A STUDY OF THE CONDENSATION OF THE
α - AND γ-AMINOPYRIDINES WITH
PYRUVIC ACID AND CERTAIN ALDEHYDES

by

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Typed by Mary Decker

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# A STUDY OF THE CONDENSATION OF THE
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## 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-Kritschenko 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:
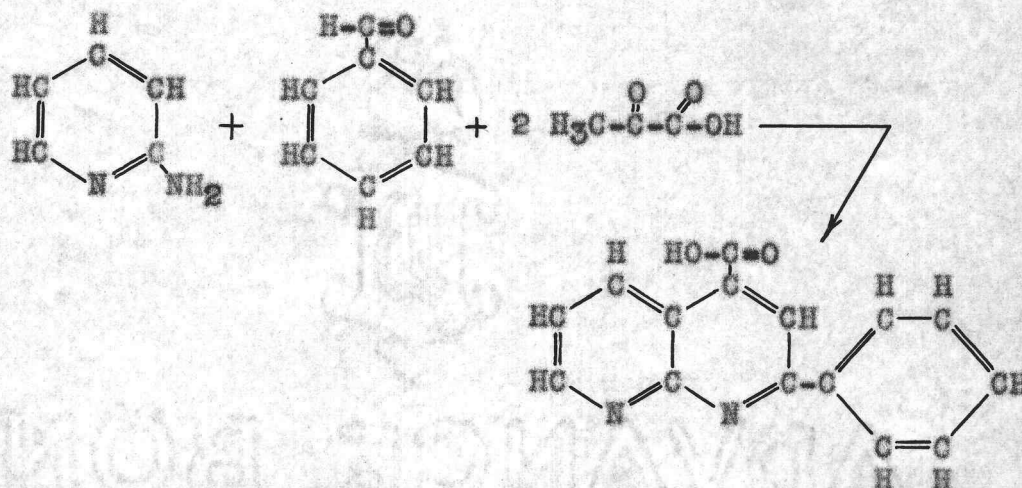


An exploratory reaction of this type was performed
by Bush (1, pp.27-28) in 1952 using paraformaldehyde,
2-aminopyridine and pyruvic acid. The paraformaldehyde
depolymerized in the course of the reaction, liberating
free formaldehyde which reacted to form 1,8-naphthyridine-
4-carboxylic acid.
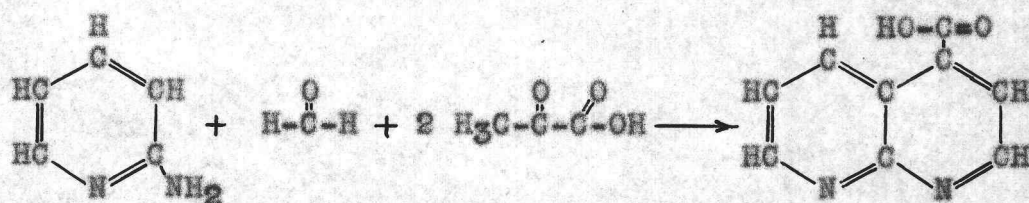
According to Bush, one other possibility was also
present and that was the cyclization of the Mannich base
to the tertiary pyridine nitrogen giving a 2-pyrido
(1.2-a) pyrimidine-4-carboxylic acid. The only difference
between these two compounds was that the latter had one
more molecule of hydrogen which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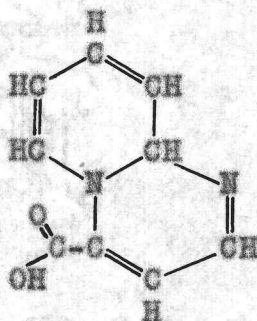


In order to establish the direction of cyclization,
it was necessary to determine the reactive tendencies in
this reaction of the number 3 carbon in the aminopyridine
molecule. Two analogous reactions were performed which
in each case, if cyclization occurred, a bicyclic
structure would be produced. 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-amino-
pyridine. The following equation demonstrates this
reaction:
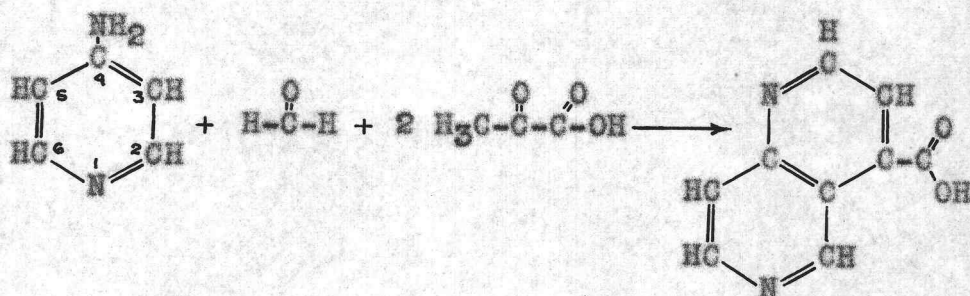


As can be seen, the product would be the same
regardless of whether the cyclization went to the number
3 or 5 carbon.

## 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 fraction-ating column. The pyruvic acid came over at 79° - 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 $CaCl_2$ 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

and HCl but was insoluble in ether, petroleum ether, water and NaOH. Analytical for $C_9H_6O_2N_2$: molecular weight = 174.15. Calculated: C, 62.1; H, 3.47; N, 16.09. Found: C, 61.64; H, 5.24; N, 10.66.

