A STUDY OF THE CONDENSATION OF THE
\( \alpha \) - AND \( \beta \) -AMINOPYRIDINES WITH
PYRUVIC ACID AND CERTAIN ALDEHYDES

by

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A STUDY OF THE CONDENSATION OF THE
\[ \alpha - \text{AND } \beta - \text{AMINOPYRIDINES WITH PYRUVIC ACID AND CERTAIN ALDEHYDES} \]

INTRODUCTION

The Mannich reaction is, in substance, a condensation involving formaldehyde condensing between a compound containing at least one active hydrogen and ammonia or a primary or secondary amine. This reaction provides a convenient method of lengthening the carbon chain by the introduction of an amino methyl or substituted aminomethyl group into the molecule. Also, by choosing the appropriate compounds, a cyclization can be initiated.

This reaction was first observed by Tollens (10) who isolated a tertiary amine from ammonium chloride, formaldehyde and acetophenone. Further work was carried on by Petrenko-Kritsenko and co-workers (9), but they failed to recognize the reaction as being one of a general nature.

In 1917 Mannich (6) studied the reaction between antipyrine salicylate, formaldehyde and ammonium chloride which formed a tertiary amine on condensation. More detailed studies, involving the use of other reactants, indicated that the condensation was one of a general nature and in most cases the final product could be predicted.
The majority of the early work done on the Mannich reaction centered around the syntheses of Mannich bases. In 1940 Mazza and Migliardi (7) applied this reaction to the syntheses of derivatives of the bicyclic structure, 1,8-naphthyridine. The amine used in the simplest cases was 2-aminopyridine and the compound containing the active hydrogen was pyruvic acid. By using benzaldehyde, the following derivative was obtained:

\[
\text{H} + \text{H-C=O} + 2 \text{H}_3\text{C-C}=\text{O-} + \text{C\text{N-CH}_2\text{CH}} \\
\text{H} \text{H} \text{H} \text{HO-C=O} \text{H} \text{HO-C=O} \text{C-N-C=O} \text{C-C} \text{C-C} \text{C-C} \text{C-C} \text{C-C} \text{C-C}
\]

An exploratory reaction of this type was performed by Bush (1, pp.27-28) in 1952 using paraformaldehyde, 2-aminopyridine and pyruvic acid. The paraformaldehyde depolymerized in the course of the reaction, liberating free formaldehyde which reacted to form 1,8-naphthyridine-4-carboxylic acid.
According to Bush, one other possibility was also present and that was the cyclization of the Mannich base to the tertiary pyridine nitrogen giving a 2-pyrido (1.2-a) pyrimidine-4-carboxylic acid. The only difference between these two compounds was that the latter had one more molecule of hydrogen which would not be conclusively evident in a combustion analysis.

In order to establish the direction of cyclization, it was necessary to determine the reactive tendencies in this reaction of the number 3 carbon in the aminopyridine molecule. Two analogous reactions were performed which in each case, if cyclization occurred, a bicyclic structure would be produced. The previously-mentioned reaction (1, pp.27-28) was run with some variation in the method. A similar reaction, using 4-aminopyridine in lieu of the 2-amino derivative, was also run which
should have formed 1,6-naphthyridine-4-carboxylic acid. In this latter case, if cyclization occurred as indicated, the activity of the number 3 carbon would be sufficient to permit the same type of cyclization using 2-aminopyridine. The following equation demonstrates this reaction:

\[
\begin{align*}
\text{NH}_2 & \quad \text{CO} \quad \text{S} \quad \text{CH} \\
\text{HC} & \quad \text{N} \quad \text{2CH} \\
\end{align*}
\]

\[+ \text{H-C-H + 2 H}_2\text{C-C-C-OH} \rightarrow \]

\[
\begin{align*}
\text{N} & \quad \text{CH} \\
\text{HC} & \quad \text{N} \quad \text{CH} \\
\end{align*}
\]

As can be seen, the product would be the same regardless of whether the cyclization went to the number 3 or 5 carbon.
EXPERIMENTAL PROCEDURE

Preparation of Pyruvic Acid (5, pp.63-64)

An intimate mixture of 300 g of finely powdered potassium bisulfate and 200 g of powdered tartaric acid were placed in a 3-liter round-bottom flask which was fitted with a distilling condenser. The flask was placed in a sand bath which was heated by a Fisher burner. In about 15 minutes, an orange distillate came over which was collected in an Erlenmeyer flask partially immersed in an ice bath.

