AN ABSTRACT OF THE THESIS OF

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Title THE SYNTHESIS OF SUBSTITUTED 1, 8-NAPHTHYRIDINES BY THE DOEBNER REACTION

Abstract approved Redacted for Privacy
(Major professor)

The possibility of synthesizing 1, 8-naphthyridines by the Doebner reaction has appeared in many reports. The method involves the introduction of electron releasing groups in the 6-position of 2-amino pyridine to activate the C-3 position. Previously Lewis used 6-methyl-2-amino pyridine with benzaldehyde and pyruvic acid, in an attempt to prepare a 1, 8-naphthyridine. He did not obtain a 1, 8-naphthyridine but an uncyclized product. He attributed his failure to produce a naphthyridine to the weak electron releasing power of the methyl group, which was unable to activate the C-3 position. Nitidandhaprabhas found later that the uncyclized compound lost one molecule of water to give 1(6-methyl-2-pyridyl)-5-phenyl-pyrrolidine -2, 3-dione. Also he found that the use of 2, 6-diaminopyridine in the Doebner reaction did produce a 1, 8-naphthyridine, because of

the strong electron releasing power of the amino group. The current work continued the investigation of the effect of electron releasing groups at position 6 in the 2-aminopyridine ring on the formation of 1, 8-naphthyridine. The result showed that 6-hydroxy-2-aminopyridine was also effective in producing ring closure at C-3 to form a 1, 8-naphthyridine. The yield was less than that produced when 2, 6-diamino pyridine was used as the starting material.

A second method for the preparation of 1, 8-naphthyridines was developed. Benzalpyruvic acid was prepared and allowed to react with the 6-substituted 2-aminopyridines. By this method the yield of 1, 8-naphthyridines was increased.

The effect of different aldehydes in producing 1, 8-naphthyridines by the Doebner reaction was studied. O-methoxy benzaldehyde was used in the reaction in comparision with benzaldehyde. The use of O-methoxy benzaldehyde did produce a better yield.

The compounds prepared were substituted 1, 2, 3, 4-tetrahydro-1, 8-naphthyridine-4-carboxylic acid monohydrochlorides. The assigned structures were confirmed on the basis of carbon-hydrogen analysis and the evidence of ultraviolet spectra similar to the spectrum of 6-bromo-2-(methyl amino-methyl)-1, 2, dihydro 1, 8-naphthyridine. This showed two well-defined maxima at 238 and 336 mμ as reported by Zhukova.

THE SYNTHESIS OF SUBSTITUTED 1, 8-NAPHTHYRIDINES BY THE DOEBNER REACTION

by

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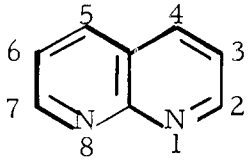
THE SYNTHESIS OF SUBSTITUTED 1, 8-NAPHTHYRIDINES BY THE DOEBNER REACTION

INTRODUCTION

Naphthyridines are compounds having two fused pyridine rings. There are six different types, depending on the relationship between the nitrogens in the two ring. All possible types are represented below:



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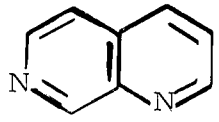

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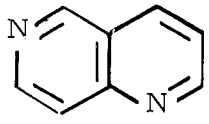

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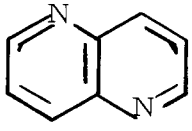

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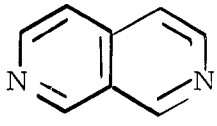

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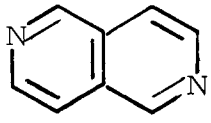


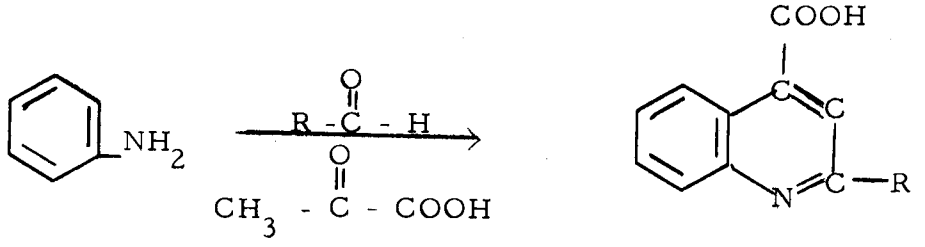
2-6

These compounds have also been called diazanaphthalenes, benzodiazines and pyridopyridines (4).

Most of the syntheses of naphthyridines are developed from quinoline syntheses, such as the Skraup, Doebner, Doebner-Miller, Combes, Conrad-Limpach and Knorr systheses.

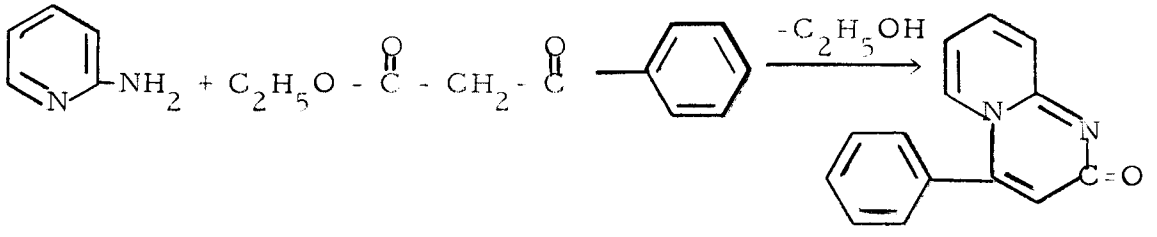
The Doebner synthesis was the method used in the preparation of quinoline 4-carboxylic acids in 1887 by refluxing aniline, aldehydes

and pyruvic acid in alcohol (3).

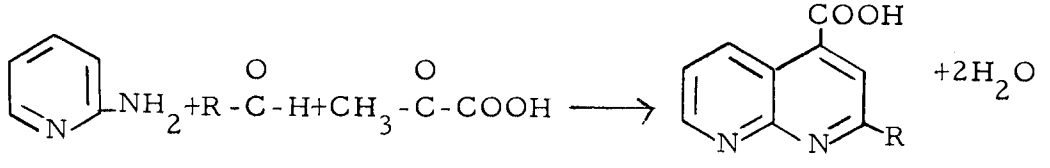


Most attempts to synthesize 1, 8-naphthyridine ring systems have not been as successful as the syntheses of quinolines.