In the original reaction (1, pp.27-28), paraformaldehyde 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 r-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 $KMnO_4$
(0.54 mole). The solution was refluxed until the purple
color had disappeared, approximately 1 hour. Another 90 g
portion of $KMnO_4$ 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 $H_2SO_4$
for 4 hours. This was poured into three times its volume
of ice and $Na_2CO_3$ added to neutralize the $H_2SO_4$. The
ester was then extracted with ether and the extract dried
with $Na_2CO_3$ overnight. This was filtered and the ether
distilled. To the oily residue was added 5 cc of 28%
$NH_4OH$. 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 recrystal-
lized 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 re-
fluxed 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 $C_9H_5O_2N_2Na$: 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 8.8 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 redissolved 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 $C_{15}H_{10}O_2N_2$:  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)
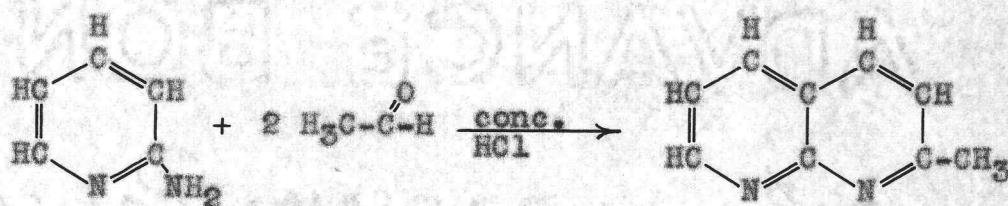
To a flask immersed in an ice bath was added 9.4 g
(0.1 mole) of 2-aminopyridine and then, with constant
stirring, 50 cc of concentrated HCl was added slowly.
The resulting solution was allowed to stand for 10 min-
utes.  After this period 8.8 g (0.2 mole) of acetaldehyde
was added and the solution allowed 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 $P_2O_5$ 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 $C_9H_8N_2$: 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 15°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 15°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 aque-
ous calcium chloride solution, the ester layer was
separated and then distilled under reduced pressure.
Almost the whole product distilled over at 62° - 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 $C_{17}H_{14}O_2N_2$: 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 ab-
sorption 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
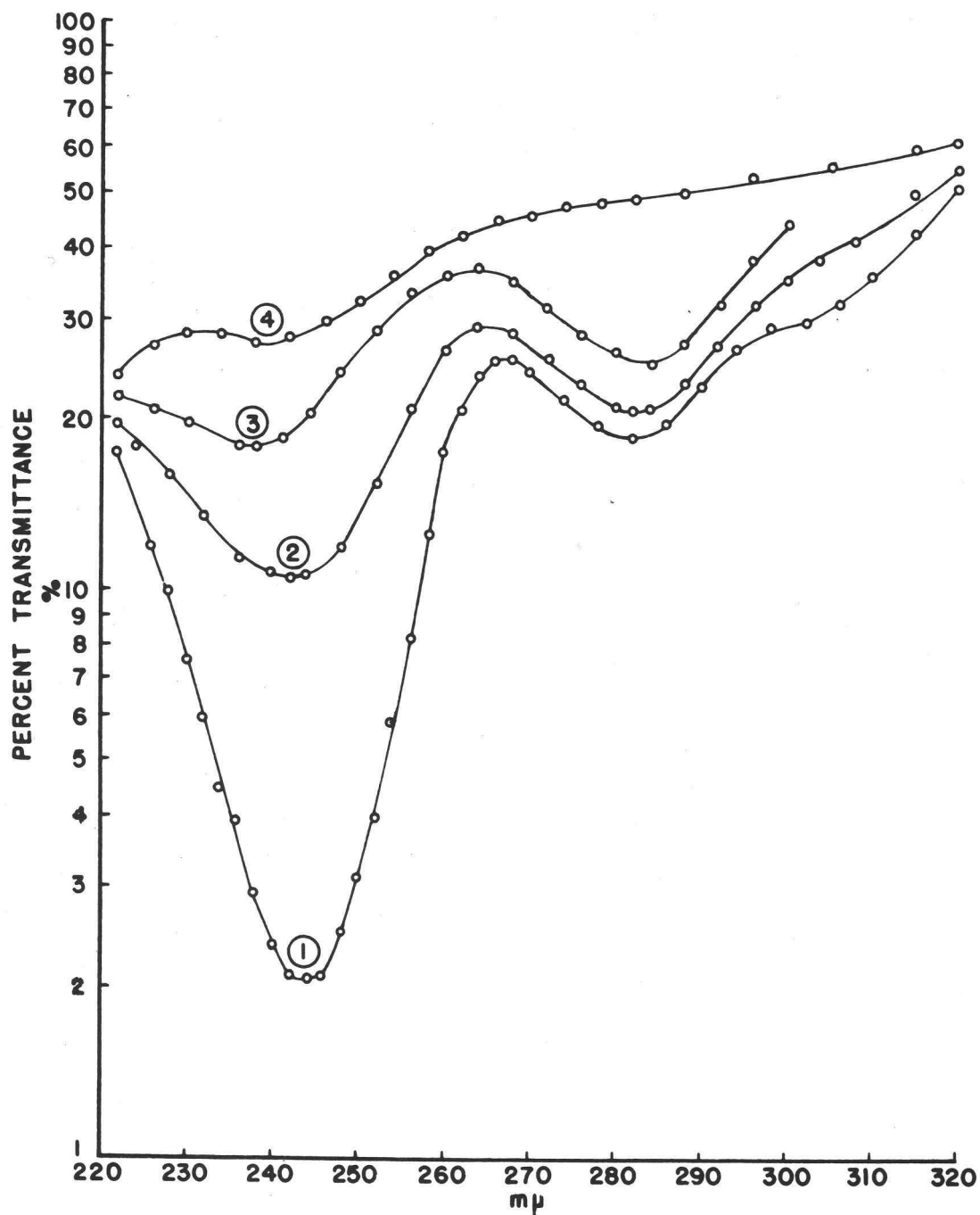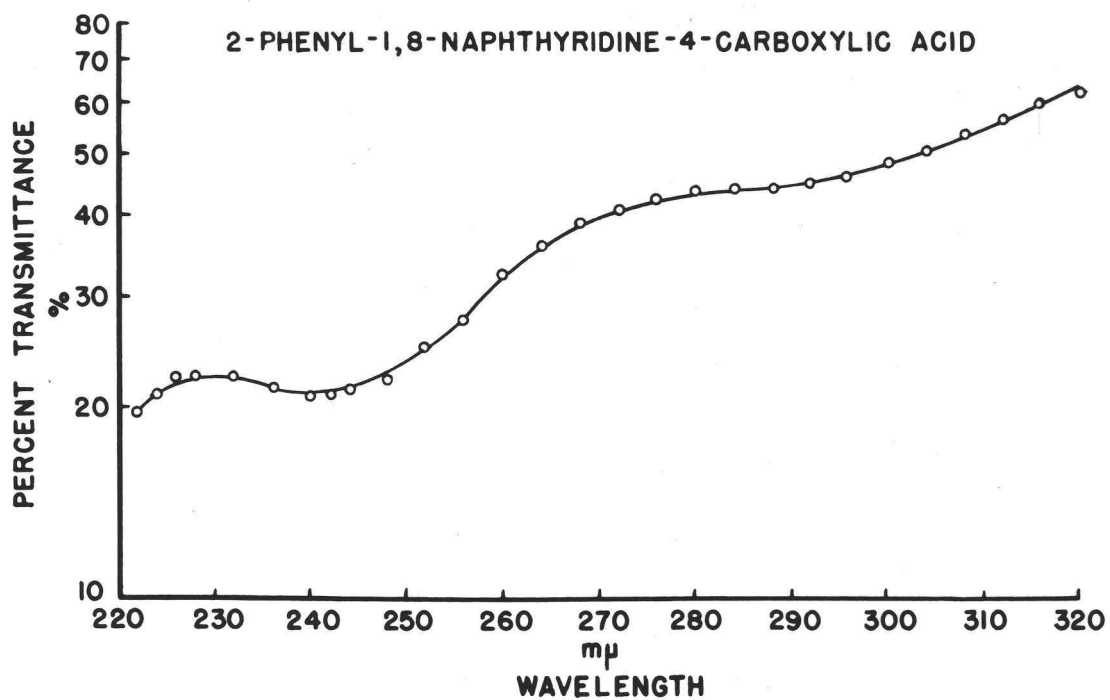
# 1,8-NAPHTHYRIDINE-4-CARBOXYLIC ACID
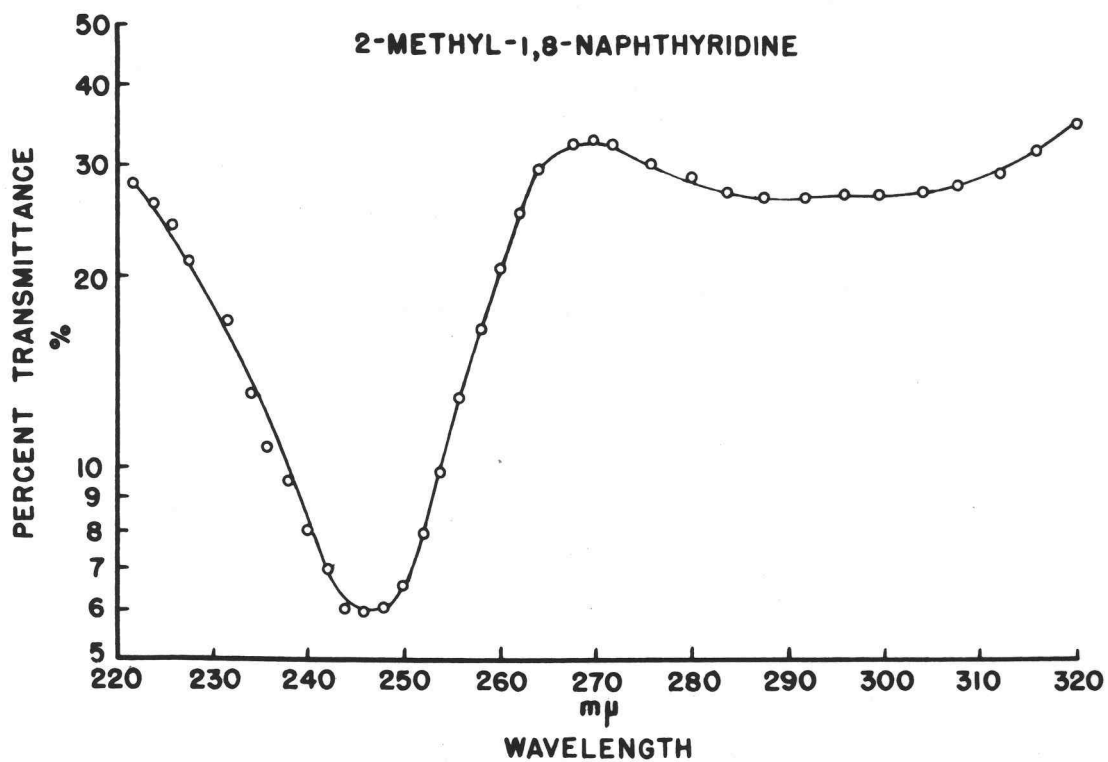