The intense heating was continued until no more distillate was produced, about 2 hours. The distillate was then distilled under reduced pressure in a fractionating column. The pyruvic acid came over at 79°C - 80°C at 28 mm. The yield was 51 g or 44% and gave a freezing point of 13.6°C.

Attempted Preparation of 1,8-Naphthyridine-4-Carboxylic Acid (1, pp.27-28)

The reaction vessel consisted of a three-necked flask which was fitted with a mechanical stirrer, reflux condenser with a CaCl₂ drying tube and, through the third neck, a 6 mm glass tube which was drawn out to a capillary at one end. The capillary extended to the bottom of the
flask. To the flask was added 75 cc of magnesium-dried alcohol, 4.7 g (0.05 mole) of 2-aminopyridine and 8.8 g (0.1 mole) of freshly-distilled pyruvic acid. The contents of the flask, while being stirred, were heated to reflux in an oil bath at 95°C. Six grams of dried paraformaldehyde were then placed in a 125 cc Erlenmeyer flask and the flask connected to the 6 mm glass tube. The flask was heated gently with a small flame to depolymerize the paraformaldehyde and generate a constant flow of formaldehyde.

After all of the formaldehyde had been released the glass tube was removed from the reaction vessel and replaced with a glass stopper. The mixture was allowed to reflux for 22 hours. By the end of this period a dark red solution had been produced. Enough alcohol was then distilled off in vacuo so that the residue was slightly viscous. The residue was poured into 500 cc of cold water which was stirred vigorously. A brown flocculent precipitate was produced immediately. The precipitate was filtered and dried in vacuo over P₂O₅. The dried tan powder was dissolved in chloroform, filtered and precipitated with petroleum ether. This was filtered and dried in the same manner. A 35% yield was obtained and gave a product melting at 140°C with decomposition starting at 130°C. The compound was soluble in most organic solvents
and HCl but was insoluble in ether, petroleum ether, water and NaOH. Analytical for C₉H₈C₂N₂: molecular weight = 174.15. Calculated: C, 62.1; H, 5.47; N, 16.09. Found: C, 61.64; H, 5.24; N, 16.66.

In the original reaction (1, pp.27-28), paraform-aldehyde was introduced directly into the reaction flask and the mixture refluxed for 2 hours. This was repeated in the current work; however, it was found that the yield amounted to 5% while the yield reported by Bush was 30%. It was not until the described reaction was run that an appreciable yield was obtained. The compounds prepared by both methods gave approximately the same elemental analyses and melting points.

A carbon and hydrogen analysis was run on a sample prepared by Bush, and the results obtained were C, 61.95 and H, 5.03 while those reported by Bush were C, 62.0 and H, 3.8. It was not possible to ascertain that the sample on which the above analysis was run was the same sample which Bush had reported.

Preparation of 4-Aminopyridine (2, pp.345-349)

Since the 4-aminopyridine to be used in the preparation of 1,6-naphthyridine-4-carboxylic acid was not commercially available, it had to be prepared by synthetic means from 4-picoline.
In a 5-liter three-necked flask, fitted with a reflux condenser and stirrer, were placed 2500 cc of water, 50 g of r-picoline (0.54 mole) and 90 g of K\textsubscript{2}MnO\textsubscript{4} (0.54 mole). The solution was refluxed until the purple color had disappeared, approximately 1 hour. Another 90 g portion of K\textsubscript{2}MnO\textsubscript{4} was added and the refluxing continued for 2-1/2 hours. The solution was cooled slightly and filtered. The manganese dioxide was washed with a liter of hot water and the combined filtrate and washings were evaporated to 200 cc. The concentrate was then made acidic to Congo Red paper with approximately 65 cc of concentrated HCl, and the precipitate was filtered and washed with water. The yield of the acid was 82.5%.