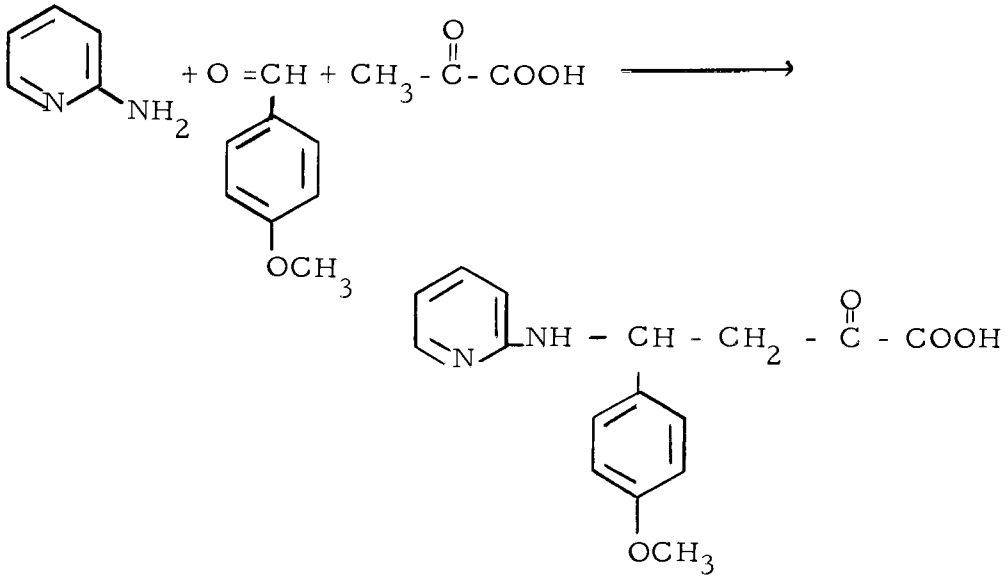
In 1925 Siede (12) found that the cyclization of the condensation product formed between 2-aminopyridine and benzoyl acetic acid ester, did not proceed through the C-3 position of the pyridine ring, but through the ring nitrogen to form a pyrimidine derivative.



In 1940 Mazza and Migliardi (7) claimed that a 2-substituted 1, 8-naphthyridine 4-carboxylic acid was isolated from the products formed by reacting 2 amino pyridine with benzaldehyde and pyruvic acid. The reaction proceeded by the following equation.



Their report was refuted by Allen and his co-workers (2). Allen's work showed that only an uncyclized product was obtained from the reaction of 2-amino pyridine with anisaldehyde and pyruvic acid. The reaction can be illustrated by the following equation.



From earlier work, the use of 2-amino pyridine as a starting material in synthesizing 1, 8-naphthyridines seems to be improbable. However, the syntheses of 1, 8-naphthyridines is possible if substituted 2-amino pyridines are used as starting materials. The most effective 2-amino pyridines are those with electron releasing groups at position 6. Lappin (5) concluded from his experiments that the nature of the substituents on the pyridine ring will affect the direction of cyclization. Two possible cyclic products can be obtained.

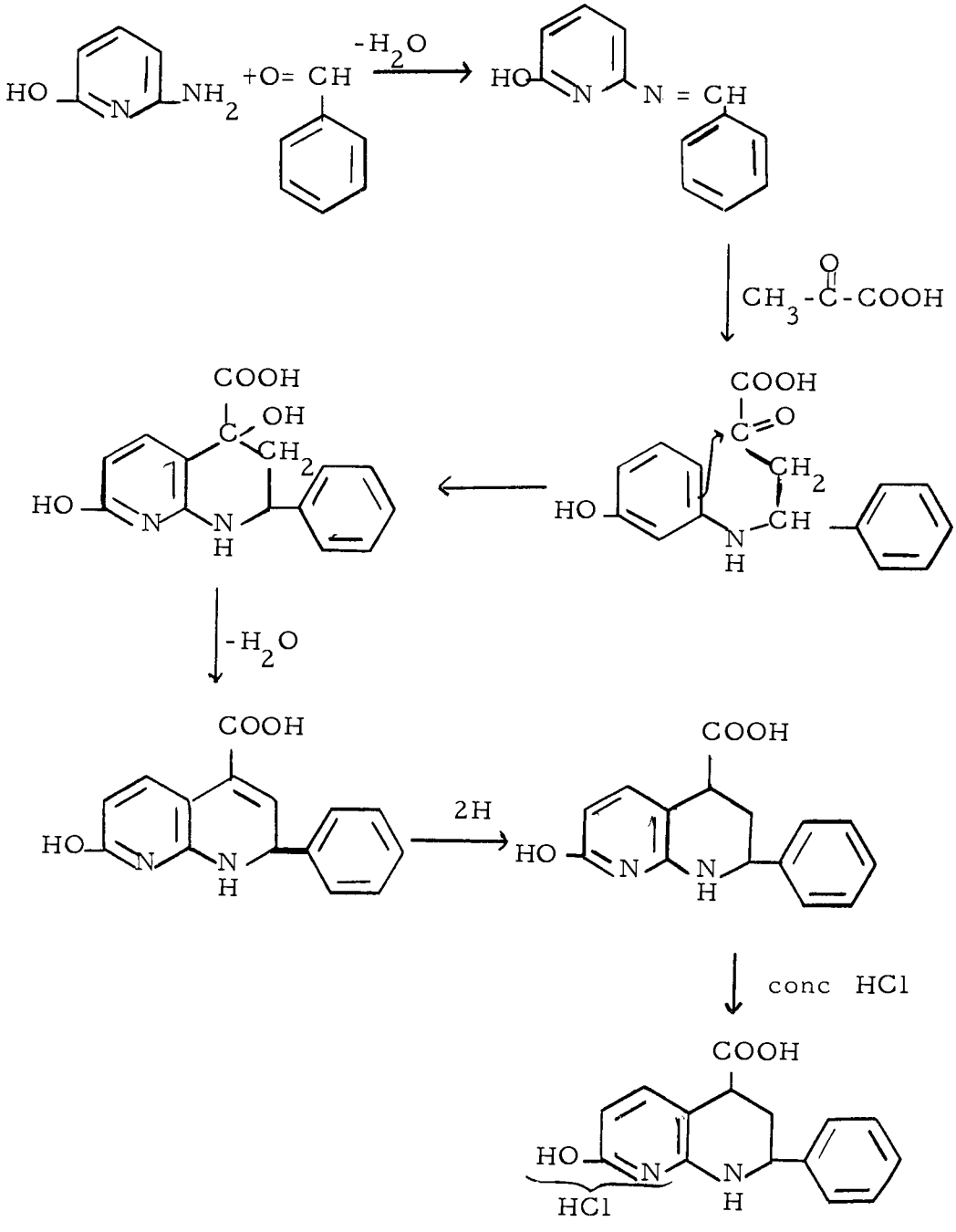
In one case the cyclization will proceed through the C-3 position; in the other the cyclization will proceed through ring nitrogen.

Previously, the syntheses of 1, 8-naphthyridines have been accomplished by condensing 2, 6-diamino pyridine with ethyl aceto-acetate, with benzoyl acetone, and with ethyl ethoxy methylene malonate, and also 2, 6-diamino; 2-amino, 6-methyl; and 2-amino, 6-ethoxy pyridines with ethyl malonate (1) and 2, 6-diamino pyridine with benzaldehyde and pyruvic acid (9).