Figure I

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Figure 2



Figure 3

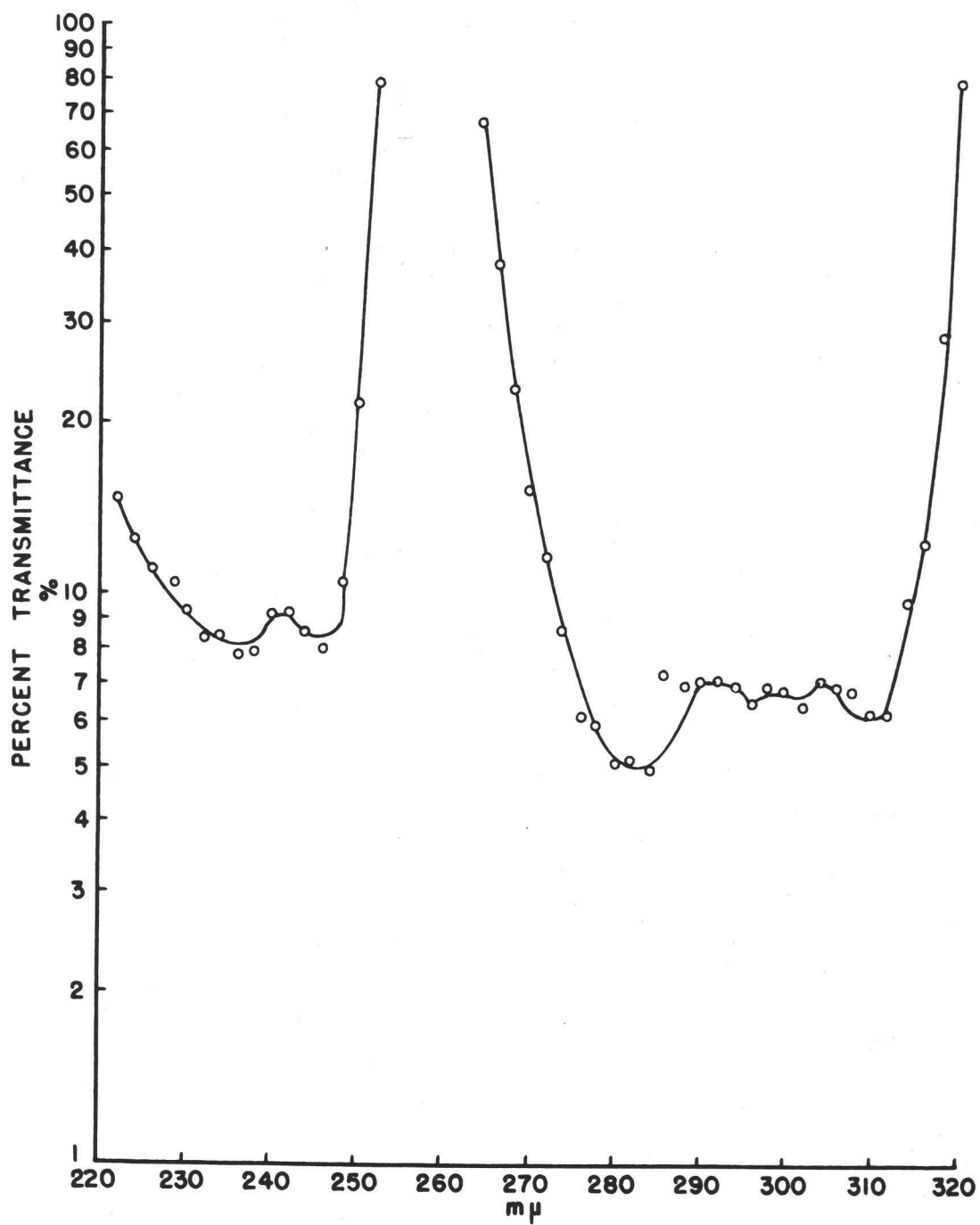2-AMINOPYRIDINE



WAVELENGTH

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 mμ
and 282 mμ 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:

| 1,8-Naphthyridine-4-Carboxylic Acid | 2-Phenyl-1,8-Naphthyridine-4-Carboxylic 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
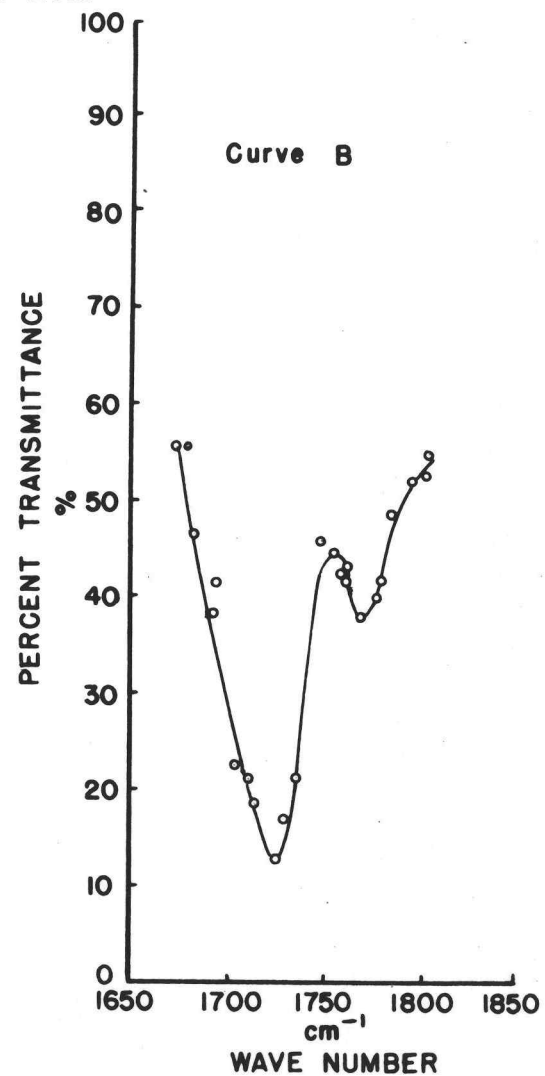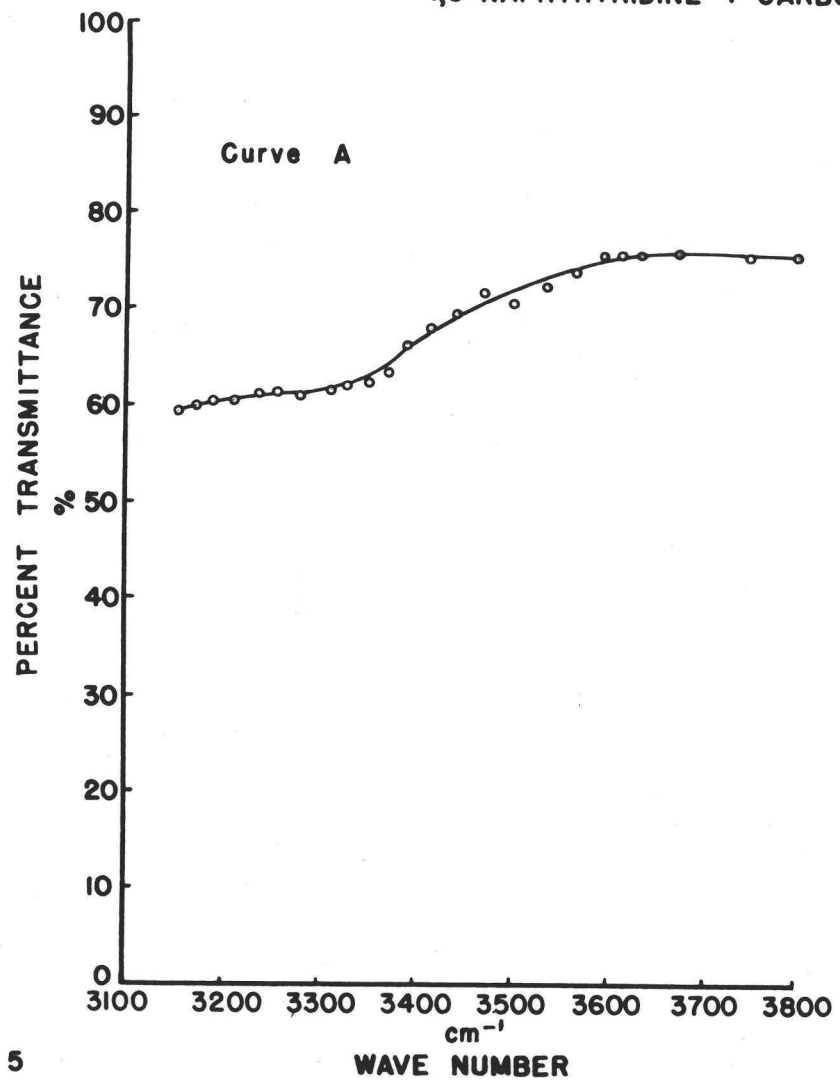
# 1,8-NAPHTHYRIDINE-4-CARBOXYLIC ACID