The isonicotine amide was prepared by esterifying the acid by refluxing together 20 g of isonicotinic acid, 40 g of absolute ethanol and 40 g of concentrated H\textsubscript{2}SO\textsubscript{4} for 4 hours. This was poured into three times its volume of ice and Na\textsubscript{2}CO\textsubscript{3} added to neutralize the H\textsubscript{2}SO\textsubscript{4}. The ester was then extracted with ether and the extract dried with Na\textsubscript{2}CO\textsubscript{3} overnight. This was filtered and the ether distilled. To the oily residue was added 5 cc of 23% \textsubscript{NH}\textsubscript{4}OH. The two-phase system was shaken for 15 minutes and allowed to stand overnight. By this time white needles had formed which were filtered and recrystallized from alcohol and benzene. The yields of the ester
and the amide were 85.5% and 63.3% respectively.

The amine was prepared from the amide by cooling to 0°C in a salt-ice bath a mixture of 9 g of bromine, 50 g of KOH in 400 cc of water. Then, with stirring, 7 g of finely-pulverized isonicotine amide was added to the cold solution all at once. After the amide had completely dissolved, the solution was heated to 70°C for 45 minutes and stirred. The solution was cooled to room temperature, saturated with NaCl and continuously extracted with ether for 4 days. The ether extract was adjusted to a volume of 1 liter and dried with 5 g of NaOH pellets. The ether was then distilled and the crude amine recrystallized from benzene. A yield of 40.4% and a melting point of 158°C were obtained.

Attempted Preparation of 1,6-Naphthyridine-4-Carboxylic Acid

To 50 cc of magnesium-dried alcohol was added 4.5 g (0.05 mole) of freshly-distilled pyruvic acid, 0.75 g (0.025 mole) of paraformaldehyde and 2.4 g (0.025 mole) of 4-aminopyridine. The mixture was refluxed for 5 hours in which time an orange solution was formed. The excess alcohol was distilled in vacuo and 200 cc of water added to the soluble viscous fluid. To this 30 cc of 6N NaOH was added and the solution allowed
to stand for 2 days. Long colorless needles formed which, when filtered and dried, gave a yield of 3.4%. The crystals melted at 326°C and were presumed to be sodium salt. The compound was soluble in most organic solvents and HCl but was insoluble in ether, petroleum ether, water and NaOH. Analytical for C₉H₅O₂N₂Na: molecular weight = 196.14. Calculated: C, 55.10; H, 2.57. Found: C, 55.59; H, 4.99.

Work on this compound was discontinued due to the small yield obtained in relation to the extremely long preparational period of the 4-aminopyridine.

**Attempted Preparation of 2-Phenyl-1,8-Naphthyridine-4-Carboxylic Acid (7)**

To 75 cc of magnesium-dried ethanol was added 4.7 g (0.05 mole) of 2-aminopyridine, 5.3 g (0.05 mole) of benzaldehyde and 3.8 g (0.1 mole) of freshly-distilled pyruvic acid. This mixture was refluxed for 22 hours. At the end of this time a dark red solution resulted. Most of the ethanol was distilled in vacuo and the viscous residue poured into 500 cc of cold water which was stirred vigorously. A tan flocculent precipitate was formed. The precipitate was filtered, dried and re-dissolved in dry chloroform, filtered and reprecipitated with petroleum ether and dried. The resulting compound
gave a melting point of 145°C with decomposition starting at 135°C. The compound was soluble in most organic solvents but was insoluble in ether, petroleum ether, water, NaOH and only slightly soluble in HCl. Analytical for C_{15}H_{10}O_{2}N_{2}: molecular weight = 250.25. Calculated: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.69; H, 5.91; N, 3.95.

Attempted Preparation of 2-Methyl-1,8-Naphthyridine (4)

To a flask immersed in an ice bath was added 9.4 g (0.1 mole) of 2-aminopyridine and then, with constant stirring, 50 cc of concentrated HCl was added slowly. The resulting solution was allowed to stand for 10 minutes. After this period 3.8 g (0.2 mole) of acetaldehyde was added and the solution allowed to stand again for 1/2 hour. The solution by this time had turned yellow. The mixture was refluxed for 5 hours. After 15 minutes of refluxing black particles began to settle. When the period of refluxing was finished the mixture was cooled and then poured into 400 cc of cold water. This solution was neutralized with 6N NaOH and a black tarry mass.
precipitated out. The tar was filtered and dissolved in ethanol, filtered and precipitated in 400 cc of cold water. A flocculent rust precipitate was produced which was filtered. The precipitate was again dissolved in ethanol, filtered and precipitated. A finely-divided suspension occurred which would not settle while standing for as long as 7 days. Various methods were tried to break the suspension, such as centrifuging, heating, cooling and stirring, but none was successful. Sodium chloride was finally added and the suspension precipitated immediately while stirring. The precipitate was filtered and dried over P₂O₅ in vacuo and then dissolved in dry acetone and filtered to remove any residual salt. The acetone was evaporated and a dark red glassy residue remained which melted at 120°C with decomposition. The compound was soluble in most organic solvents and HCl but was insoluble in ether, petroleum ether, water and NaOH. Analytical for C₉H₇N₂: molecular weight = 144.17. Calculated: C, 74.97; H, 5.59; N, 19.50. Found: C, 71.05; H, 7.46; N, 16.76.

