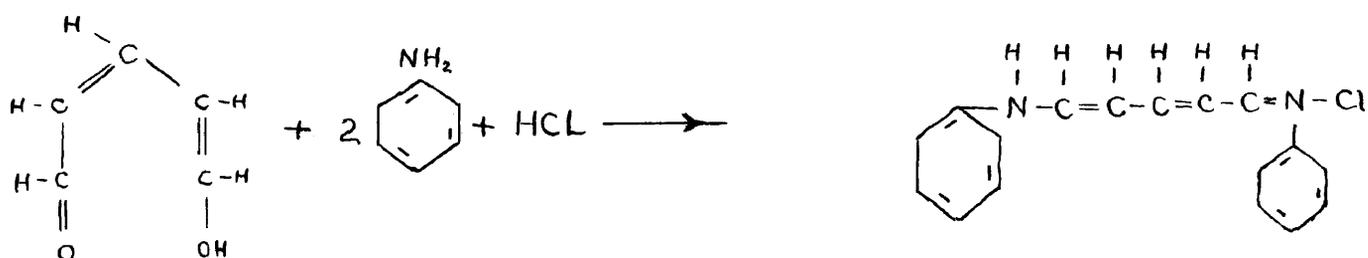
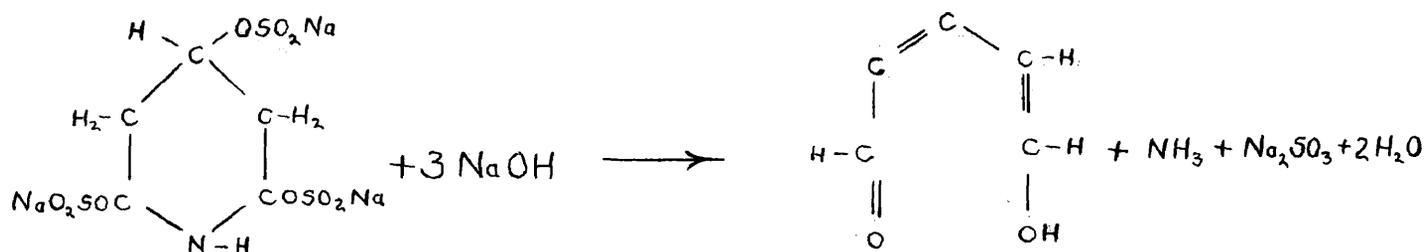
Bucherer and Schenkel were able to decompose pyridine by the use of sodium bisulfite.<sup>1</sup> They heated one part of pyridine with ten parts of a forty per cent sodium bisulfite solution under reflux for twenty-four to thirty hours. At the end of this time, the mixture was homogeneous. If one treats a small sample of the homogeneous mixture with strong sodium hydroxide solution, large quantities of ammonia are given off. Attempts to isolate in the pure state, the pyridine-sodium bisulfite addition product, were very difficult. When the complex was made just acid, and subjected to a steam distillation, it decomposed, giving pyridine and sulfurous acid. Later experiments showed that the intermediate was alcohol insoluble. Purification of the intermediate could be accomplished through precipitation of the excess sulfites and sulfates with an alcoholic solution of a barium salt of such an acid, whose sodium salt is alcohol soluble. This requirement was met by barium iodide. The reaction mixture was carefully neutralized with sodium hydroxide solution, and enough barium iodide added in the cold, to precipitate the sulfites and sulfates. In order to tell if the precipitate is complete, it was necessary to treat the filtrate with barium iodide. Next, the filtrate was evaporated in a vacuum at as low a temperature as possible, and the residue extracted several times with ninety-six per cent alcohol.

When mixed with alkali it turned brown (more quickly by warming), with evolution of ammonia. From his analysis, Bucherer believed that the equation for the formation of the bisulfite intermediate could be represented as follows:

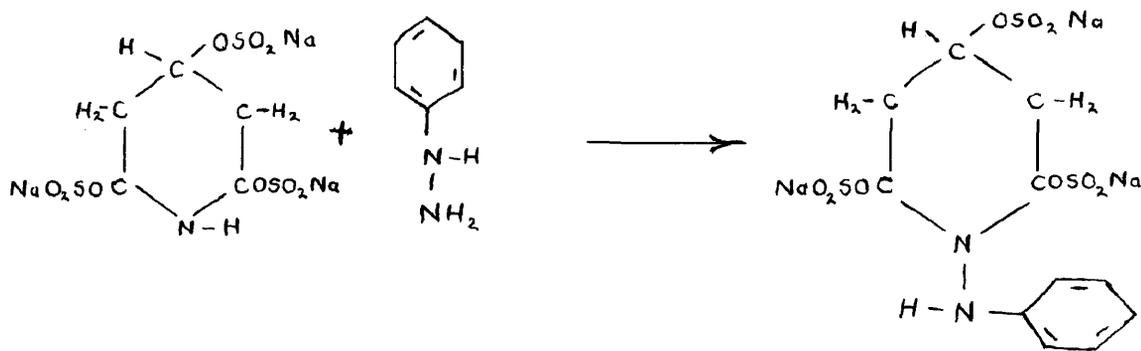


The product formed when this intermediate was treated with sodium hydroxide solution, was not isolated by Bucherer and Schenkel. They believed that the product was a dialdehyde polymer, however.

Later, Schenkel was able to isolate a derivative of the dialdehyde which he and Bucherer had believed to be formed.<sup>2</sup> This was accomplished by heating an aqueous solution of the ester with sodium hydroxide solution until no further ammonia was given off. The sulfite precipitate was filtered off, and aniline added. The mixture was warmed on a water bath and then acidified cautiously with hydrochloric acid. A dianilide precipitated as red needles. Schenkel believed the equations involved could be represented as follows:



Schenkel was also able to prepare a derivative of the pyridine-sodium bisulfite addition product, by allowing this intermediate to react with phenyl hydrazine.<sup>2</sup> His analysis suggests the following equation:



## PART I

## EXPERIMENTAL

## Preparation of a Bisulfite Addition Product of Quinoline

Sulfur dioxide was passed into one hundred fifty-four grams of sodium hydroxide in six hundred grams of water, thus giving one thousand grams of a forty per cent sodium bisulfite solution. To this solution was added one hundred grams of quinoline, purified by a vacuum distillation. The resulting mixture was heated under reflux for five days. Every fifteen hours, a small sample of the reaction mixture was withdrawn and treated with strong caustic solution. At no point, was the odor or a test for ammonia observed. During the period of refluxing, the reaction changed from a reddish yellow one phase system to a light yellow two phase system, with the evolution of sulfur dioxide. Every fifteen hours the reaction mixture was cooled, and sulfur dioxide passed into it for thirty minutes, after which the refluxing was continued. At the end of the five-day reflux, the mixture was cooled and two layers separated. The top layer contained forty-five grams of unreacted material. Hence, approximately fifty-five grams of quinoline reacted. The bottom layer, which was yellow in color, was extracted three times with ether. The ether did not remove the yellow color from this layer. The ether extracts contained no quinoline. The clear yellow aqueous solution was concentrated under partial vacuum, three hundred sixty c.c. of clear liquid being distilled. The distilled liquid was doubt-

lessly sulfur dioxide and water, since no quinoline or ammonia was formed when a sample was heated with sodium hydroxide solution. At this point, the residue liquid became red-yellow in color, probably due to concentration. After a short time, a solid separated from the residual liquid. This solid was collected on a filter and saved for further consideration. Next, the filtrate from the last operation was cooled in an ice-sodium chloride mixture, and the solid fraction which separated was collected as above. The filtrate was next cooled in an ice hydrochloric acid medium. The solid formed was also collected as above. Next, the filtrate from the latest operation was placed in a "dry ice" ethyl alcohol mixture. A solid separated, which was yellow in color. If a sample of this material was heated with sodium hydroxide solution, quinoline was formed. All the other samples above, when heated with sodium hydroxide, gave no ammonia or quinoline. In fact, they seemed to be entirely inorganic in nature.

An attempt was made to free the last-mentioned yellow solid from sodium bisulfite. By analogy to the pyridine complex, it was decided to use barium iodide as a precipitating agent for the sulfite remaining as an impurity in the yellow solid.<sup>1</sup> Therefore, thirteen grams of this substance, dissolved in a small quantity of water, was allowed to react with a solution of barium iodide containing eighteen grams of barium iodide. After standing over night, the mixture was filtered and six grams more of barium iodide added. The mixture from this operation was filtered, the filtrate was then evaporated

in a partial vacuum. The residue thus obtained was extracted with hot alcohol. The solubilities of the yellow substance and barium iodide are so nearly the same, that it was found impossible to separate the yellow substance from barium iodide. Hence, the attempt at purification by use of barium iodide was a failure.