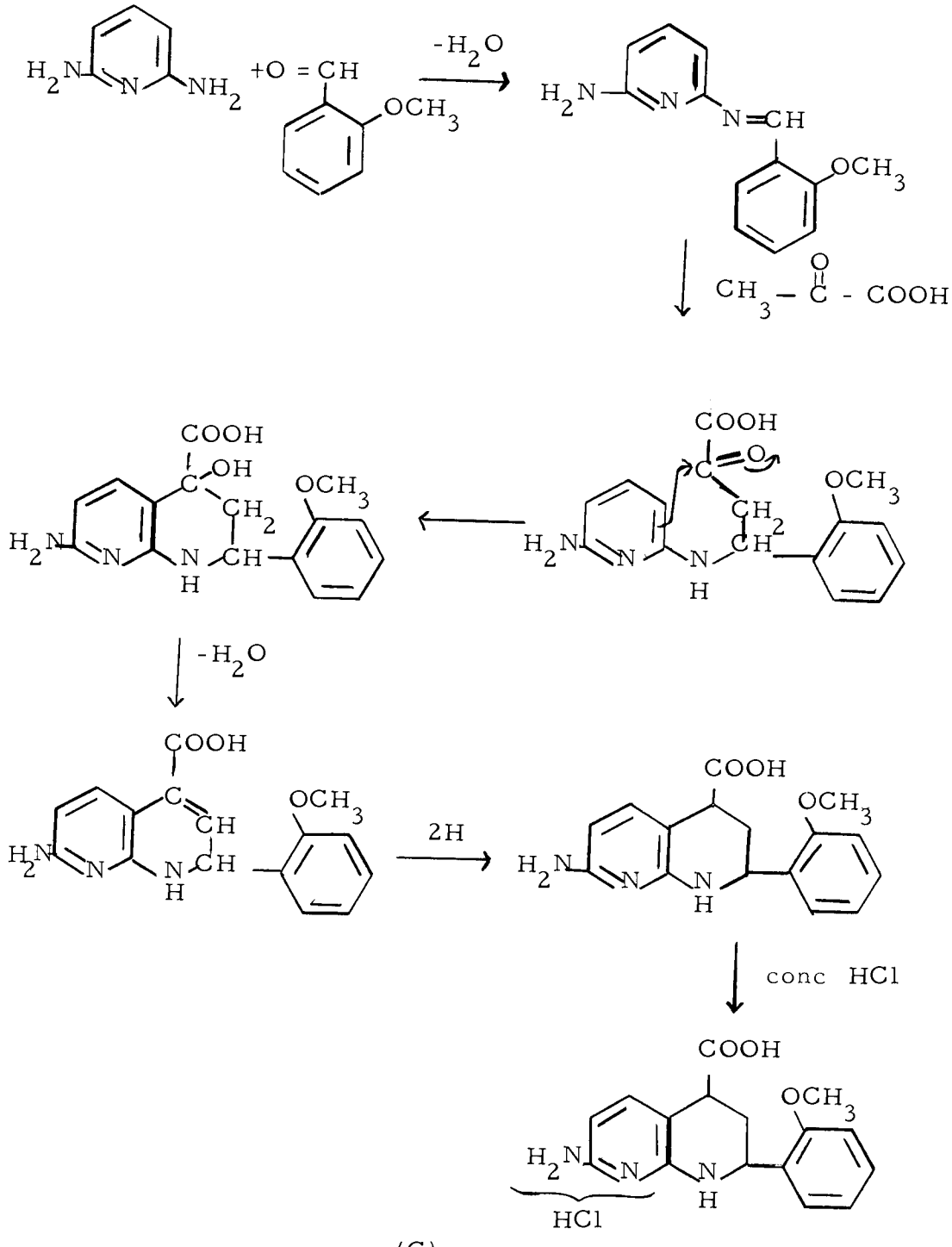
The use of 6-methyl-2-amino pyridine as a starting naterial in the Doebner reaction has been reported by Lewis (6). One product obtained was the uncyclized product similar to the one described by Allen. However, this uncyclized product loses one molecule of water to give another product, found later by Nitidandhaprabhas to be pyrrolidine-2, 3-dione derivative.

Lewis attributed his failure to obtain a 1, 8-naphthyridine to the weak electron releasing power of the methyl group.

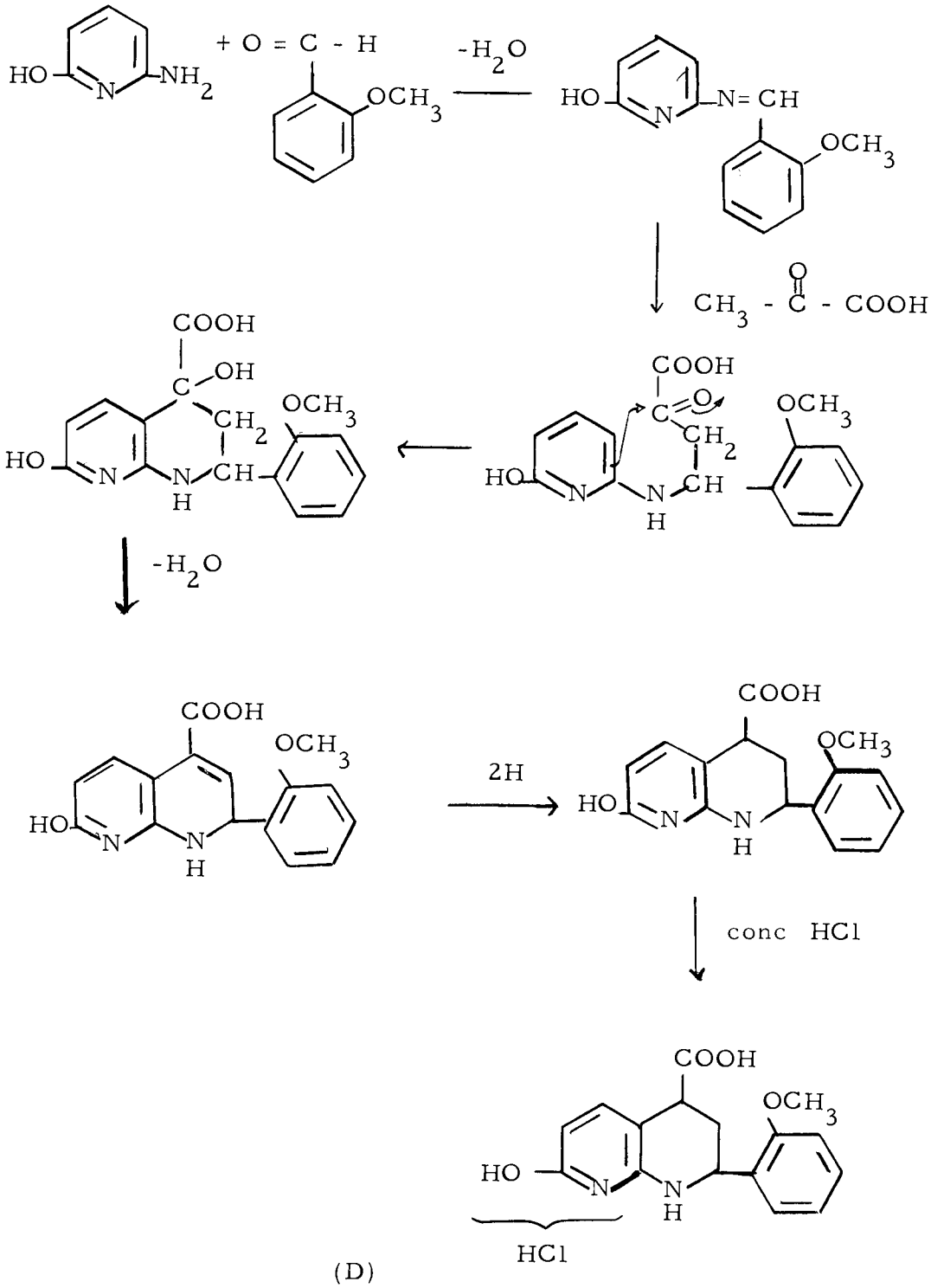
FLOW SHEET OF THE SYNTHESIS OF SUBSTITUTED 1, 8-NAPHTHYRIDINES BY THE DOEBNER REACTION