Preparation of Ethyl Pyruvate (11, pp.59-61)

In a 1-liter round-bottomed flask, fitted with a thermometer and mechanical stirrer, were placed 130 ml of a saturated aqueous magnesium sulfate solution, 500 ml of
petroleum ether, 50 g (0.42 mole) of ethyl lactate and 20 g (0.13 mole) of sodium dihydrogen phosphate dihydrate. The stirrer was started, the temperature brought to 150°C by means of an ice-water bath, and 55 g (0.35 mole) of powdered potassium permanganate was added during the next 25- to 30-minute period. Stirring was continued until the oxidation was complete. The temperature was kept near 150°C throughout the process. The petroleum ether solution was decanted and the sludge stirred with three 50-cc portions of petroleum ether. The combined petroleum ether extracts were evaporated on a steam bath under a short fractionating column. The residual oil was shaken thoroughly with two 10-ml portions of a saturated aqueous calcium chloride solution, the ester layer was separated and then distilled under reduced pressure. Almost the whole product distilled over at 62°C — 63°C at 20 mm. The yield was 25 g or 51%.

**Attempted Preparation of 2-Phenyl-1,8-Naphthyridine-4-Carboxylic Acid Ethyl Ester**

To 75 cc of magnesium-dried alcohol was added 5.3 g (0.05 mole) of benzaldehyde, 11.6 g (0.1 mole) of ethyl pyruvate and 4.7 g (0.05 mole) of 2-aminopyridine. The mixture was refluxed for 2 hours and then most of the alcohol distilled in vacuo. A viscous dark red
liquid remained which, when poured into 500 cc of cold water and vigorously stirred, settled to the bottom as a liquid. Attempts were made to extract a solid from this liquid but none was successful.

Steam distillation was attempted but the liquid would not distill. When the mixture had cooled, the liquid solidified to form a tarry mass. This was dissolved in alcohol, precipitated with water and then filtered. A brown residue was obtained. This was dried, redissolved in chloroform, filtered and precipitated with petroleum ether. When dried, the compound melted at 150°C with decomposition. The compound was soluble in most organic solvents but was insoluble in ether, petroleum ether, water, NaOH and only slightly soluble in HCl. Analytical for C_{17}H_{14}O_{2}N_{2}: molecular weight = 278. Calculated: C, 73.39; H, 5.03. Found: C, 69.81; H, 5.84.

These results coincide more closely with that of the free acid than with the ester. Since the product obtained on the first attempted precipitation was an oil, it might be concluded that this was an ester and, on the attempted steam distillation at 100°C, hydrolysis could occur although the solution was neutral. This would account for obtaining the solid in the second precipitation, giving the approximate melting point and
carbon-hydrogen analysis of the free acid.

Development of the Ultraviolet Spectra of Certain Proposed 1,8-Naphthyridines and 2-Aminopyridine

At this point, portions of the ultraviolet absorption spectra were plotted to determine some similarity between the compounds made thus far. Figure 1 gives the absorption spectra of the proposed 1,8-naphthyridine-4-carboxylic acid. Curves 1 and 4 were from samples prepared by Bush, and curves 2 and 3 were prepared by the author. The curves, especially 1, 2 and 3, show much similarity insofar as locations of the maxima are concerned but differ greatly with respect to the amounts of transmittance. These differences could be due to a variation in concentration; but since the same amount of sample was used in each curve, the only solution would be that the compounds were impure thereby lowering the concentration of the compound in question. This reasoning becomes more evident when it is considered that all of these compounds were isolated by "salting out".