Figure 5

20

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

Figure 6

2-METHYL-1,8-NAPHTHYRIDINE
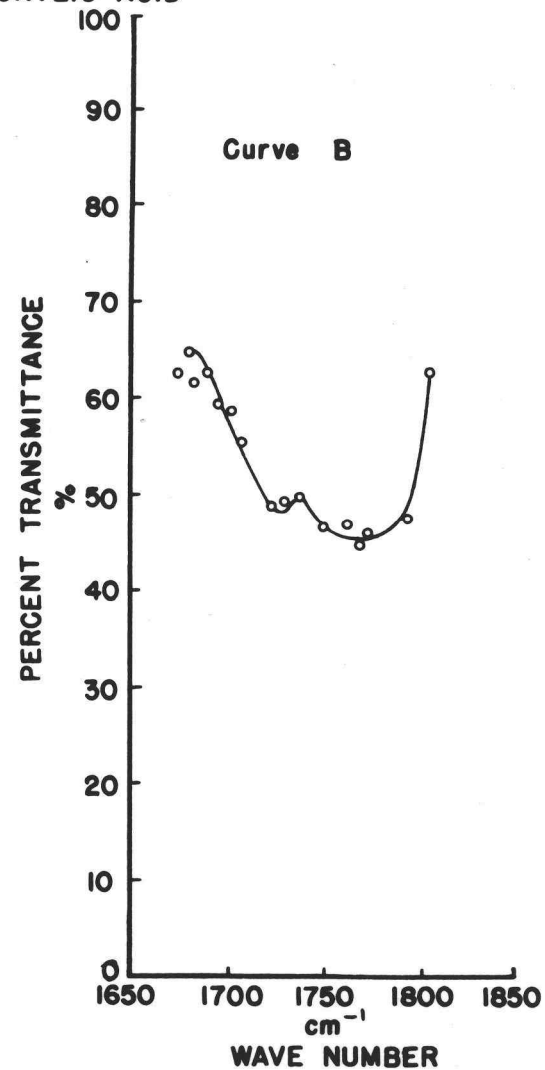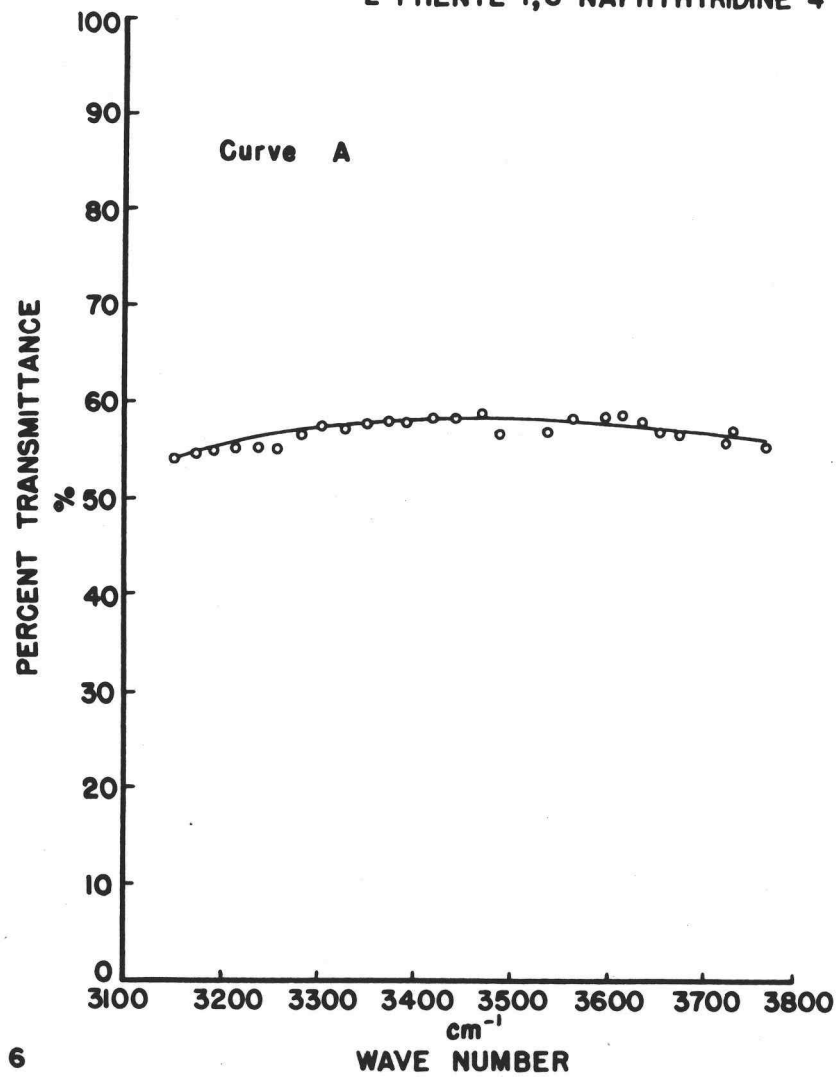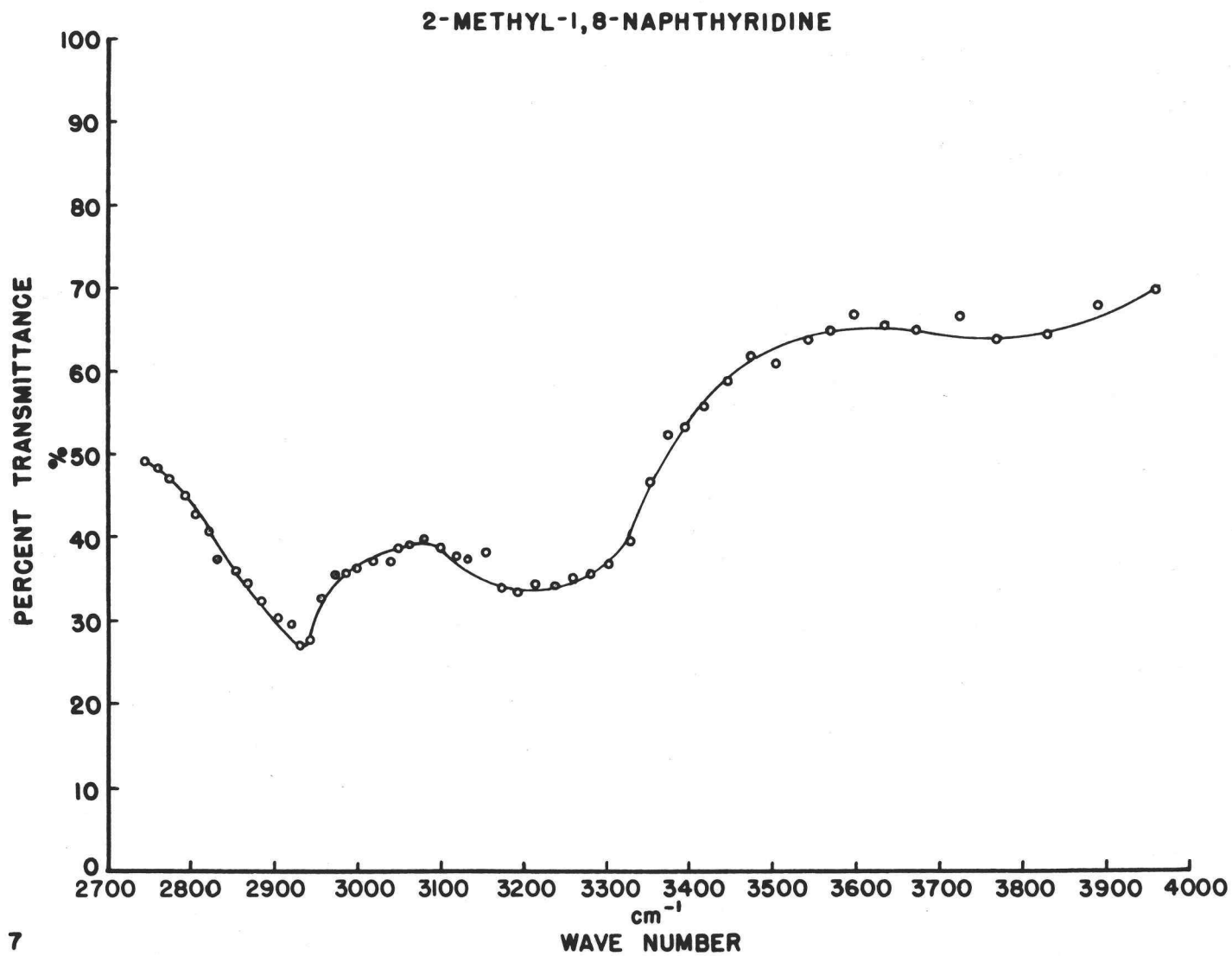
Figure 7