(B)



(C)



(D)

DISCUSSION

The difficulty of synthesizing 1, 8-naphthyridines by the Doebner reaction is due to the tendency of the heterocyclic nitrogen to withdraw the electrons from the ring (4). Because of this C-3 becomes a weaker nucleophile, unable to attack the carbon of the carbonyl group.

The introduction of a substituent on the pyridine ring to activate C-3 makes the formation of 1, 8-naphthyridine possible.

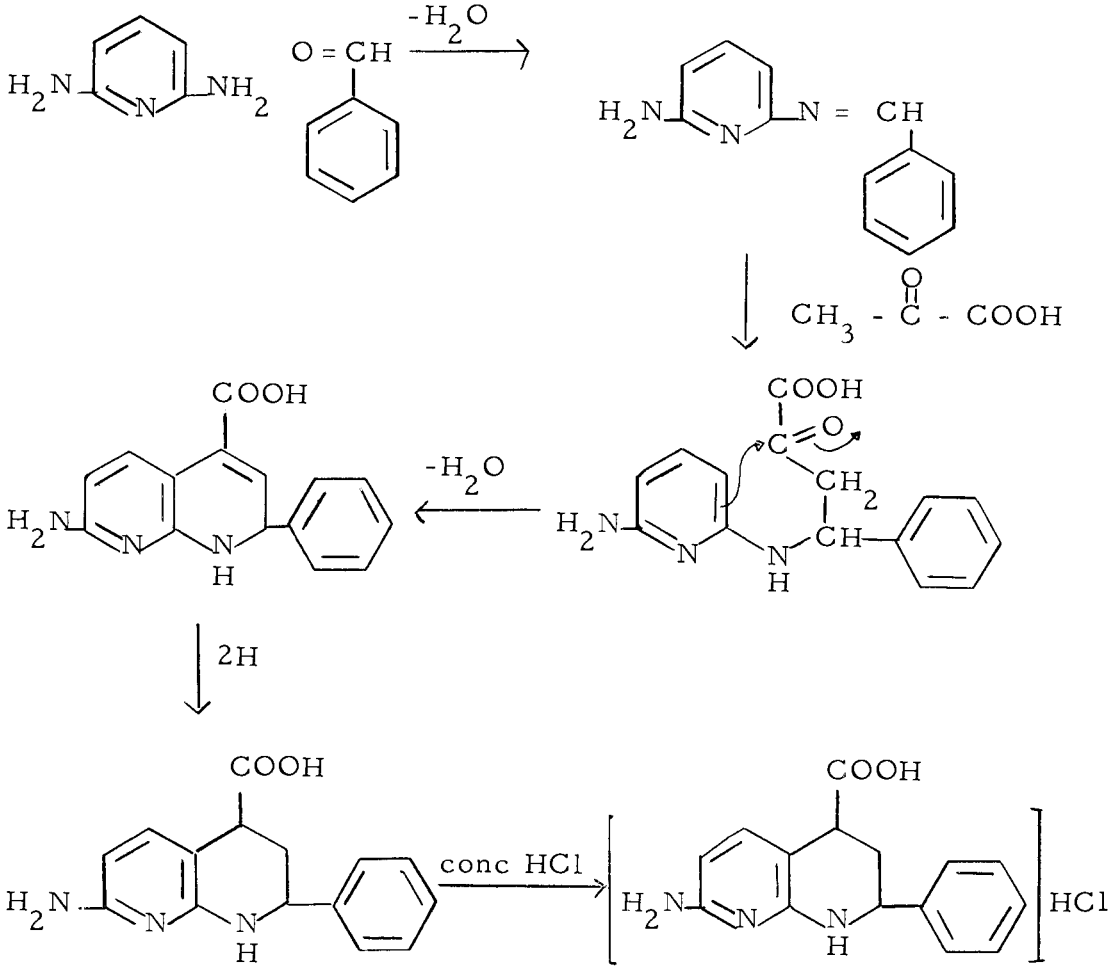
In order to activate C-3, the electron releasing group can be located at either C-4 or C-6. Substituents at C-6 appear to be more effective than substituents at C-4. The group at C-6 not only activates C-3, but also prevents a possible ring closure at the ring nitrogen, to form a cyclic compound reported by Seide. A substituent at C-4 does not affect ring closure at the ring nitrogen.

Lappin (5) reported that the yield of 1, 8-naphthyridine when a substituent was at C-4 was lower than the one when a substituent was at C-6. He concluded that this is due to the steric effect of the substituent at C-4 reducing the amount of ring closure at C-3.

The current work was undertaken to continue the study of the effect of the electron releasing power of substituents at the C-6 position in the formation of 1, 8-naphthyridines by the Doebner

reaction, and the steric effects involved in the formation of 1, 8-naph thyridines.