Figure 2 shows the curve of the proposed 2-phenyl-1,8-naphthyridine-4-carboxylic acid. The curve in this instance has a much less pronounced maximum but still has somewhat the same general shape, especially when it is compared with curve 4 of Figure 1. Various concentrations
1,8-NAPHTHYRIDINE-4-CARBOXYLIC ACID

PERCENT TRANSMITTANCE

WAVELENGTH

Figure 1
2-PHENYL-1,8-NAPHTHYRIDINE-4-CARBOXYLIC ACID

Figure 2

2-METHYL-1,8-NAPHTHYRIDINE

Figure 3
2-AMINOXYRIDINE

Figure 4
were used with this compound but the difference in trans-
mittance did not increase appreciably.

Figure 3 is the plot of the proposed 2-methyl-
1,8-naphthyridine. In this case it compares favorably
with Figure 1.

Figure 4 is the curve obtained from the 2-amino-
pyridine. Although this curve is much more irregular
than those previously plotted, there are maxima at 246 μ
and 282 μ which coincide quite closely to the other
curves. It is therefore proposed that the 2-aminopyridine
is present in the compounds that have been prepared.

Determination of Portions of the Infrared Absorption
Spectra of Certain Prepared Compounds

The portions of the infrared spectra shown are in
those regions where the most likely functional groups and
linkages of the compounds would appear. The peaks ob-
tained are listed in the following table as wave numbers:

| 2-Phenyl-1,8-
| Naphthyridine- |
| 1,8-Naphthyridine- |
| 4-Carboxylic Acid |
| Acid |
| 2-Methyl-1,8-
| Naphthyridine |

| 1725 | 1725 | 2940 |
| 1770 | 1770 | 3200 |

It was believed at the time these curves were ob-
tained that a secondary amine was present in the compounds
Figure 5

I,8-NAPHTHYRIDINE-4-CARBOXYLIC ACID

**Curve A**

**Curve B**
Figure 6

2-PHENYL-1,8-NAPHTHYRIDINE-4-CARBOXYLIC ACID

Curve A

Curve B

WAVE NUMBER

PERCENT TRANSMITTANCE

WAVE NUMBER
listed and that the only other functional groups were the carboxyl and methyl groups. These would appear in the following range of wave numbers:

<table>
<thead>
<tr>
<th>Secondary Amine</th>
<th>Nonconjugated Acid</th>
<th>Conjugated Acid</th>
<th>Methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>3049-3470</td>
<td>1689-1754</td>
<td>1661-1697</td>
<td>2710-3117</td>
</tr>
</tbody>
</table>

It is possible that a secondary amine is present in the 2-methyl derivative as well as a methyl group which is indicated by a fairly strong peak. In the other two compounds the possible carboxyl groups appear to be non-conjugated.

Comparison of Bush's and the Currently Prepared Samples of the Proposed 1,8-Naphthyridine-4-Carboxylic Acid by Chromatographic Analysis

The foregoing ultraviolet spectra of these compounds seem to indicate that they are of the same nucleus and probably the same in structure. Another possible means of substantiating this is through the use of chromatographs.

Chromatographs were run using phenol saturated with water and butanol-water-glacial acetic acid. Five different preparations of the currently prepared samples were used along with four samples prepared by Bush. In the phenolic media all nine samples gave $R_f$ values of...
0.94 while in the butanol solution eight of the samples had \( R_f \) values of 0.96 and one, prepared by Bush, gave a value of 0.81. In all cases the chromatographs were developed with ultraviolet light. Here again it appeared that the separately prepared compounds were the same.

Determination of the Neutralization Equivalents of the Proposed 1,8-Naphthyridine-4-Carboxylic Acid and 2-Phenyl-1,8-Naphthyridine-4-Carboxylic Acid

The actual presence of carboxyl groups in these two compounds seems to raise one of the greatest problems. If the presence or absence of these groups could be ascertained, a possible structure for these compounds could be more easily assumed. The uncertainty of their presence is exhibited by the insolubility of the compounds in 5% and 6N NaOH. This is a general test, however, and there can be exceptions due to an undetected slight solubility or the physical characteristics of the compounds, such as their ability to be wetted. Assuming that this was an exception, the neutralization equivalents of the two compounds were determined in an alcoholic medium (12, p.129).