#### Preparation of Barium Iodide

Barium iodide solution was prepared by adding an excess of constant boiling hydrogen iodide solution to a barium hydroxide solution. To get rid of the excess hydrogen iodide, there was added an excess of barium carbonate prepared from barium hydroxide and carbon dioxide.

Next, another batch of quinoline-sodium bisulfite intermediate was made, using the same quantities of reagents as were used above. The only changes in the procedure were as follows: The period of refluxing this time was three days, and the reaction mixture was stirred with a mechanical stirrer. At the end of three days, the reaction mixture was allowed to cool and stood in a well corked flask for three months. Only one phase was observed at the end of this time. The reaction mixture was extracted twice with ether. The ether extract contained no quinoline. The aqueous portion was worked up as follows:

On cooling with ice and hydrochloric acid, a yellow solid precipitated and was filtered. This material, which became

semi-liquid at room temperature, was collected on a filter (Sample I), and the water removed from the filtrate by a vacuum distillation (Sample II). Next, the filtrate from the ice-hydrochloric acid treatment was cooled with a mixture of "dry ice" and ethyl ether. A solid, which we shall call Sample III, was obtained. The filtrate from Sample III was concentrated to one-half its original volume by a distillation under a partial vacuum. The concentrate was cooled with ice and hydrochloric acid, Sample IV being precipitated. The filtrate from Sample IV was cooled with "dry ice" and ethyl ether, Sample V being precipitated. The filtrate from Sample V was concentrated to one-half its original volume and a yellow precipitate, Sample VI, was obtained on cooling with ice. The filtrate from Sample VI was cooled with ice and hydrochloric acid. A precipitate was formed which we shall call Sample VII. The seven different samples listed above were dried in desiccators, and a micro sodium determination run on each sample. 24

#### Results of Sodium Analysis

##### Sample I

|          |                                 |   |
|----------|---------------------------------|---|
| Trial 1. | Weight of sample-               | 4.400 mg.                                   |
|          | Weight of sample after heating- | 4.266 mg.<br>(as $\text{Na}_2\text{Se}_4$ ) |
|          | Sodium in compound-             | 31.14%                                      |
| Trial 2. | Weight of sample-               | 3.462 mg.                                   |
|          | Weight of sample after heating- | 3.3391 mg.                                  |

Sodium in compound- 31.73%

Sample II

Trial 1. Weight of sample- 4.698 mg.  
 Weight of sample after heating- 4.118 mg.  
 Sodium in sample- 28.40%

Trial 2. Weight of sample- 4.274 mg.  
 Weight of sample after heating- 3.698 mg.  
 Sodium in sample- 28.03%

Sample III

Trial 1. Weight of sample- 5.495 mg.  
 Weight of sample after heating- 4.962 mg.  
 Sodium in sample- 29.25%

Trial 2. Weight of sample- 3.865 mg.  
 Weight of sample after heating- 3.487 mg.  
 Sodium in sample- 29.22%

Sample IV

Trial 1. Weight of sample- 5.462 mg.  
 Weight of sample after heating- 4.990 mg.  
 Sodium in sample- 29.60%

Trial 2. Weight of sample- 5.241 mg.  
 Weight of sample after heating- 4.791 mg.  
 Sodium in sample- 29.61%

Sample V

Trial 1. Weight of sample- 3.417 mg.  
 Weight of sample after heating- 1.443 mg.  
 Sodium in compound- 13.68%

Trial 2. Weight of sample- 3.944 mg.  
 Weight of sample after heating- 1.675 mg.

Sodium in sample- 13.67%

Sample VI

Trial 1. Weight of sample- 4.765 mg.  
 Weight of sample after heating- 2.498 mg.  
 Sodium in sample- 16.98%

Trial 2. Weight of sample- 3.058 mg.  
 Weight of sample after heating- 1.606 mg.  
 Sodium in sample- 17.01%

Sample VII

Trial 1. Weight of sample- 4.215 mg.  
 Weight of sample after heating- 1.763 mg.  
 Sodium in sample- 13.55%

Trial 2. Weight of sample- 5.054 mg.  
 Weight of sample after heating- 2.125 mg.  
 Sodium in sample- 13.64%

Sample V was purified in the following way:

Thirty-two and four-tenths grams of the material were dissolved in a small quantity of water, and ninety-five per cent alcohol added until cloudiness just appeared. The water-alcohol solution was now cooled in an ice-hydrochloric acid mixture. Beautiful cream colored crystals were obtained. The results of the sodium analysis are as follows:

Trial 1. Weight of sample- 8.296 mg.  
 Weight of sample after heating- 3.444 mg.  
 Sodium in sample- 13.45%

Trial 2. Weight of sample- 3.590 mg.  
 Weight of sample after heating- 1.505 mg.

Sodium in sample- 13.60%

Sample VII was crystallized in a manner similar to Sample V. Sample VII, after several crystallizations, gave a sodium analysis practically identical to that given above for Sample V.

Sample VI was also crystallized in a manner similar to Sample V. The precipitate thus formed gave an ash analysis almost identical with that of Sample V. The solid material obtained by evaporation of the filtrate, gave an ash analysis as follows:

Trial 1. Weight of sample- 5.020 mg.  
 Weight of sample after heating- 4.767 mg.  
 Sodium in sample- 30.90%

Trial 2. Weight of sample- 5.230 mg.  
 Weight of sample after heating- 4.928 mg.  
 Sodium in sample- 30.50%

Theory:

Sodium in sodium bisulfite- 22.1%  
 Sodium in sodium sulfite- 32.4%  
 Sodium in quinoline + 2 moles sodium bisulfite- 13.65%  
 Sodium in quinoline + 1 mole sodium bisulfite- 9.8%

#### Results of Nitrogen (Dumas) Analysis

Sample V.

Trial 1. Weight of sample- 5.712 mg.

Pressure- 29.9 inches of mercury

Temperature- 21° C.

Volume of gas- .192 c.c.

Nitrogen in sample- 3.81%

Trial 2. Weight of sample- 11.65 mg.

Pressure- 29.9 inches of mercury

Temperature- 21.4° C.

Volume of gas- .381 c.c.

Nitrogen in sample- 3.75%

#### Theory:

Quinoline + 2 moles of sodium bisulfite- 4.10% N<sub>2</sub>.

#### Treatment of the Quinoline-Sodium Bisulfite Compound with Sodium Hydroxide Solution

Two grams of the intermediate dissolved in twenty c.c. of water were refluxed for thirty minutes with eighty-eight hundredths grams of sodium hydroxide. Then the mixture was cooled and extracted with ether. Both the ether extract and the aqueous layer were made acid with hydrochloric acid. A white solid mass was isolated from the ether extract. This material was identified as quinoline hydrochloride. During the refluxing of the intermediate with sodium hydroxide, no ammonia was given off.

In an effort to prove that quinoline was the only organic product formed in the above reaction, both reactants and pred-

ucts were weighed on a rough analytical balance.

Data:

Weight of intermediate taken- 2.00 grams

Weight of sodium hydroxide (C.P.)- 0.88 grams

0.88 grams sodium hydroxide = 1.28 grams sodium chloride

2 grams of intermediate should give 0.912 grams sodium  
chloride

Total sodium chloride (theory)- 2.19 grams

Weight of quineline hydrochloride obtained- .48 grams

Weight of sodium chloride obtained- 2.10 grams

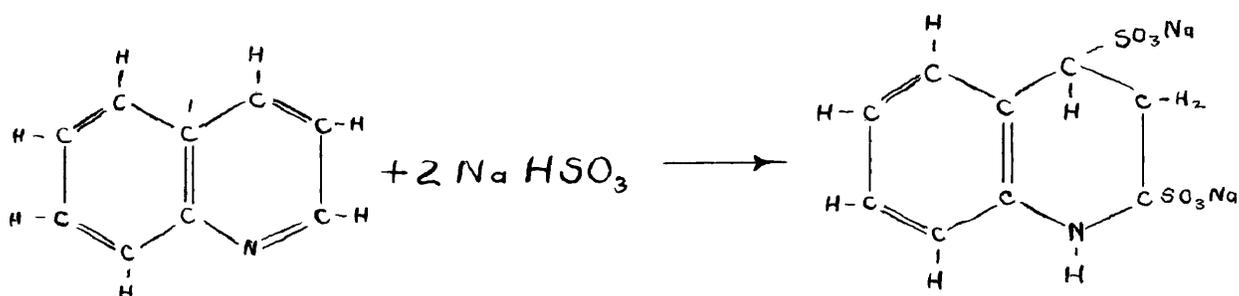
## PART I

## DISCUSSION OF EXPERIMENTAL RESULTS

Bucherer and Schenkel were able to prepare a compound containing one mole of pyridine to three moles of sodium bisulfite, by heating pyridine and sodium bisulfite solution.<sup>1</sup> When this material was treated with sodium hydroxide solution, large quantities of ammonia were given off. Later, Schenkel was able to isolate a derivative of the aldehyde, from the reaction mixture.<sup>2</sup>