The synthesis of compound A was accomplished by Nitidandhaprabhas in 1961. He attributed his success in the preparation of this compound to the amino group at C-6 activating C-3. His method is illustrated by the following:

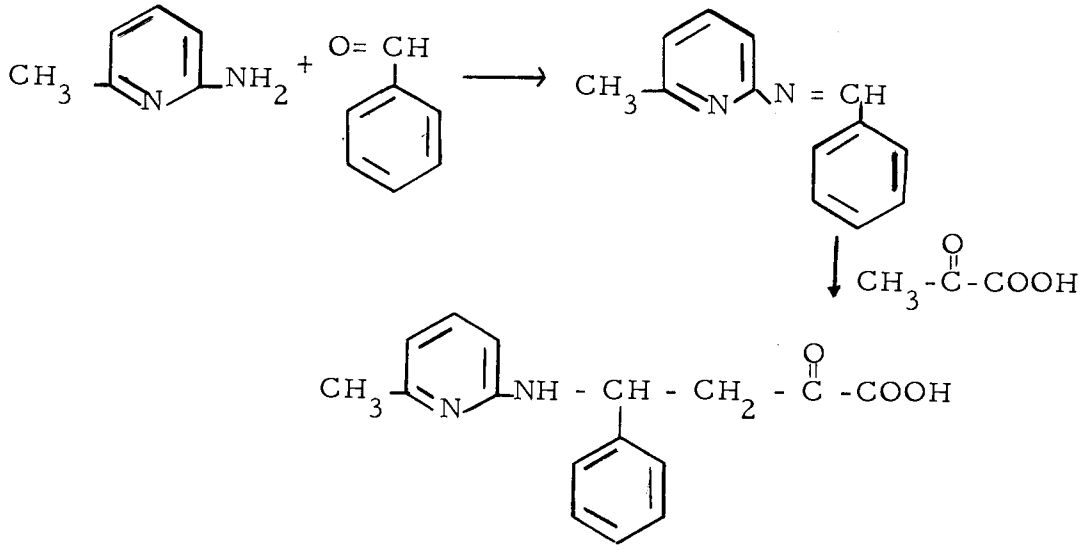


(A)

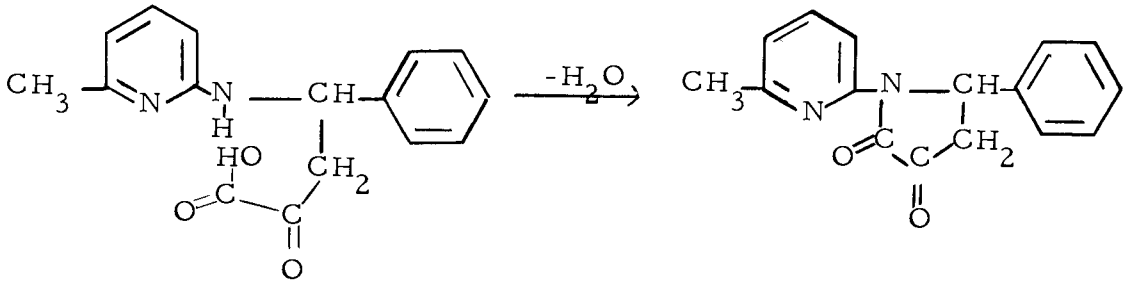
In the current work 6-hydroxy-2-aminopyridine was used instead of 2, 6-diamino pyridine in the Doebner reaction. Thus a comparison could be made of the effect of the hydroxy group with the amino group at the C-6 position of the pyridine ring in effecting ring closure at C-3. The electron releasing power of the hydroxy group and the amino group are about the same, but the amino group will cause m more steric effect than the hydroxy group in preventing ring closure at the ring nitrogen. The current work has shown that 6-hydroxy-2-aminopyridine did effect 1, 8-naphthyridine formation in the Doebner reaction. However, the yield of 1, 8-naphthyridine was a little lower than the one obtained using 2, 6-diaminopyridine as the starting material. Also the evidence indicates that the steric effect of the group at C-6 might affect the yield of 1, 8-naphthyridines.

The work reported by Lewis and Nitidandhaprabhas on the condensation product of 6-methyl-2-aminopyridine in the Doebner reaction could be considered as additional evidence of the steric effect of a substitutent on the C-6 position in preventing ring closure at the heterocyclic nitrogen.

Lewis (6) found that the use of 6-methyl-2-aminopyridine in the Doebner reaction produced an uncyclized product, as represented by the following equation.



This uncyclized product as was shown later by Nitidandhaprabhas, lost one molecule of water and gave another product, as is shown by the following equation:



The methyl group has weak electron releasing power, unable to activate C-3 to effect cyclization at this position. Besides being a weak electron releasing group, the methyl group also has more steric effect, and prevents the cyclization at the ring nitrogen. The

only possible way to lose one molecule of water is by proceeding through the hydrogen on the other nitrogen.

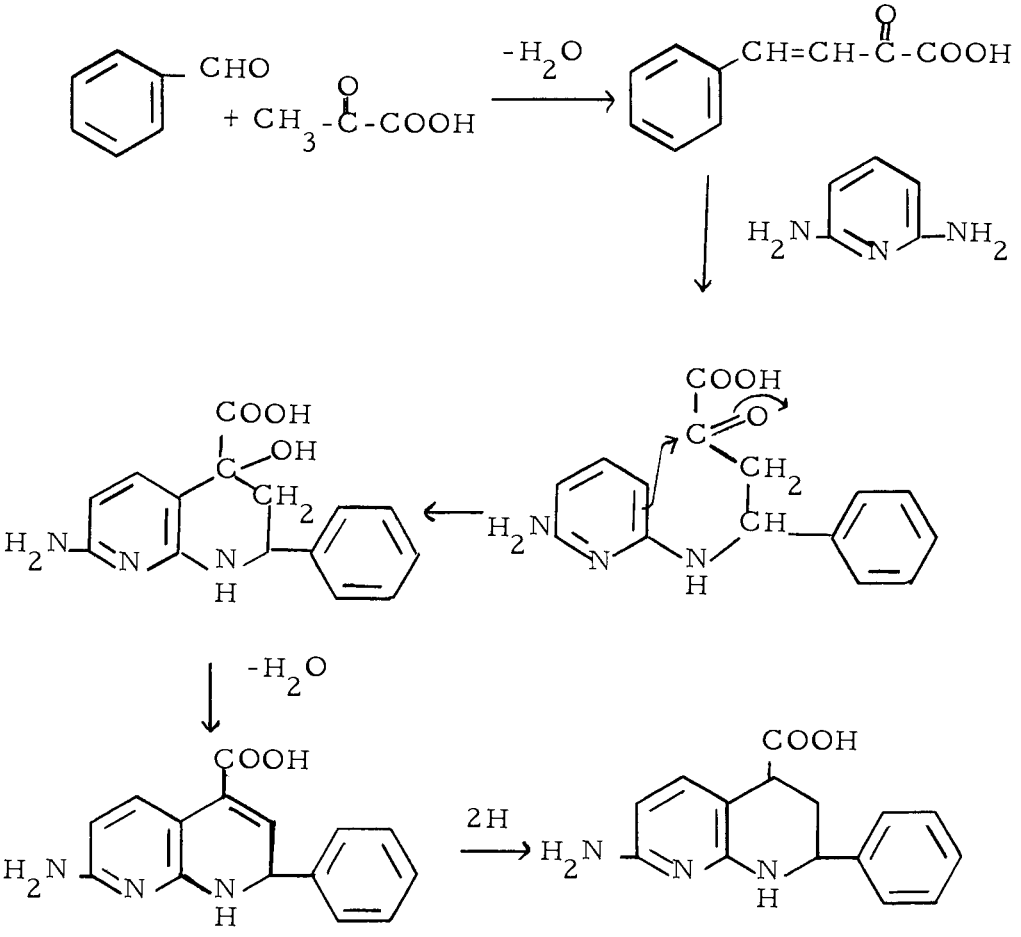
Since the methoxy group has less electron releasing power than the hydroxy group and a steric effect similar to the methyl group, it was proposed to use 6-methoxy-2-aminopyridine as starting material in the Doebner reaction. However, the attempt to convert 6-hydroxy -2-aminopyridine into 6-methoxy-2-aminopyridine for use as a starting material failed in many attempts. Two methylating agents, methyl iodide in base, and dimethylsulfate were used unsuccessfully. Another procedure used phosphorus oxychloride refluxed with 6-hydroxy-2-aminopyridine to form 6-chloro-2-aminopyridine. The product was then treated with sodium methoxide in methanol. Again, the pure form of 6-methoxy-2-aminopyridine could not be isolated. The attempted isolation of the pure 6-methoxy-2-aminopyridine was abandoned. However, the product, which might contain some 6-methoxy-2-aminopyridine, was heated and stirred with benzaldehyde and pyruvic acid. The yellow precipitate appeared to be a 1, 8-napthathyridine, but the product could not be separated by the previously described procedure or other methods.