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

| Secondary Amine | Nonconjugated Acid | Conjugated Acid | Methyl |
|---|---|---|---|
| 3049-3470 | 1689-1754 | 1661-1697 | 2710-3117 |

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 com-
pounds 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 1787. The proposed 2-phenyl derivative gave an equivalent between 663 and

949. 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 pre-
pared 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 methylations 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 Ochiai (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 tetra-hydro 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:

$$\text{(naphthyridine-NH}_2) + H\text{-C-H} + 2\ H_3C\text{-C-C-OH} \xrightarrow{\ I\ } \text{(product)}$$

$$\xrightarrow{\ II\ }$$

III          IV
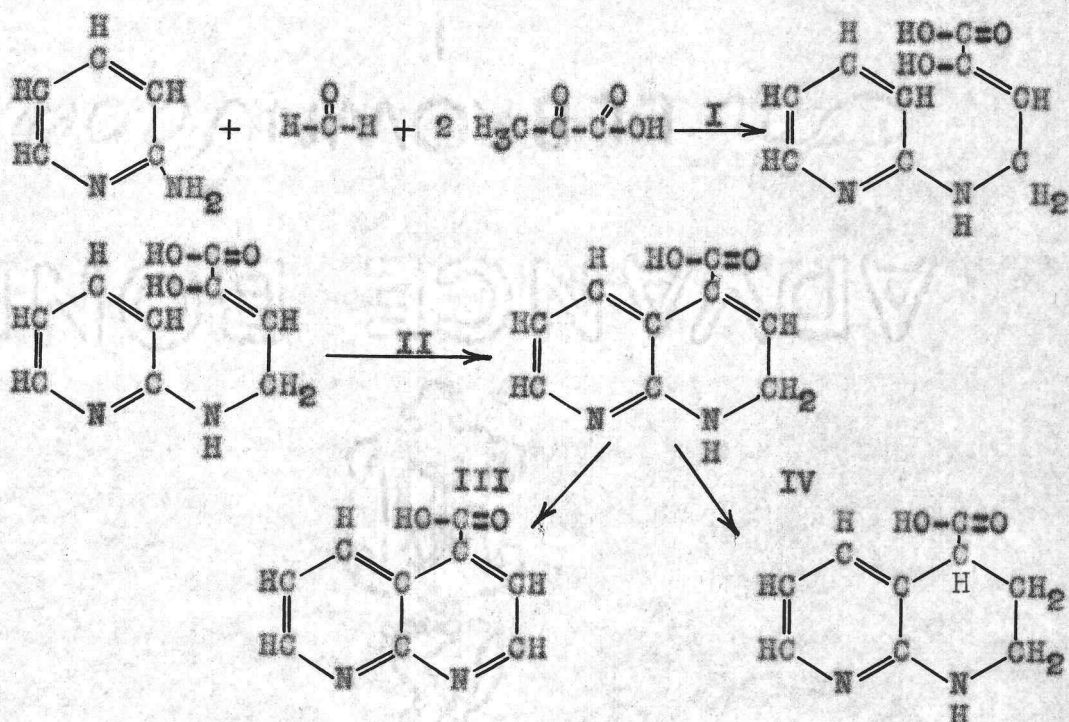
Reaction I is a conventional Mannich type reaction. Reactions II and III correspond quite closely to a

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:

|  |  | Aromatic | Dihydro | Tetrahydro |
|---|---|---|---|---|
| 1,8-Naphthyridine-<br>4-Carboxylic Acid | C | 62.1 | 61.35 | 60.66 |
|  | H | 3.47 | 4.57 | 5.66 |
|  | N | 16.09 | 15.90 | 15.72 |
| 2-Phenyl-1,8-<br>Naphthyridine-<br>4-Carboxylic Acid | C | 71.99 | 71.41 | 70.85 |
|  | H | 4.03 | 4.79 | 5.55 |
|  | N | 11.19 | 11.11 | 11.02 |
| 2-Methyl-1,8-<br>Naphthyridine | C | 74.97 | 73.93 | 72.93 |
|  | H | 5.59 | 6.89 | 8.16 |
|  | N | 19.50 | 19.17 | 18.90 |

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.
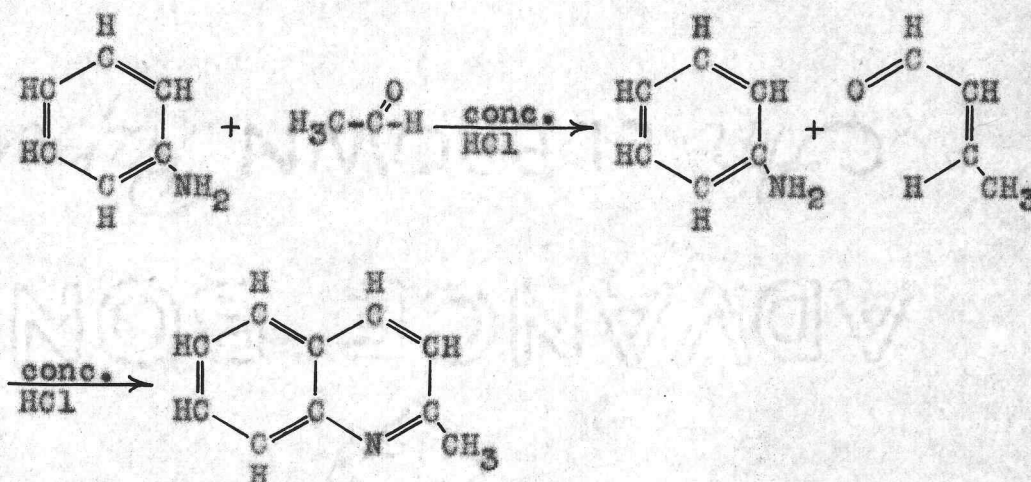
The only variation in this reaction is that
2-aminopyridine was used in lieu of aniline. The ultra-
violet spectra indicates that the 2-aminopyridine is
present and the infrared spectra tends to show that a
methyl group and a secondary amine are also present.