The purpose of this investigation was to apply this reaction to quinoline. Therefore, a mixture of quinoline and sodium bisulfite were heated under reflux for several days. From the reaction mixture, was isolated a mixture of inorganic salts and a quinoline-containing material. It was very difficult to separate the inorganic salts from the quinoline sodium bisulfite intermediate, because of their great similarity in solubilities. Barium iodide was used as the salt to precipitate the excess sulfite, because it was hoped that it would be possible to extract the residual sodium iodide and excess barium iodide by use of alcohol- just as Bucherer was able to do in case of the pyridine sodium bisulfite intermediate.<sup>1</sup> It was found, however, that the quinoline sodium bisulfite intermediate was too soluble in alcohol to make this separation possible. The quinoline-sodium bisulfite intermediate was purified by crystallizing from water the various fractions frozen out of the reaction mixture. By running sodium analyses, one was able to ascertain which fractions were rich in inter-

mediate product, and which ones were chiefly sodium bisulfite and sodium sulfite. After a number of crystallizations, a sample was obtained which was analyzed for one mole of quinoline to two moles of sodium bisulfite. Doubtlessly the intermediate was somewhat impure, since the nitrogen analysis was not as good as it should have been. The equation for the reaction may be represented as follows:



When the quinoline sodium bisulfite intermediate was treated with sodium hydroxide solution, the quinoline ring did not break as expected, but instead, quinoline was regenerated.

## PART I

## SUMMARY

1. An intermediate containing one mole of quinoline to two moles of sodium bisulfite, was obtained by heating a mixture of quinoline and sodium bisulfite solution.

2. When this material is heated with sodium hydroxide solution, quinoline is formed. No ammonia is formed.

## PART II

THE APPLICATION OF THE BUCHERER REACTION  
TO 5 AMINO AND 5 HYDROXY QUINOLINES

## INTRODUCTION

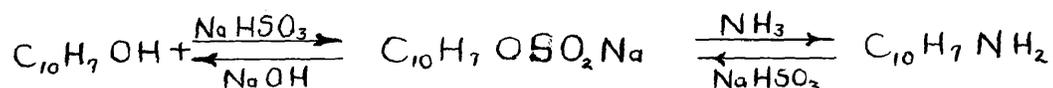
The Bucherer Reaction is a reaction involving the use of ammonium bisulfite plus excess ammonia in the conversion of a phenolic substance into an amine. The reaction is reversible, hence it is possible to use this reaction for the conversion of aromatic amines into the corresponding phenols. One may use primary or secondary aliphatic or aromatic amines and a bisulfite in the place of ammonium bisulfite. In this case one obtains either a secondary or tertiary amine, depending upon the amine used.

Bucherer was not the first person to use a sulfite as a catalyst in amination reactions. The first information concerning this reaction is found in a patent issued to von R. Lepetit in 1899.<sup>5</sup> Lepetit found that by boiling naphthionic acid for a long time with a concentrated solution of sodium bisulfite, adding dilute hydrochloric acid to decompose the excess bisulfite, and finally adding sodium hydroxide solution, ammonia is evolved, and a good yield of alpha naphthol sulfonic acid is produced. Several years later, similar reactions (involving 1-naphthylamine-7-sulfonic acid, 1, 8 amino-naphthol-4-sulfonic acid, etc.) were patented by a German dye company. It was not until several years later, that Bucherer began to work with the reaction. The reaction

should be considered largely Bucherer's, because he and his students did most of the early work on the reaction. It was Bucherer who showed that the reaction was reversible.<sup>4</sup> Perhaps the reaction should be called the Lepetit-Bucherer Reaction.

The Bucherer Reaction has a great commercial use in the dye industry. It offers an easy method for the preparation of beta-naphthyl amine. It is also possible to make various carbazoles by use of the Bucherer Reaction.

Bucherer and his students developed a mechanism by which the reaction was supposed to take place.<sup>5</sup> Bucherer's mechanism has been discarded for one more nearly in accord with the facts. It did serve as a very useful working hypothesis, however. According to Bucherer, the naphthol or naphthyl amine first reacts with the bisulfite to give a naphthyl sulfurous acid ester moderately stable in dilute mineral acids; that with an alkali it would saponify readily; and with ammonia would be transformed into naphthyl amine. The reaction may be represented as follows:

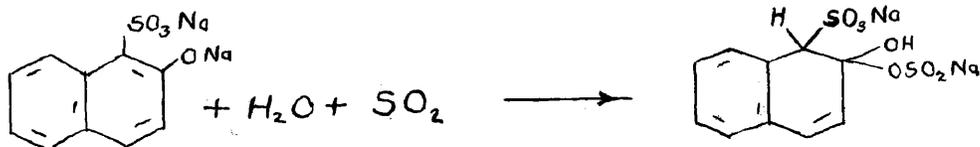


The experimental evidence for the above mechanism is not very good. Bucherer was not fortunate enough to isolate the addition product in a form pure enough for a good analysis.

Bucherer's sulfurous ester intermediate did not behave as a



alcohol and then dried carefully at 100° C. The reaction may be represented by the following equation:



Woroshtzew's analysis is as follows:

|          |       |    |      |    |       |     |       |
|----------|-------|----|------|----|-------|-----|-------|
| Found %C | 34.61 | %H | 2.73 | %S | 18.41 | %Na | 12.88 |
|          | 34.43 |    | 2.69 |    |       |     |       |

Calculated for the addition product,  $\text{C}_{10}\text{H}_9\text{S}_2\text{O}_7\text{Na}_2$  :

|    |       |    |     |    |       |     |       |
|----|-------|----|-----|----|-------|-----|-------|
| %C | 34.26 | %H | 2.3 | %S | 18.32 | %Na | 13.13 |
|----|-------|----|-----|----|-------|-----|-------|

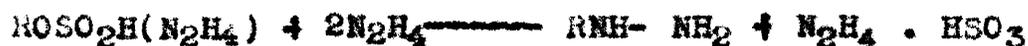
Calculated for the sulfurous acid ester,  $\text{C}_{10}\text{H}_6\text{S}_2\text{O}_6\text{Na}_2$

|    |       |    |      |    |       |     |       |
|----|-------|----|------|----|-------|-----|-------|
| %C | 36.12 | %H | 1.81 | %S | 19.31 | %Na | 13.85 |
|----|-------|----|------|----|-------|-----|-------|

From the data given, it is obvious that the true intermediate is that given above. The above intermediate is by no means the only one of its kind ever isolated. A number of such intermediates have been isolated. Fuchs and his students isolated the bisulfite addition product of 2,7-dihydroxynaphthalene,<sup>6</sup> They found that by passing dry ammonia over the addition product contained in a combustion tube at 100°C., one was able to substitute an amine group for the hydroxy group in the bisulfite addition product. They used a U-tube charged with solid potassium hydroxide to collect the water set free. The reaction may be represented by the following equation:

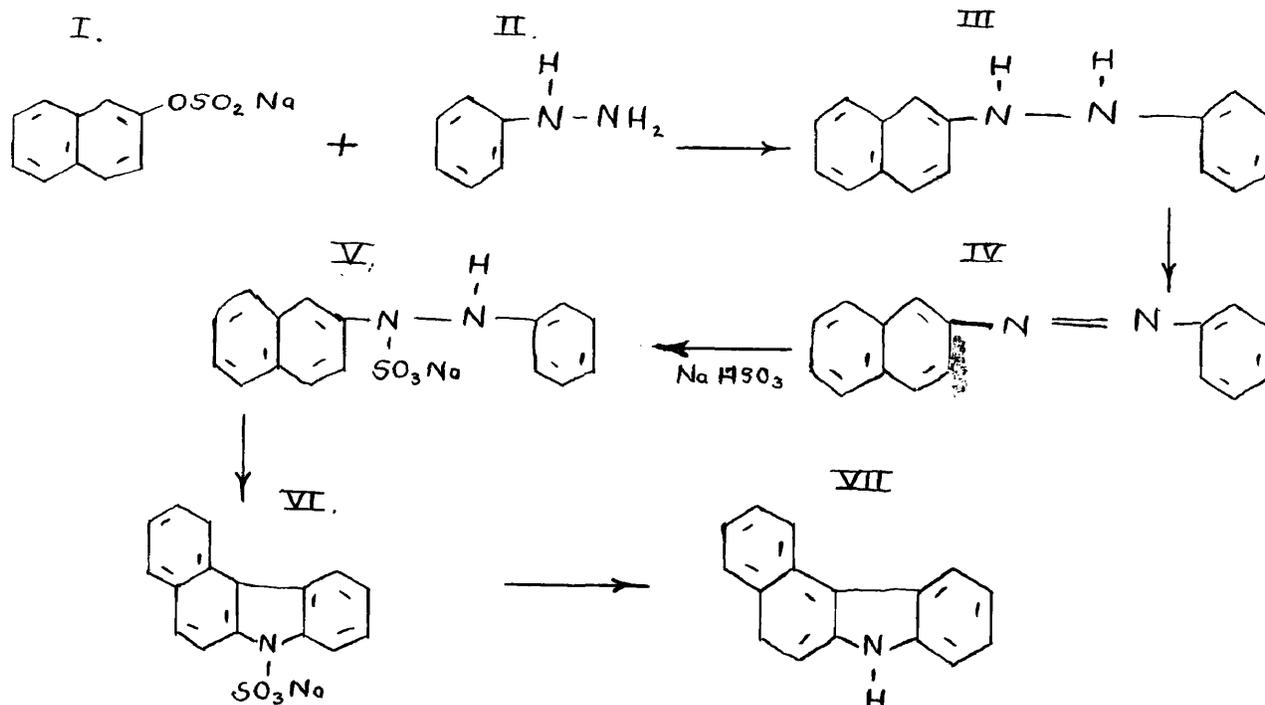


alpha-naphthol, hydrazine sulfite (excess), and hydrazine hydrate for a long time under reflux.<sup>9</sup> He was unable to isolate alpha-naphthylhydrazine in the pure form; he was able to isolate the hydrazine as a hydrazene, however. Franzen was able to obtain 2,3-naphthyldihydrazine from 2,3-dihydroxynaphthalene, hydrazine sulfite, and hydrazine hydrate. According to Franzen, the formation of hydrazines by the Bucherer Reaction may be represented by the following equations:



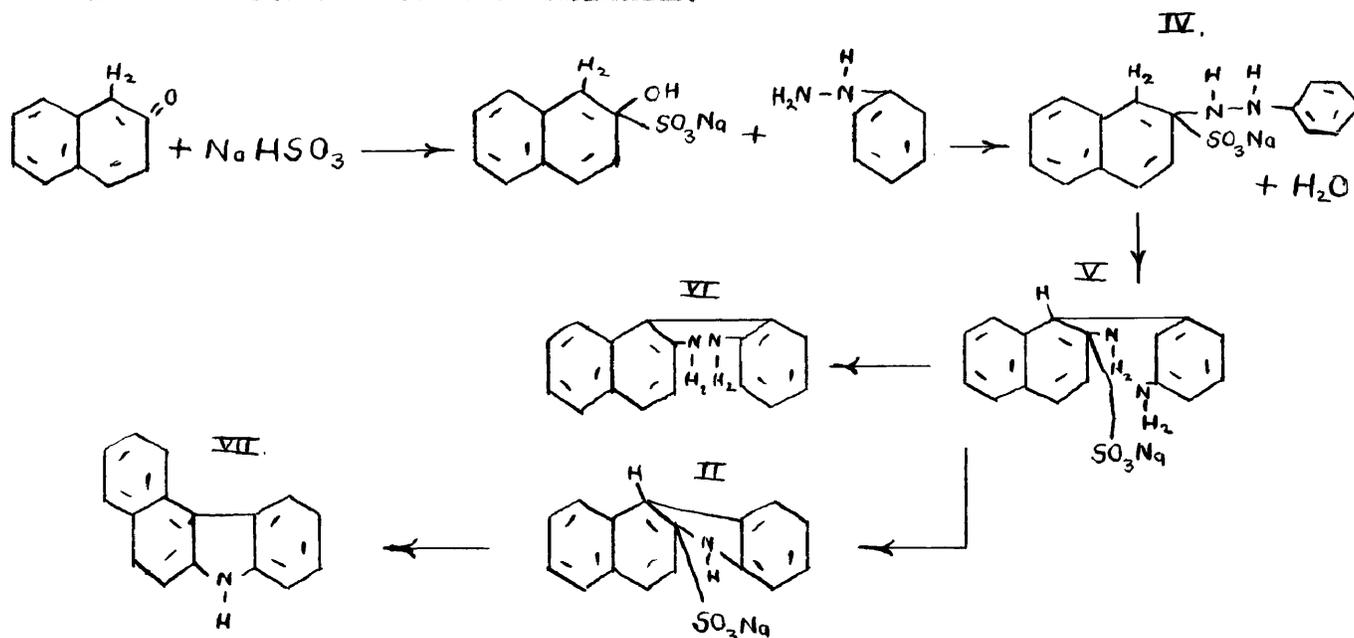
However, later work has shown that this mechanism is probably incorrect. The chief difficulty in the preparation of hydrazines by the Bucherer Reaction, is that the hydrazine formed also reacts with bisulfite, giving a carbazole.

Bucherer and his students suggested a mechanism by which carbazoles may be produced by the Bucherer Reaction.<sup>10</sup> The following equations illustrate Bucherer's mechanism:

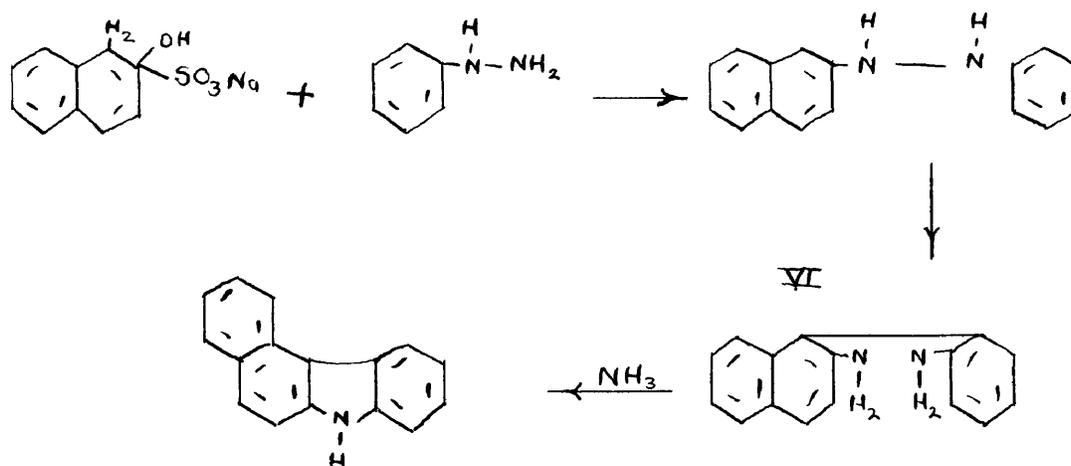




formation through use of the Bucherer reaction. The equations below illustrate Fuch's mechanism:



The reaction may also occur as follows:

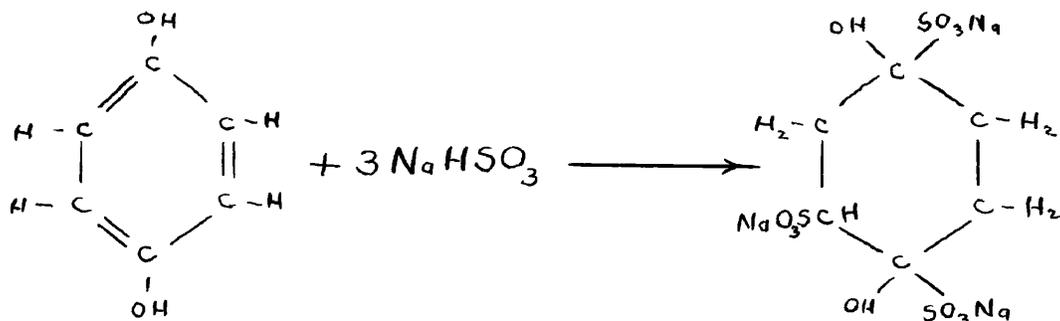


Compound II was isolated by Friedländer. A small quantity of VI was isolated by Fuchs in the preparation of the carbazole. Fuchs was able to make the carbazole by heating for two and one-half hours, a solution of this diamine saturated with

sulfur dioxide. The yield is reported to be eighty-nine per cent that of theory.