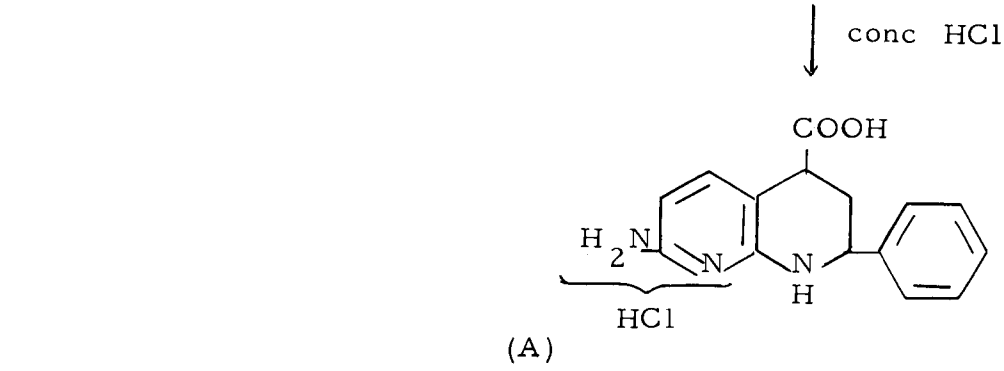
The use of diazomethane as the methylating agent might have been more effective, but it was not available at that time.

An alternate method of preparing compounds A and B was

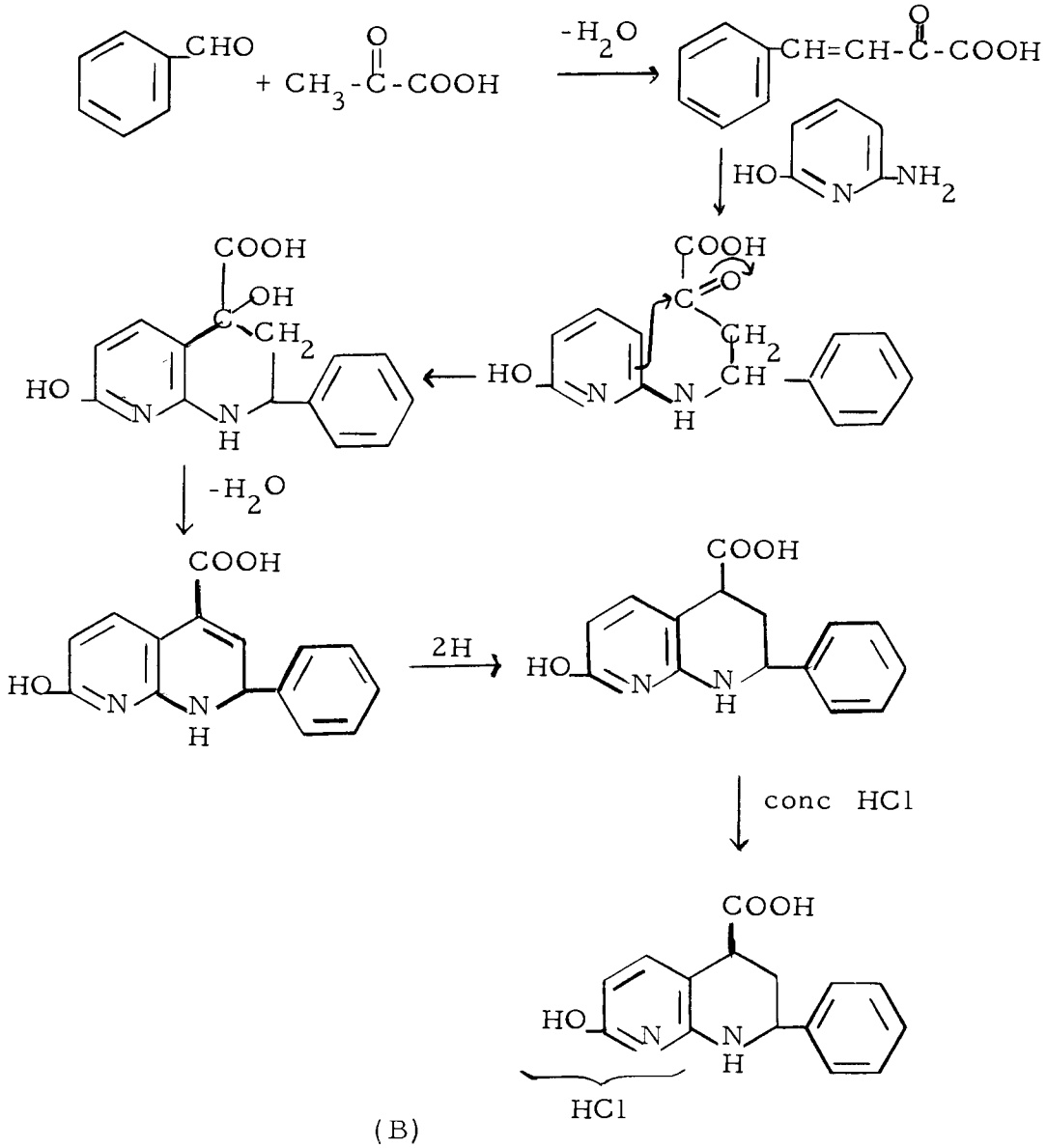
attempted. In this method the aldehydes were condensed with pyruvic acid to form benzalpyruvic acid. The substituted pyridines were added to benzalpyruvic acid to form the 1, 8-naphthyridines. The yields obtained in this procedure were better than those obtained in the first method. The better yields might be due to the ease of 1, 4-addition to the benzalpyruvic acid as contrasted with 1, 2-addition to the Schiff's base in the earlier method.