The proposed 1,8-naphthyridine-4-carboxylic acid equivalent was between 1007 and 1767. The proposed 2-phenyl derivative gave an equivalent between 663 and
Phenolphthalein was first used but no definite end point could be determined due to the orange color of the solution. M-cresol purple was then used and, though the exact end point could not be determined, the purple color produced gave an approximate end point. These results furnished little help in determining the molecular weight; however, they did indicate that these two compounds could be titrated and therefore might possibly contain a carboxyl group.

**Attempted Preparation of Derivatives (3, 12) of the Proposed 1,8-Naphthyridines**

The utilization of the tertiary nitrogen was attempted by preparing the hydrochlorides and picrates (3, p.264 and 12, p.181). In each case a satisfactory product could not be isolated.

Since the hydrogens in all of the compounds prepared are exceedingly high, a possibility exists that the primary amine of the aminopyridine may still contain one of its hydrogens. Attempts were made to prepare the acetyl, benzoyl, benzene sulfonyl and p-toluene sulfonyl derivatives (3, pp.257-259 and 12, pp.177-178) of this possible secondary amine but in all cases no derivative was formed.

Since carbonyl groups could be present in the
resulting product, the preparation of derivatives of these functional groups were attempted with phenyl hydrazine (3, p.246 and 12, p.171) and 2,4-dinitrophenylhydrazine (3, p.247 and 12, p.171), but again the desired product was not obtained.

Degradative Reactions Attempted

In the course of these reactions, a possible 1,2-di- or 1,2,3,4-tetrahydro derivative could form, and if this did occur the ring could be broken by exhaustive methylation to give either pyridine or 2-aminopyridine with a side chain attached to the number 3 position on the pyridine nucleus. Exhaustive methylation were attempted, but in each case a product was obtained which had degraded itself to an extent far beyond that expected by this type reaction and could not be identified.

Dehydrogenation of the compounds was attempted, first with nitrobenzene, then with zinc and finally with sulfuric acid. In all cases decomposition occurred. Other methods of dehydrogenation were not attempted as these compounds decomposed very rapidly at the elevated temperatures at which these methods would be performed.

The compounds were then oxidized in an aqueous potassium permanganate solution. The purpose of this was to obtain the 2-aminopyridine-3-carboxylic acid as
described by Chiai (8). No compound of this type was obtained from any of the prepared compounds. Only in the case of the 2-phenyl derivative was an identifiable product obtained and this was benzoic acid.
DISCUSSION OF RESULTS

The original problem on which this thesis was based, as indicated on Page 2, became subordinate when the proposed 1,8-naphthyridine derivatives consistently failed to give the required analyses.

It was believed at first that a dihydro or tetrahydro derivative had formed. This assumption was based on the proposed course of the reaction and on the analyses obtained. It was thought that the condensation proceeded according to the following steps:

\[
\text{H}_2\text{C-CH}_2\text{N} + \text{H}_2\text{C-CH}_2\text{NH}_2 + \text{H}_2\text{C-CH}_2\text{OH} \rightarrow \text{H}_2\text{C-CH}_2\text{N-CH} = \text{C} = \text{OH}
\]

Reaction I is a conventional Mannich type reaction. Reactions II and III correspond quite closely to a
Doebner-Miller type condensation, but in the case of this named reaction a dehydrogenating agent is always present to reduce the newly-formed dihydro ring to an aromatic structure. In the reactions using benzaldehyde and paraformaldehyde, there were no known dehydrogenating agents and no known hydrogenating agents to give Reaction IV. The only uncertainty, in relation to the purpose of the reactants, is that two moles of pyruvic acid are used in all cases where it is specified. When one mole is used, the yield is reduced to about one-seventh of that reported. Whether this extra mole functions in some way as one of the previously-mentioned agents is not known.

Analytical values for the three possible compounds, based on their degree of saturation, are shown in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Aromatic</th>
<th>Dihydro</th>
<th>Tetrahydro</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,8-Naphthyridine</td>
<td>C 62.1</td>
<td>61.35</td>
<td>60.66</td>
</tr>
<tr>
<td></td>
<td>H 3.47</td>
<td>4.57</td>
<td>5.66</td>
</tr>
<tr>
<td></td>
<td>N 16.09</td>
<td>15.90</td>
<td>15.72</td>
</tr>
<tr>
<td>2-Phenyl-1,8-</td>
<td>C 71.99</td>
<td>71.41</td>
<td>70.85</td>
</tr>
<tr>
<td>Naphthyridine-</td>
<td>H 4.03</td>
<td>4.79</td>
<td>5.55</td>
</tr>
<tr>
<td>4-Carboxylic Acid</td>
<td>N 11.19</td>
<td>11.11</td>
<td>11.02</td>
</tr>
<tr>
<td>2-Methyl-1,8-</td>
<td>C 74.97</td>
<td>73.93</td>
<td>72.93</td>
</tr>
<tr>
<td>Naphthyridine</td>
<td>H 5.59</td>
<td>6.89</td>
<td>6.16</td>
</tr>
<tr>
<td></td>
<td>N 19.50</td>
<td>19.17</td>
<td>18.90</td>
</tr>
</tbody>
</table>