Let us now consider the conditions under which the Bucherer Reaction takes place. The reaction is carried out in the liquid phase (water solution), and usually a large excess of bisulfite is added. The time and conditions vary with the particular reaction in question. Some of the reactions must be carried out in a sealed tube. It is not necessary to isolate the bisulfite addition product in the reaction. The yield of product will depend upon the substances used in the reaction, and most of the yields are reported as being good. It is usually easier to convert an aromatic amine into a phenol, than it is to convert a phenol into an amine. Very often the latter requires a sealed tube reaction.

There is no mention of a Bucherer Reaction being carried out with phenol. However, dihydroxybenzenes do react with sodium bisulfite. It was found that when ten grams of hydroquinone and one hundred grams of forty per cent sodium bisulfite solution, were heated under reflux for five to eight days, a colorless solid separated from the reaction mixture.<sup>13</sup> From the analysis, one learns that the solid is a compound containing three sodium bisulfite molecules to one molecule of hydroquinone. Fuchs states that the compound is formed by the following reaction:



Fuchs oxidized the free acid derivative of the bisulfite complex listed above. He obtained oxalic, maleic, and succinic acids. This is further evidence that the above formula is the true formula. Similar results were obtained when other dihydroxy benzenes were used. The addition product was not treated with ammonia to give the corresponding diamine, for Fuchs was interested in studying the tautomerism of phenols, not amination reactions.

With diamine naphthalenes and sodium bisulfite, the main reaction consists in the conversion of one amine group into the sulfite intermediate. Thus, 1,8-diaminenaphthalene gives the sulfite addition product of 8-amine- $\alpha$ -naphthol which can be converted into 8-amine- $\alpha$ -naphthol. In case of the 1,5-diaminenaphthalene, the main product is 5-amine- $\alpha$ -naphthol sulfite, which gives on hydrolysis, 5-amine- $\alpha$ -naphthol. Small quantities of 1,5-dihydroxynaphthalene are

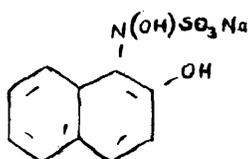
also formed in the reaction.

Let us now consider the effect of sulfonic acid groups on the comparative ease with which the Bucherer Reaction takes place.<sup>14</sup> For all practical purposes, a sulfonic acid group substituted in a ring which does not contain the hydroxyl group, has no effect on the speed of the reaction. Substitution in the para position increases the ease of the reaction; substitution in the meta position decreases the speed of the reaction. The nature of the amine used also has an effect on the speed of the reaction. For example, para-phenylenediamine and para-anisidine react easier than does aniline.<sup>15</sup>

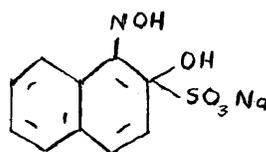
If one treats 2-hydroxy-3-naphthoic acid with ammonia and ammonium sulfite, beta-naphthol is formed.<sup>16</sup> At first glance, one would think it unusual that the compound mentioned above should lose carbon dioxide. However, if one considers the "keto" mechanism for the Bucherer Reaction, one can see that it is possible to consider 2-hydroxy-3-naphthoic acid as a beta-keto-acid. Beta-ketoacids lose carbon dioxide readily. Hence, one would expect this compound to lose carbon dioxide.

Weroshtzew and Bagdanow applied the Bucherer Reaction to certain nitroso naphthols.<sup>17</sup> They report that 1-nitroso-beta-naphthol unites with sodium hydrogen sulfite to give an intermediate which has an empirical formula of  $C_{10}H_8O_5NSNa$ . This does not agree with Bucherer's mechanism. Weroshtzew states that this intermediate has one of the two possibilities listed below:

I.



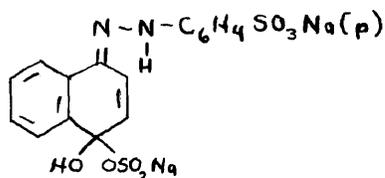
II



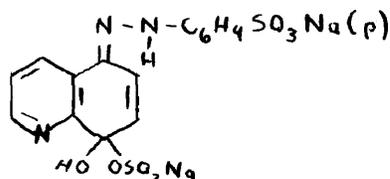
Now the N-methyl ether of 1-nitroso-beta-naphthol reacts with sodium bisulfite to give an addition product that has properties quite similar to that formed from 1-nitroso-beta-naphthol. From this it seems that the nitroso compound reacts in the quinone-exime form, and II is the correct intermediate. When 4-and 2-nitroso-alpha-naphthols were treated with sodium bisulfite, only the 4-nitroso-alpha-naphthol gave the addition product. Ability to add sodium bisulfite is found only in those azo, nitroso, and sulfenic acid derivatives of naphthols in which the groups occupy positions one, while the hydroxyl group is in position two or four. Naphthol derivatives, in which the azo, sulfenic acid, or nitroso group is in position 2, while the hydroxyl derivative is in position one, do not add hydrogen sulfite.

Weroshtzow and Kogan have applied the Bucherer Reaction<sup>18</sup> to hydroxyquinolines. They compared the similar properties of the two following bisulfite intermediates:

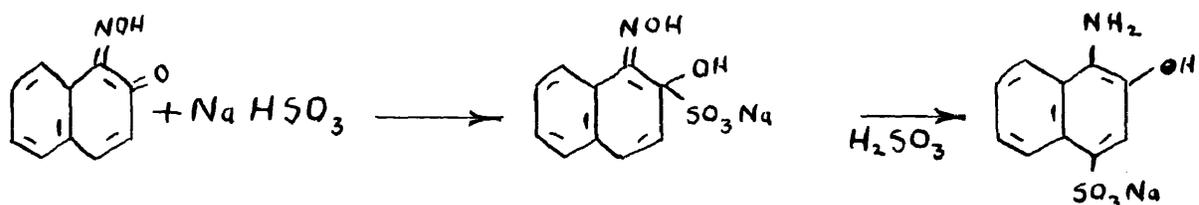
I.



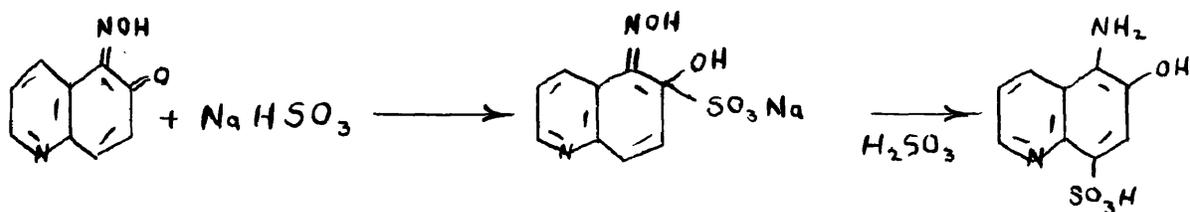
II



They found that the hydroxyquinoline derivative acted similar to the corresponding naphthol derivative. For example, hydrogen ions increased its stability; hydroxyl ions increased its decomposition; the extent of dissociation increased on dilution. Kogan compared the properties of 5-nitroso-6-hydroxyquinoline with those of 1-nitroso-beta-naphthol. Now, 1-nitroso-beta-naphthol reacts with sodium bisulfite according to the following equation:

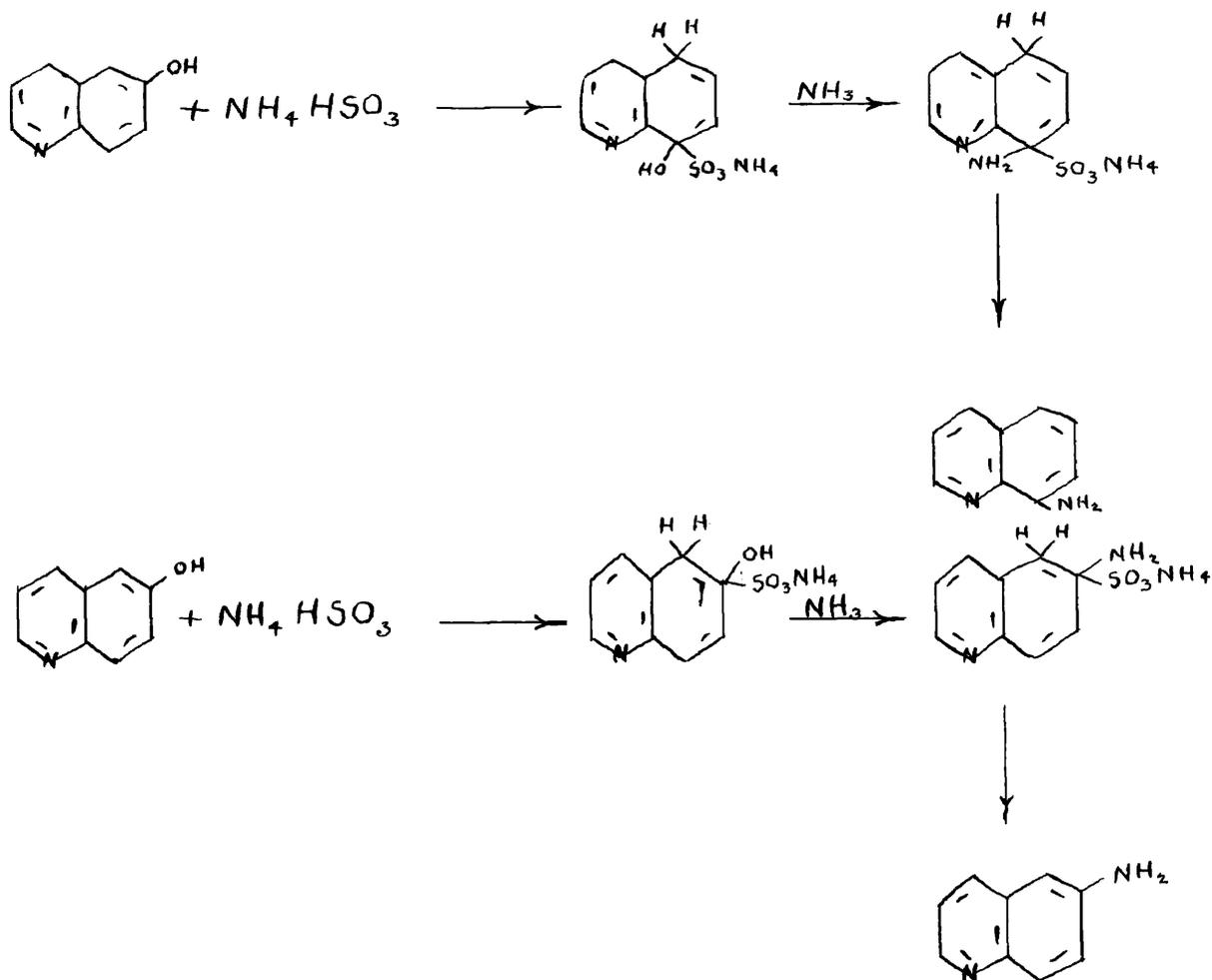


Kogan showed that the following similar reaction occurred for quinoline derivatives:<sup>19</sup>



Shreshtzew and Kogan applied the Bucherer Reaction to 6- and 8-hydroxyquinoline. They heated thirty grams of 8-hydroxyquinoline, one hundred and twenty grams of ammonium sulfite solution (from thirty grams twenty per cent ammonia and sulfur dioxide), and forty grams of twenty per cent ammonia in an autoclave at 150° C. for six to seven hours. On

working up the reaction mixture, twenty-six and four-tenths grams of 8-aminequinoline were obtained. 6-aminequinoline and 8-aminequinoline-5-sulfenic acid were prepared under similar conditions. The reactions may be represented by the following equations:



## PART II

## EXPERIMENTAL

## Preparation of 5-Nitroquinoline

To fifty grams of quinoline (purified by a vacuum distillation) in a porcelain evaporating dish cooled by cold water, was added gradually from a burette sixteen and five-tenths c.c. of fuming nitric acid (sp. g. 1.5).<sup>21</sup> When cold, the solid cake of nitrate was roughly powdered, and added in five portions to fifty c.c. of concentrated sulfuric acid contained in a liter flask; ten c.c. of fuming sulfuric acid (sp. g. 1.7) was added after each addition of nitrate, keeping the mixture cold at all times. The completion of the reaction was recognized by diluting a few drops of the mixture with water, and neutralizing with caustic soda. When the odor of the quinoline no longer existed, the reaction was considered complete. The entire reaction mixture was then poured into two liters of water, cooled and filtered from a small quantity of yellow crystalline material, and then gradually neutralized with sodium hydroxide solution. The precipitate formed was collected and crystallized twice from dilute nitric acid (twenty c.c. concentrated nitric acid to two hundred and forty c.c. of water). This process separated the 5-nitro compound from the 8-nitro compound.

The nitrate of the 5-nitro compound was mixed with water, and caustic soda was added until the mixture was decidedly basic. The mixture was then boiled until it remained basic to

litmus paper. The 5-nitre compound was then filtered, dried in a vacuum desiccator over phosphorus pentoxide, and crystallized from petroleum ether (b.p. 90-100°). The m.p. was 72°, and the yield was seventeen and five-tenths grams.

#### Preparation of 5-Aminequinoline

##### I. By Reduction of 5-Nitrequinoline with Iron and Acetic Acid

Twenty grams of 5-nitrequinoline were dissolved in two hundred c.c. of warm (50° C.) fifty per cent acetic acid, and reduced with sixteen grams of iron powder. It was necessary to add the iron powder slowly. At no time, was the temperature of the reaction mixture allowed to go above 60° C. Next, the reaction mixture was diluted to six times its volume with water, and heated for one hour under reflux. During this time, air was blown through the mixture, the object being to oxidize ferrous ions to ferric ions. The mixture was next filtered (to remove iron oxide), and the filtrate evaporated to dryness. The residue was extracted several times with ether. The ether extract contained three grams of 5-aminequinoline, which after crystallizing from petroleum ether had a melting point of 109 to 109.5°. The hydrochloride made from the above amine was not insoluble in dilute hydrochloric solution, as reported by Dikshreem<sup>22</sup>. For this reason, it was decided to make the acetyl derivative as a check on the identity of the amine.

### Preparation of the Acetyl Derivative of 5-Aminoquinoline

Six c.c. of acetic anhydride and a small quantity of the amine were refluxed for twenty minutes. The solution was then poured into approximately one hundred c.c. of water. After hydrolysis of the unreacted acetic anhydride, the solution was made basic with sodium hydroxide, and extracted with ether. The ether extract was evaporated and the residue, after a crystallization from benzene, melted at 178.5-179°. The recorded melting point of the acetyl derivative, is 178°

### II. Attempts to Prepare 5-Aminoquinoline by Catalytic Reduction of 5-Nitro Compound

Ten grams of 5-nitroquinoline was dissolved in fifty-eight c.c. of dioxane, and the resulting solution was subjected to catalytic reduction in the presence of Raney nickel catalyst. During the reaction the pressure was raised to two hundred pounds per square inch, and then was allowed to fall to forty pounds per square inch. The pressure was then raised again to two hundred pounds per square inch, and again allowed to fall to forty pounds per square inch. This process was repeated until no further drop in pressure was observed. The temperature during the reduction varied from 60 to 66° C. The time required for the reaction was approximately six and one-half hours.

After filtering the reaction mixture and evaporating the solvent, a tar remained. By extracting with ether and water, a small quantity of solid was obtained. After two crystalli-

zations from hot water, this solid had a melting point of 109°.

#### Further Attempts to Prepare 5-Aminoquinoline by Catalytic Reduction

Five grams of 5-nitroquinoline dissolved in fifty-eight c.c. of dioxane was reduced at one thousand pound pressure and 22° C. The catalyst used was Raney nickel. The quantity of hydrogen used was slightly more than the calculated amount. The time required for the reaction was two hours and fifteen minutes. The reaction mixture was filtered and the dioxane removed by a vacuum distillation in the presence of nitrogen; a tar remained.

Part of the tar was dissolved in benzene, dried, and dry hydrogen chloride was passed into the solution. A red precipitate was formed. The precipitate was collected, treated with sodium hydroxide, and the resulting mixture extracted with benzene. After removal of the solvent from the dried benzene solution, an oil was obtained which on standing gave "oily crystals". This substance could not be purified.<sup>15</sup>

The other part of the tar obtained from the reaction mixture was extracted several times with dry ether. After removing the ether from the ether extract, a tar remained. This tar was treated with hot petroleum ether (b.p. 90-100°). When the solution cooled, crystals of very impure 5-aminoquinoline remained. This material was purified by recrystallizing it from petroleum ether (b.p. 90-100°). The yield, however,

was extremely poor.

#### Further Attempts to Reduce 5-Nitroquinoline Catalytically

Since the above two attempts at reducing 5-nitroquinoline to 5-aminequinoline were not entirely successful, it was decided to carry out a reduction at atmospheric pressure. Therefore, five grams of 5-nitroquinoline dissolved in absolute alcohol and two and three-tenths grams of Raney nickel were placed in a shaker, and slightly more than the calculated volume (one thousand nine hundred and fifty c.c.) of hydrogen added. The reaction took place slowly at a temperature of 25°.