The reactions are represented by the following equations.




conc HCl
COOH
H2N
N
N
H
HCl

(A)


CHO
+ CH3-C-COOH
O
-H2O
CH=CH-C-COOH
O
HO
N
NH2
COOH
OH
CH2
HO
N
N
H
COOH
C
O
CH2
HO
N
N
CH
H
-H2O
COOH
HO
N
N
H
2H
COOH
HO
N
N
H
conc HCl
COOH
HO
N
N
H
HCl

(B)

To determine the effect of the aldehyde in the Doebner reaction, two different aromatic aldehydes, benzaldehyde and O-methoxy benzaldehyde, were used in the current work. O-methoxy benzaldehyde with 2, 6-diaminopyridine or with 6-hydroxy-2-aminopyridine and pyruvic acid in the Doebner reaction did produce better yields than were obtained from the use of benzaldehyde. The better yields were attributed to the bulky methoxy group tending to swing or push the cyclization sites closer together, thus, increasing the ease of ring closure.

The strong electron releasing power of the hydroxy or the amino groups at C-6 of pyriding ring did increase the electron density at C-3, and promoted the tendency of the C-3 position to attack the C of the carbonyl group. The steric effect of the big methoxy group, forcing the carbonyl group closer to the activated C-3 position, increased the ease of the attack.

Identification of compounds B, C, D

The products from the reaction mixtures were insoluble in most solvents, thus making the purification more difficult. Nitidandhaprabhas had found that he could isolate 1, 8-naphthyridines from the Doebner reaction by converting them to the insoluble hydrochloride salts. The free bases of the 1, 8-naphthyridines dissolve in

concentrated hydrochloric acid easily, but a method of producing the free bases has not been developed. The attempt to convert the hydrochloride salts to the free bases by treating them with sodium carbonate also failed.

The carbon-hydrogen analyses for compound B, C, D agreed with that required for 1, 2, 3, 4-tetrahydro-1, 8-naphthyridines which are similar to compound A reported by Nitidandhaprabhas.

An attempt was made to obtain the N. M. R. spectra for compounds A, B, C and D, to determine whether the new ring was saturated or unsaturated. Unfortunately, not enough information could be obtained.

The I.R. spectra of compounds B, C, D were similar to the I. R. spectrum of compound A, and so the structure of B, C, D were supposed to be the same as the structure of compound A (9). The U. V. analysis of compounds B, C, D were also useful to confirm the proposed structure:

Compound A showed two well-defined maxima at wavelengths: 236 mμ (log E=4.01) and 352 mμ (log E=3.96).

Compound B showed two well-defined maxima at wavelengths: 237 mμ (log E=3.98) and 348 mμ (log E=3.91).

Compound C showed two well-defined maxima at wave-lengths: 237 mμ (Log E=3.98) and 342 mμ (log E=3.95).

Compound D showed two well-defined maxima at wave-lengths: 238 mμ (log E=3.89) and 338 mμ (log E=3.94).

The U. V. spectrum of 6-bromo-2-(methylaminomethyl)-1, 2-dihydro-1, 8-napthyridine showed two well defined maxima at wave lengths: 238 m (log E=3.98) and 336 mμ (log E=3.66) as reported by Zhukova (15).

The carbon-hydrogen analyses and the similarity of the U. V. spectra of compounds A, B, C, and D to the one reported by Zhukova is evidence that the structures assigned to compounds A, B, C, and D are correct.

EXPERIMENTAL

Benzalpyruvic acid (11)

Benzaldehyde (95.5 g., 0.9 mole) and freshly distilled pyruvic acid (79.2 g., 0.9 mole) were mixed in a 1-liter three necked flask equipped with a stirrer, a thermometer, and a separatory funnel, and cooled to about 5° C in an ice bath. Then 248 cc of a 25% solution of potassium hydroxide in methanol were added, with stirring, at a rate to keep the temperature at 5°-10°C. A white precipitate formed which changed to a cream color as the rest of the base was added. The ice bath was replaced with a cold water bath, and the precipitate then disappeared. After two to three minutes at room temperature, a yellow precipitate of the potassium salt began to form. The reaction mixture remained for more than 12 hours at room temperature. The yellow precipitate was filtered off, washed with small amounts of methanol and ether, and air-dried. The free acid was generated from the potassium salt by treating with cold 6N. hydrochloric acid. The yellow product was recrystallized from benzene. M. P. 59°-60°C.

Preparation of the monochloride of 2-phenyl-7-amino 1, 2, 3, 4-tetrahydro-1, 8-naphthyridine-4-carboxylic acid (9) (compound A)

In a 500 ml. three-necked, round bottomed flask equipped with a mechanical stirrer, a condenser with a calcium chloride tube and a separatory funnel, 10.9 g. (0.1 mole) of 2, 6-diaminopyridine (dried over P_2O_5) was dissolved in 200 ml absolute alcohol. The mixture was stirred and heated to boiling, and then 10.6 g. (0.1 mole) of benzaldehyde were added. The solution was stirred and heated until a yellow precipitate formed. Then 8.8 g. (0.1 mole) of freshly distilled pyruvic acid was added, dropwise, from the separatory funnel. Refluxing was continued six hours. The yellow product was filtered off, aid-dried, and then dissolved in concentrated hydrochloric acid and filtered. The filtrate was diluted with distilled water. A yellow precipitate formed. The mixture was filtered and the solid was washed with distilled water, dried in an oven and then over P_2O_5. The dried product was a pale green solid. The yield was about 4 g. Decomposition of the product was apparent at about 240°C, but melting did not occur up to 300°C. The compound was insoluble in water, alcohol, chloroform, carbon disulfide, carbon tetrachloride, and acetone. However, it was soluble in acetic acid and diethylene glycol.

Anal. Molecular formula: $C_{15}H_{16}N_3O_2Cl$. Molecular weight, 305.5. Theoretical: C = 58.91%; H = 5.23%. Found: C = 59.5%' H = 5.30%.