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 deriva-
tive. The latter reason is therefore the probable solu-
tion.

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 forma-
tion. 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:
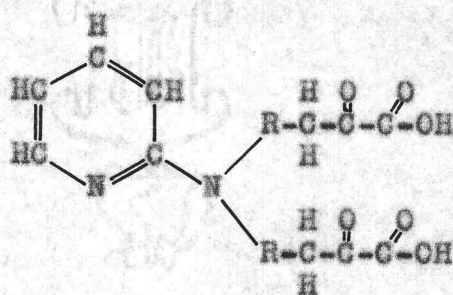


The "R" can be derived from either formaldehyde
or benzaldehyde. This structure would be inadequate as
a final product due to the prepared compounds' apparent
insolubility in alkali, extremely low nitrogen content
and failure to give a ketone test.

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.
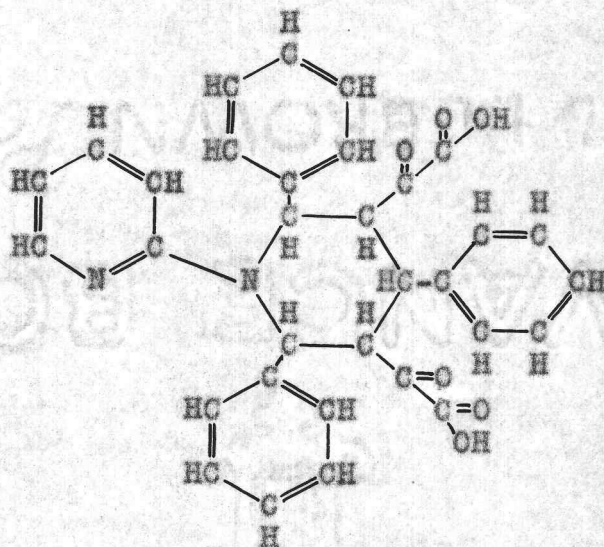


This compound gives a calculated analysis of C, 71.9; H, 4.9; N, 5.3 which is comparable to that found. The negative carbonyl test could be caused by steric hindrance, but the alkali solubility still remains doubtful. The infrared spectra shows the possibility of a nonconjugated acid and also a peak at $1770\bar{v}$ which is in the range of a carbonyl, $1600 - 1828\bar{v}$. 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 100°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 uncyclized 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.

|  | C | H | N | O |
|---|---|---|---|---|
| 2-Phenyl-1,8-Naphthyridine-4-Carboxylic Acid | 42.6 | 42.2 | 2 | 6.2 |
| 1,8-Naphthyridine-4-Carboxylic Acid | 13.5 | 13.76 | 2 | 3.69 |
| 2-Methyl-1,8-Naphthyridine | 9.04 | 12.50 | 2 | - |

The 2-phenyl-4-carboxyl derivative appears to be even more complex than was originally proposed on Page 33 where an empirical formula of $C_{32}H_{26}N_2O_6$ 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 carbonyl 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

empherical 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.

# BIBLIOGRAPHY

1. Bush, David C. Applications of the mannich reaction. Ph.D. thesis. Corvallis, Oregon state college, 1953. 35 numb. leaves.

2. Camps, Von Rudolf. Ueber einge Harnstoffe, Thioharstoffe und Urethane des Pyridins. Archiv der pharmazie und berichte der deutschen pharmazeuischen Gesellschaft 240:345-370. 1902.

3. Cheronis, Nicholas D. and John B. Entrikin. Semimicro qualitative organic analysis. New York, Thomas Y. Crowell, 1947. 498p.

4. Doebner, O. and W. von Miller. Ueber Chinaldinbasen. Berichte der deutschen chemischen Gesellschaft 16(B):2464-2476. 1883.

5. Kamm, Oliver. Organic syntheses. Vol. 4. New York, John Wiley, 1925. 89p.

6. Mannich, C. and W. Krosche. Ueber ein Kondensationsprodukt aus Formaldehyde, Ammoniak und Antipryin. Archiv der pharmazie und berichte der deutschen pharmazeutischen Gesellschaft 250:647-667. 1912.

7. Mazza, Francesco Paolo and C. Migliardi. 2-Phenyl-1,8-naphthyridine-4-carboxylic acid and 2-phenyl-1,8-naphthyridine. Atti della reale accademia della scienze di Torino. Tomo I. Classe di scienze fische, matematiche e naturali 71:438-444. 1940. (Abstracted in Chemical abstracts 36(17):5477(7). 1942.)

8. Ochiai, Eiji and Komei Miyaki. Synthese von 1,8-Naphthyridine-Homologen und ihre Hydrierung. Berichte der deutschen chemischen Gesellschaft 74(B):1115-1126. 1941.

9. Petrenko-Kritschenko, P. and N. Zoneff. Ueber die condensation von Aceton-dicarbonsaureestern mit Benzaldehyde unter anwendung von Ammoniak. Berichte der deutschen chemischen Gesellschaft 39:1358-1361. 1906.

10. Schafer, H. and B. Tollens. Ueber die bildung von
    basen aus Acetophenone, Formaldehyde und
    Chlorammonium. Berichte der deutschen
    chemischen Gesellschaft 39:2181-2189. 1906.

11. Schreiber, R. S. Organic syntheses. Vol. 31. New
    York, John Wiley, 1951. 122p.

12. Shriner, Ralph L. and Reynold C. Fuson. Identifi-
    cation of organic compounds. 3d ed. New York,
    John Wiley, 1948. 370p.