The only large discrepancy is that exhibited by the percentage of nitrogen. In the compounds analyzed, except for the 2-methyl derivative, the nitrogen content
was far below any of those listed. Much time was spent on the above theory since the nitrogen percentages were not determined until recently.

The 2-methyl-1,8-naphthyridine seems to be the most reliable compound insofar as the desired results are concerned. This is based on the experimental data and on the actual mechanism of the reaction. The original Doebner-Miller quinaldine synthesis (4) was based on the condensation of aniline with acetaldehyde in the presence of concentrated HCl. In this reaction the acetaldehyde formed crotonaldehyde which in turn condensed with aniline, dehydrogenated and gave quinaldine.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}=\text{C}-\text{CH}_2&+\text{H}_2\text{C}=\text{C}-\text{H} \xrightarrow{\text{conc.} \text{HCl}} \text{C}_6\text{H}_5\text{C}=\text{C}-\text{CH}_2\text{NH}_2 \\
\rightleftharpoons \xrightarrow{\text{conc.} \text{HCl}} \text{C}_6\text{H}_5\text{N}=\text{C} \text{CH}_3
\end{align*}
\]

The only variation in this reaction is that 2-aminopyridine was used in lieu of aniline. The ultraviolet spectra indicates that the 2-aminopyridine is present and the infrared spectra tends to show that a methyl group and a secondary amine are also present.
This would indicate possibly a dihydro derivative since the secondary amine could not be present unless the number 2 carbon was saturated. The analytical data indicates a tetrahydro derivative; however, this could be an error due to the purity of the compound. The one conflicting result is that a derivative could not be obtained with the proposed secondary amine.

The other compounds prepared do not appear to be of the 1,8-naphthyridine structure. This is enigmatic since both the 4-carboxyl and 2-phenyl-4-carboxyl derivatives have been reportedly prepared and their analyses checked with the theoretical values of the desired compound while the currently prepared samples give carbon and hydrogen percentages close to the theoretical but with low nitrogen results. The 2-phenyl-4-carboxyl derivative was prepared from abstracted directions (7) since the journal could not be obtained. There is, therefore, no actual proof on hand as to how the structure was determined. The melting points of the latter prepared compounds also coincide with those reported in literature.

In order to have such a low nitrogen content, one of two things could have happened. The nitrogen determination could be in error or a large molecule developed around the 2-aminopyridine. The former is doubtful since two different commercial laboratories duplicated
the results using the same 2-phenyl-4-carboxyl derivative and two different preparations of the 4-carboxyl derivative. The latter reason is therefore the probable solution.

In both of these reactions, the most likely first step is the formation of a Mannich base. It was thought that the product of Reaction I was formed but there is no reason why a double-Mannich base could not result. This could be substantiated by the absence of the secondary amine in the infrared spectra and the derivative formation. Another support for this is the tremendous increase in yield when excess formaldehyde and two moles of pyruvic acid are used. This would give the following compound:

![Structural formula](image)

The "R" can be derived from either formaldehyde or benzaldehyde. This structure would be inadequate as a final product due to the prepared compounds' apparent insolubility in alkali, extremely low nitrogen content and failure to give a ketone test.

In order to compensate for these inadequacies in the reaction where benzaldehyde was used, a third mole
of benzaldehyde could condense between the two side chains.