Preparation of the monochloride of 2-phenyl-7-hydroxy 1, 2, 3, 4-tetrahydro-1, 8-naphthyridine-4-carboxylic acid (compound B)

In a 500 ml. three-necked, round bottomed flask, equipped with a mechanical stirrer, a separatory funnel and a condenser with a calcium chloride tube, 11.0 g. (0.1 mole) of 6-hydroxy-2-amino-pyridine was dissolved in 200 ml. absolute ethanol. The solution was heated and stirred on an oil bath at 130°-140°C until all the solid was dissolved, then 10.6 g. (0.1 mole) of benzaldehyde was added. The mixture was heated and stirred until a pale green-yellow precipitate was formed in the solution. After stirring and heating for five minutes, 8.8 g. (0.1 mole) of distilled pyruvic acid was added, dropwise, from the separatory funnel. The solution was refluxed for six hours. The pale green-yellow product was filtered off, washed with several portions of absolute alcohol and air-dried. The product was dissolved in 300 ml. of concentrated hydrochloric acid and then filtered. The filtrate was diluted with 500 ml. of distilled water, the pale yellow precipitate was removed by filtration, and washed with several portions of distilled water. After drying in an oven and over

P_2O_5, a green solid was obtained. The yield was about 3 g. Decomposition of the monochloride of 7-hydroxy-2-phenyl-1, 8-naphthyridine-4-carboxylic acid was apparent at about 240°C but melting did not occur up to 300°C. The salt is insoluble in water, alcohol, chloroform, carbondisulfide, and acetone; however, it is soluble in acetic acid and diethylene glycol.

Anal. Molecular formula; $C_{15}H_{15}N_2O_3Cl$. Molecular weight, 306.5. Theoretical: C = 58.5%; H = 4.89%. Found: C = 57.9%; H = 4.84%.

Alternate preparation of compounds A and B

In a 500 ml. three-necked, round bottomed flask, equipped with a mechanical stirrer, a separatory funnel and a condenser with a calcium chloride tube, 10.9 g. (0.1 mole) of 2, 6-diaminopyridine (dried over P_2O_5), 10.8 g. (0.1 mole) of benzalpyruvic acid were mixed in 150 ml. absolute alcohol. The mixture was refluxed on an oil bath at 130°-140° C for six hours. The isolation of 7-amino-2-phenyl-1, 8-naphthyridine-4-carboxylic acid (compound A) as a monohydrochloride was the same as previously described. The yield was about 6 g.

The alternate preparation for compound B differed only that 6-hydroxy-2-aminopyridine was used in place of 2, 6-diaminopyridine.

The yield was about 5 g.

Preparation of the monohydrochloride of 2 (O-methoxy phenyl) -7-amino-1, 2, 3, 4-tetrahydro-1, 8-naphthyridine -4-carboxylic acid (compound C)

In a 500 ml. three-necked, round bottomed flask, equipped with a mechanical stirrer, a condenser witha calcium chloride tube and a separatory funnel, 10.9 g (0.1 mole) 2, 6-diaminopyridine (dried over P_2O_5) was dissolved in 200 ml. of absolute ethanol. The mixture was heated and stirred on an oil bath at 130°-140°C until all the solid was dissolved and then 13.6 g (0.1 mole) of O-methoxy benzaldehyde was added. Heating and boiling were continued until a yellow precipitate was formed in the solution. After five minutes 8.8 g. (0.1 mole) of distilled pyruvic acid were added, dropwise, from the separatory funnel. The solution was refluxed for three hours. The yellow precipitate was filtered off and dissolved in 300 ml. of concentrated hydrochloric acid. The solution was filtered. The filterate was diluted with 500 ml. of distilled water, and then the yellow precipitate was filtered off and washed with distilled water. The product (compound C) was dried in an oven and over P_2O_5. The yield was about 10 g.

Decomposition of compound C was apparent at about 240°C, but melting point did not occur up to 300°C. It is insoluble in water,

alcohol, chloroform, carbondisulfide and acetone, however, it is soluble in acetic acid and diethylene glycol.

Anal. Molecular formula: $C_{16}H_{18}N_3O_3Cl$. Molecular weight, 335.5. Theoretical: C = 57.5%; H = 5.67%. Found: C = 57.0%; H = 5.52%.

Preparation of the monochloride of 2(O-methoxy phenyl) -7-hydroxy-1, 2, 3, 4-tetrahydro-1, 8-naphthyridine -4-carboxylic acid (compound D)

In a 500 ml. three-necked, round bottomed flask, equipped with a condenser with calcium chloride tube, a mechanical stirrer, and a separatory funnel, 11.0 b (0.1 mole) of 6-hydroxy-2-amino-pyridine (dried over P_2O_5) was dissolved in 200 ml. of absolute alcohol. The mixture was heated and stirred on an oil bath at 130°-140°C until all the solid was dissolved and then 13.6 g. (0.1 mole) of O-methoxy benzaldehyde was added. Heating and stirring continued until a pale green-yellow solid was formed in the solution. After five minutes 8.8 g. (0.1 mole) of distilled pyruvic acid were added, dropwise, from the separatory funnel. The solution was refluxed for three hours. The product was filtered off, washed with absolute alcohol and air-dried. It was then dissolved in 300 ml. concentrated hydrochloric acid and the solution was filtered. The filtrate was diluted with 500 ml. of distilled water. The pale green-yellow

precipitate formed was filtered off and washed with distilled water several times. After drying in an oven and over P_2O_5 the pale green-yellow color changed to a deep green color (compound D). The yield was bout 9 g. Decomposition of compound D was apparent at about 240°C, but melting did not occur up to 300°C. It is insoluble in water, alcohol, chloroform, and acetone; however, it is soluble in acetic acid and diethylene glycol.

Anal. Molecular formula: $C_{16}H_{17}N_2O_4Cl$. Molecular weight, 336.5. Theoretical: C = 57.0%; H = 5.05%. Found: C = 56.3%; H = 5.00%.

Determination of ultraviolet spectra of compounds A, B, C and D

In order to confirm the structure of compounds B, C and D, their ultraviolet spectra were determination. A solution of 25 ml. of glacial acetic acid diluted to one liter with distilled water was used as the solvent. The $m\mu_{max}$, E_{max}, and log E_{max} for compounds A. B, C and D are shown in the following table.

Table 1. Data of ultraviolet spectra.

Compounds	$m\mu_{max}$	E_{max}	$\log E_{max}$
Compound A	236	1.03×10^4	4.01
	352	9.10×10^3	3.96
Compound B	237	9.56×10^3	3.98
	348	8.23×10^3	3.91
Compound C	237	9.60×10^3	3.98
	342	8.85×10^3	3.95
Compound D	238	7.80×10^3	3.89
	338	8.65×10^3	3.94

SUMMARY

The strong electron releasing power of the hydroxy group at C-6 of the pyridine ring was shown to be effective for ring closure at C-3 in the Doebner reaction. The yield of 1, 8-naphthyridine was slightly lower than that produced from the amino substituted pyridine ring. The lower yield might be attributed to a lower electron releasing power of the hydroxy group. The alternate method of producing 1, 8-naphthyridine by using benzalpyruvic acid with 6-hydroxy-2-amino pyridine or 2, 6-diamino pyridine did increase yield of 1, 8-naphthyridines. Also the use of different aromatic aldehydes did effect the yields of 1, 8-naphthyridines. The result showed that the use of O-methoxybenzaldehyde could produce a 1, 8-naphthyridine in a higher yield than the use of benzaldehyde.

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