The reaction mixture was filtered and the filtrate evaporated. An oil was obtained. By extracting the oil with petroleum ether (b.p. 90-100°), three-tenths grams of 5-aminequinoline was obtained. Obviously, the above conditions are not the correct ones for the preparation of 5-aminequinoline.

#### Reduction of 5-Nitroquinoline by Use of the Parr Low-Pressure Hydrogenator

##### Calibration of the Apparatus

Twelve grams (one-tenth mole) of nitrobenzene were added to one hundred c.c. of ninety-five per cent alcohol containing one-half teaspoon of freshly prepared Raney nickel catalyst. The mixture thus obtained was heated to boiling on a steam bath, and then placed in the hydrogenator. Hydrogen was passed into the reaction mixture at a pressure of forty-three

pounds per square inch, and the shaker started. The reaction was allowed to proceed until there was no further drop in pressure. The pressure dropped to twenty-three pounds in forty minutes, after which there was very little drop in pressure. It is obvious that three-tenths mole of hydrogen represents a twenty pound drop in pressure.

#### Reduction of 5-Nitroquinoline

Seventeen and four-tenths grams of 5-nitroquinoline and one hundred and thirty c.c. of ninety-five per cent alcohol containing one-half teaspoon of Raney nickel catalyst were heated to boiling on a steam bath, and the mixture placed in the Parr Hydrogenator. Hydrogen was passed into the reaction mixture at a pressure of forty-three pounds per square inch, and the shaker started. The reaction was complete in eleven minutes. The reaction bottle became very hot. The reaction mixture was then filtered to remove the Raney nickel, and the alcohol was removed at reduced pressure in the presence of nitrogen. A solid which gave almost pure 5-aminequinoline when crystallized from petroleum ether (b.p. 90-100°), was obtained. The yield was eighty-one and two-tenths per cent that of the theoretical amount.

The above procedure was repeated. This time the yield was 86.1%, however.

In the above reductions, the reaction was stopped before all the hydrogen had been taken up that the reaction mixture was capable of taking up. Therefore, a reduction was run in which the mixture was allowed to take up all the hydrogen it

desired. From this reaction mixture, no pure product was isolated. Hence, a controlled reduction is necessary.

#### Conversion of 5-Aminequinoline into 5-Hydroxyquinoline

One gram of 5-aminequinoline, four grams of sodium bisulfite, and eleven c.c. of water were heated under reflux for twenty-seven hours. At the end of this time, the solution was made alkaline with sodium hydroxide solution and boiled until no more ammonia came off. The reaction mixture was then extracted three times with benzene, to remove any unreacted 5-aminequinoline. The aqueous portion was filtered to remove a small quantity of black organic material which was insoluble in both water and benzene. To the aqueous solution was added an excess of carbon dioxide until no further precipitate formed. The precipitate thus obtained was crystallized from dilute alcohol. The substance melted at 220-221°, and the yield was twenty-five per cent of the theoretical amount. The melting point recorded in literature is 224°. The benzene extract yielded two-tenths gram of the unreacted amine.

#### Attempts to Improve the Yield of 5-Hydroxyquinoline

One gram of 5-aminequinoline, four grams of sodium bisulfite, and thirty c.c. of water were heated under reflux for twelve hours. The reaction mixture was worked up as outlined above. The crude phenol was crystallized from hot water. The melting point of the phenol was 223-224°. The yield of the product was twenty per cent of the theoretical amount. The unre-

acted amine amounted to three-tenths gram.

Five grams of 5-aminequineline and twenty grams of sodium bisulfite, all in one hundred and fifty c.c. of water, were refluxed (with continuous stirring) for twenty hours. The reaction mixture was worked up as above. The yield of hydroxyquineline was forty per cent of that theoretically possible, and two and fifteen-hundredths grams of 5-aminequineline were recovered from the benzene extract.

With continuous stirring, five grams of aminequineline and sixty grams of sodium bisulfite in one hundred and fifty c.c. of water were refluxed for twenty hours. The material recovered was black and weighed seven-hundredths gram. The benzene extracted yielded eighty-nine thousandths gram of 5-aminequineline. The yield of 5-hydroxyquineline was ninety-one per cent theory.

#### Conversion of 5-Hydroxyquineline into 5-Aminequineline

One gram of 5-hydroxyquineline, three and six-tenths grams of ammonium sulfite, twelve c.c. of fifteen normal ammonium hydroxide solution and thirty-seven c.c. of water were heated at 150° in a small bomb for six hours. The reaction mixture was treated with an excess of sodium hydroxide and extracted three times with benzene solution. The yield of 5-aminequineline from the benzene extract was sixty per cent. The melting point was 110° after crystallizing from petroleum ether (b.p. 90-100°).

Two grams of 5-hydroxyquinoline, twenty grams of ammonium sulfite, ten c.c. of water, and thirty-eight c.c. of fifteen normal ammonium hydroxide were heated at 150° C. in a small bomb for six hours. The reaction mixture was worked up as above. The yield of 5-aminequinoline was fifty-nine per cent of the amount theoretically possible.

#### Preparation of N-Methyl-5-Aminequinoline

One gram of 5-hydroxyquinoline, four c.c. of thirty-five per cent methyl amine solution saturated with sulfur dioxide, and thirty c.c. of water were placed in a small bomb and heated at 150° C. for six and one-half hours. The reaction mixture was made strongly alkaline with sodium hydroxide solution and extracted three times with benzene. Crystalline N-methyl-5-aminequinoline was obtained from the benzene extract after removal of the solvent. This crystalline material had a melting point of 132-133° after a crystallization from hot water. The yield was fifty-five and five-tenths per cent of that theoretically possible.

Weight of sample- 2.673 mg.  
 Volume of gas- 0.430 ml.  
 Temperature- 28° C.  
 Pressure- 759 mm.  
 Nitrogen- 17.85%

Weight of sample- 2.786 mg.  
 Volume of gas- 0.445 ml.  
 Temperature- 27° C.  
 Pressure- 759 mm.  
 Nitrogen- 17.97%

Calculated for  $C_{10}H_{10}N_2$  per cent nitrogen- 17.72

Weight of sample- 2.701 mg.  
 Weight of carbon dioxide- 7.543 mg.  
 Carbon- 76.1%

Weight of sample- 2.902 mg.  
 Weight of carbon dioxide- 8.077 mg.  
 Carbon- 75.9%

Calculated for  $C_{10}H_{10}N_2$ , per cent carbon- 76.6

Weight of sample- 2.701 mg.  
 Weight of water- 1.650 mg.  
 Hydrogen- 6.8%

Weight of sample- 2.902 mg.  
 Weight of water- 1.705 mg.  
 Hydrogen- 6.6%

Calculated for  $C_{10}H_{10}N_2$ , per cent hydrogen- 6.4

#### Attempts to Prepare N-N-Dimethyl-5-Aminoquinoline

One gram of 5-hydroxyquinoline, eight c.c. of dimethyl amine solution (thirty-three per cent) and forty c.c. of water were heated in a small bomb at  $150^{\circ}$  C. for six and one-half hours. The reaction mixture was worked up in the way previously mentioned. A small amount of solid material was isolated from the benzene extract. This material was identified as N-methyl-5-aminoquinoline. Obviously the dimethyl amine solution contained a small amount of methyl amine. The quantity of 5-hydroxy compound recovered was four-hundredths gram. No other product was isolated.

An additional attempt was made to prepare N-N-dimethyl-5-aminoquinoline. One gram of 5-hydroxyquinoline and twenty grams of sodium bisulfite were placed in a small bomb and enough dimethyl amine solution (thirty-three per cent) was added to make the mixture basic. Then ten c.c. more of the amine solution

and ten c.c. of water were added. At this point, the total volume of the reaction mixture was approximately forty-five c.c.. This mixture was heated at 150° C. for six and one-half hours. The reaction mixture was worked up as outlined above. No crystalline product was isolated.

#### Preparation of N-p-Methoxyphenyl-5-Aminequinoline

One gram of 5-hydroxyquinoline, one gram of p-anisidine and eight grams of sodium bisulfite were added to forty c.c. of water and heated in a small bomb at 170° C. for six and one-half hours. The reaction mixture was worked up in the usual way. The substance in the benzene extract had a melting point of 155° C. after crystallization from very dilute alcohol. The yield was seventy-five hundredths gram.