This compound gives a calculated analysis of C, 71.9; H, 4.9; N, 5.3 which is comparable to that found. The negative carbonyl test could be caused by steric hindrance, but the alkali solubility still remains doubtful. The infrared spectra shows the possibility of a nonconjugated acid and also a peak at 1770 which is in the range of a carbonyl, 1600 - 1820. Another possible support for the acid group, as mentioned before, is the neutralization equivalent. In the preparation of the 2-phenyl-4-ethyl carboxylate, the supposedly free acid was obtained as determined by the analysis and melting point. It appeared as if the ester of the above compound was the product before the steam distillation since it was a liquid and then after the attempted
distillation the acid was obtained from the hydrolysis that could occur at 1000°C. This would indicate that the carboxyl group did not enter into the reaction and that it could still be present in the resulting compound.

The reaction with formaldehyde presents a different problem since many more possibilities exist. Again the unicyclized compound shown above appears to be the most logical first step but from that point numerous compounds could form. For instance, formaldehyde could attach itself to the pyridine nucleus to give a 3- and/or 5- (hydroxymethyl) pyridine derivative. This would permit further condensation at these points. A lactone ring is also possible but did not appear to be present in the infrared spectra. Polymerization could occur since all of the traditional groups are present but the same degrees of polymerization would have to result in each different reaction since the melting points are reproducible and also, in this particular case, the nitrogen content would be much higher. An anhydride structure is also possible though not probable as it would be alkali soluble. The reaction with benzaldehyde could also result in one of the aforementioned possibilities but the example described appears to be a more likely structure.

As a final means of determining the structures
for these compounds, the empirical formulas were determined. They are not too reliable, insofar as the exact formulas are concerned, as the purity of the compounds is uncertain; however, they do give an indication of the molecular size. These formulas are based on the presence of two nitrogens.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Phenyl-1,8-Naphthyridine-4-Carboxylic Acid</td>
<td>42.6</td>
<td>42.2</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>1,8-Naphthyridine-4-Carboxylic Acid</td>
<td>13.5</td>
<td>13.78</td>
<td>2</td>
<td>9.69</td>
</tr>
<tr>
<td>2-Methyl-1,8-Naphthyridine</td>
<td>9.81</td>
<td>12.50</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

The 2-phenyl-4-carboxyl derivative appears to be even more complex than was originally proposed on Page 33 where an empirical formula of C₁₂H₂₆N₂O₆ can be derived. It is indicative from the table that one or even two carboxyl groups are present in the molecule. It does not seem probable that eight oxygens could be attributed to carboxyl groups as carboxyl derivatives should have easily been obtained.

The empirical formula of the 4-carboxyl derivative does not offer any definite results for theorizing purposes since too many possibilities are present.

The 2-methyl derivative coincides quite closely with the tetrahydro derivative which would have an
empirical formula of $C_9H_{12}N_2$.

In conclusion it might be said that the two proposed acid derivatives appear to be definite and reproducible compounds of a fairly complex nature and that the 2-methyl derivative is quite possibly 2-methyl (1,2,3,4-tetrahydro)-1,8-naphthyridine.

It is regretted that, due to lack of time, further work on these compounds could not be undertaken.
SUMMARY

1. The reaction of 2-aminopyridine, paraformaldehyde and pyruvic acid was investigated which should have resulted in a formation of 1,8-naphthyridine-4-carboxylic acid, but the product was not identified.

2. The reaction of 4-aminopyridine, paraformaldehyde and pyruvic acid was investigated which should have resulted in a formation of 1,6-naphthyridine-4-carboxylic acid, but the product was not identified. Work on this compound was discontinued due to the small yield obtained in relation to the extremely long preparational period of the 4-aminopyridine.

3. The preparation of the supposedly known 2-phenyl-1,8-naphthyridine-4-carboxylic acid was attempted in order to use the compound as a standard in ultraviolet and infrared work, but the product was not identified.

4. The reaction of 2-aminopyridine and acetaldehyde in concentrated HCl was investigated and a compound obtained that might possibly be 2-methyl-(1,2,3,4-tetrahydro)-1,8-naphthyridine. This is a new method of preparation of a compound which had been listed in literature as an uncertain compound.

5. Portions of ultraviolet and infrared absorption
spectra were determined on all but the 1,6-naphthyridine-4-carboxylic acid.

6. Various reactions were performed on these compounds such as oxidation, dehydrogenation, exhaustive methylation and derivative formation with the intent of characterizing the compounds.

7. Chromatographs were run on samples of 1,8-naphthyridine-4-carboxylic acid which had been prepared by Bush and the author.

8. Neutralization equivalents were determined on the compounds containing carboxyl groups.