Weight of sample- 2.391 mg.  
 Volume of gas- 0.237 c.c.  
 Temperature- 25° C.  
 Pressure- 763 mm.  
 Nitrogen- 11.16%

Weight of sample- 2.780 mg.  
 Volume of gas- 0.275 c.c.  
 Pressure- 763 mm.  
 Temperature- 26° C.  
 Nitrogen- 11.13%

Calculated for  $C_{16}H_{14}ON_2$ , per cent nitrogen- 11.2%

Weight of sample- 3.541 mg.  
 Weight of carbon dioxide- 9.921 mg.  
 Carbon- 76.4%

Weight of sample- 3.690 mg.  
 Weight of carbon dioxide- 10.33 mg.  
 Carbon- 76.3%

Calculated for  $C_{16}H_{14}ON_2$ , per cent carbon- 76.8

Weight of sample- 3.541 mg.  
 Weight of water- 1.921 mg.  
 Hydrogen- 6.03%

Weight of sample- 3.690 mg.  
 Weight of water- 1.960 mg.  
 Hydrogen- 5.9%

Calculated for  $C_{16}H_{14}ON_2$ , per cent hydrogen- 5.6

#### Attempt to Prepare N-Phenyl-5-Aminequineline

Two grams of 5-hydroxyquineline, eight c.c. of aniline, ten grams of sodium bisulfite, and fifty c.c. of water were heated in a bomb for six and one-half hours at  $200^{\circ}$  C. The reaction mixture was worked up in the usual way. A tar was obtained from the benzene extract. All efforts to purify this material failed. Obviously the above conditions are not the most suitable ones for making N-phenyl-5-aminequineline.

#### Preparation of N-(n)-Butyl-5-Aminequineline

To a solution of eight grams of sodium bisulfite in forty c.c. of water, was added one and seven-tenths grams of 5-hydroxyquineline and five c.c. of n-butyl amine. The mixture was heated in a bomb for six and one-half hours at  $150^{\circ}$  C. The reaction mixture was made strongly basic with sodium hydroxide solution, and extracted three times with benzene. The yield of n-butyl-aminequineline from the benzene extract equals seventy per cent of that theoretically possible. This compound has a melting point of  $123-124^{\circ}$  C. after a crystallization from dilute alcohol.

Weight of sample- 2.411 mg.  
 Volume of gas- 0.300 ml.  
 Pressure- 762 mm.  
 Temperature-  $26^{\circ}$  C.  
 Nitrogen- 13.96%

Weight of sample- 2.489 mg.  
Volume of gas- 0.310 c.c.  
Pressure- 761 mm.  
Temperature- 28° C.  
Nitrogen in sample- 13.95%

Calculated for  $C_{13}H_{16}N_2$ , per cent nitrogen- 14.0

Weight of sample- 3.979 mg.  
Weight of carbon dioxide- 11.33 mg.  
Carbon- 77.6%

Weight of sample- 4.351 mg.  
Weight of carbon dioxide- 12.42 mg.  
Carbon- 77.8%

Calculated for  $C_{13}H_{16}N_2$ , per cent carbon- 78.0

Weight of sample- 3.979 mg.  
Weight of water- 2.801 mg.  
Hydrogen- 7.8%

Weight of sample- 4.351 mg.  
Weight of water- 2.940 mg.  
Hydrogen- 7.5%

Calculated for  $C_{13}H_{16}N_2$ , per cent hydrogen- 8.0

## PART II

## DISCUSSION OF EXPERIMENTAL RESULTS

Woreshtzew and his co-workers applied the Bucherer Reaction to several hydroxy quinoline derivatives.<sup>20</sup> Since 5-hydroxy and 5-amine-quinolines were not investigated, it was decided to apply the Bucherer Reaction to these two compounds.

Obviously, the first thing that had to be done was the preparation of the 5-hydroxy and 5-amine quinolines. It was desired to use reactions involving the fewest steps and giving the best yields. For this reason, it was decided to nitrate quinoline according to the method of Duften.<sup>21</sup> One obtains a mixture of 5 and 8 nitro quinolines. Duften found that the nitrate of 5 nitro quinoline is very slightly soluble in dilute nitric acid solution. The nitrate of the 8 nitro compound is very soluble in dilute nitric acid. Hence, we have a way of separating the two isomers. The yield of 5-nitroquinoline was reported by Duften to be good, and this was found to be true.

Attempts to reduce 5-nitroquinoline, caused some difficulty. Dikshoorn reduced 5-nitroquinoline by use of iron and acetic acid.<sup>22</sup> By Dikshoorn's method, a very poor yield of 5-aminequinoline was obtained. For this reason, it was decided to use a catalytic method. If one reduces 5-nitroquinoline at two hundred pounds pressure and 60° C., using Raney nickel as a catalyst, a tar is produced, from which only small quantities of 5-aminequinoline were isolated. If the reduction is carried out at one thousand pounds pressure and 23°C., a tar of similar

characteristics is produced. Winterbottom reports that he reduced 5-nitroquinoline in a Parr Hydrogenator, using Raney nickel as catalyst.<sup>23</sup> His yield was reported as seventy-five per cent of the theoretical amount. Winterbottom did not give full details in his report, however. By reducing 5-nitroquinoline in a Parr Hydrogenator at forty-three pounds pressure, and using Raney nickel as catalyst, it was possible to produce 5-aminoquinoline in yields from eighty-one to eighty-six per cent of the theoretical amount. The secret of a successful reduction seems to lie in having the reactants warm when they are placed in the hydrogenator. The reduction took about fifteen minutes, although Winterbottom stated that it took approximately one hour for the reaction to go to completion. It was found that if the reaction proceeds slowly, a tar is formed, from which only small quantities of 5-aminoquinoline can be produced. The best thing to do with the tar is to discard it. It is usually not worthwhile to attempt purification.

It was found that 5-aminoquinoline was converted into 5-hydroxyquinoline in good yield by refluxing the former substance with sodium disulfite solution for several hours. After the reaction mixture had been made strongly basic with sodium hydroxide, and refluxed until no more ammonia came off, the hydroxyquinoline could be recovered from the alkaline solution by the addition of carbon dioxide.

Also, 5-hydroxyquinoline was converted into 5-aminoquinoline by heating ammonium sulfite, the hydroxyquinoline, excess ammonia,

and water under pressure for six and one-half hours. Sodium hydroxide was added, and the amine extracted from benzene. The yield of aminoquinoline was good. The product formed in this way is much easier to purify than that formed by a reduction of 5-nitroquinoline. It is possible to take very crude 5-aminoquinoline (very hard to purify), and purify it by its conversion into hydroxy compound, and back into the amine, both by use of the Bucherer Reaction.

As expected, 5-hydroxyquinoline could be converted into the N-methyl-5-amino compound by use of methyl amine sulfite and methyl amine in water solution. The reaction was carried out in a bomb, and the yield was fairly satisfactory. The N-n-butyl-5-amino compound was obtained in a similar way.

N-p-methoxy phenyl-5-aminoquinoline was prepared by heating an excess of p-anisidine with 5-hydroxyquinoline in a strong bisulfite solution. The yield was good.

The two attempts to prepare N-dimethyl-5-aminoquinoline failed. A very disagreeable odor of amines was produced. Further work must be done to find the correct conditions for making this material.

An attempt to prepare N-phenyl-5-aminoquinoline also failed to yield a crystalline product. Obviously more experimental work must be done to ascertain the correct conditions for preparing this substance.

## PART II

## SUMMARY

1. 5-aminequinoline was prepared according to the method of Dikshoorn. The yield was much less than that reported, however.
2. Various attempts to prepare 5-aminequinoline from 5-nitroquinoline by high pressure reduction in the presence of Raney nickel as the catalyst, failed to yield any appreciable quantities of amine.
3. 5-aminequinoline was prepared according to the method of Winterbottom. The yield was better than that reported, however.
4. 5-aminequinoline was converted into 5-hydroxyquinoline by the Bucherer Reaction. The yield was approximately ninety per cent of that theoretically possible.
5. 5-hydroxyquinoline was converted into 5-aminequinoline by the Bucherer Reaction, with a yield of fifty-nine to sixty per cent of the theoretical amount.
6. N-methyl-5-aminequinoline was prepared by the Bucherer Reaction with a yield of fifty-five and five-tenths per cent of the theoretical amount possible.
7. Attempts to prepare N-dimethyl-5-aminequinoline by use of the Bucherer Reaction failed.

8. N-(n)-butyl-5-aminequineline was prepared by use of the Bucherer Reaction, the yield being seventy per cent the theoretical amount.
9. An attempt to prepare N-phenyl-5-aminequineline by use of the Bucherer Reaction, was not successful.
10. N-(p)-methoxy-phenyl-5-aminequineline was prepared by use of the Bucherer Reaction, the yield being forty-seven per cent that theoretically possible.

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