THE CONDENSATION PRODUCTS OF 2-AMINO, 6-METHYL PYRIDINE WITH BENZALDEHYDE AND PYRUVIC ACID

by

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TO MY WIFE

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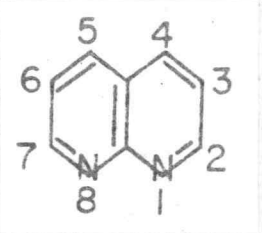
THE CONDENSATION PRODUCTS OF 2-AMINO, 6-METHYL PYRIDINE WITH BENZALDEHYDE AND PYRUVIC ACID

INTRODUCTION

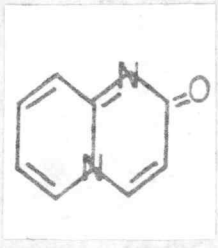
The naphthyridines, one of the many nitrogen heterocyclic systems, have been defined by Allen as "...the fused ring system(s) resulting from the fusion of two pyridine rings through two adjacent carbon atoms, each ring containing only one nitrogen atom."(1, p.275) Reissert proposed this name in 1893 when he synthesized 1,8-naphthyridine, which was regarded as the naphthalene analog of pyridine. There are six possible naphthyridines; 1,8-naphthyridine is illustrated below:



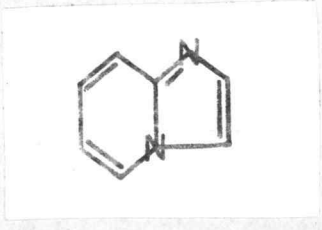
These ring systems were also indexed as pyridinopyridines and benzodiazines before 1936. In addition they may be named as diazanaphthalenes.

The synthesis of the naphthyridine ring systems usually involves cyclization reactions employing amino-pyridines. These reactions parallel those used in quinoline chemistry, for example, the Skraup, Doebner-Miller, Doebner,

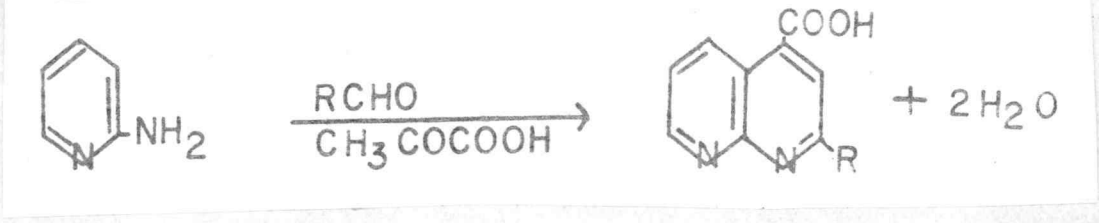
and Knorr. Since the synthesis of 1,8-naphthyridines would require an α-aminopyridine, 2-aminopyridine was logically the first one used. However Chichibabin (1, p.299 and 300), Seide (1, p.299-301), and Khitrik (1, p.300) found that ring closure did not proceed through the 3-position of 2-aminopyridine, but through the nuclear nitrogen atom (1-position) to form derivatives of 2-keto-1,4a diazanaphthalene:



or pyrimidazole:

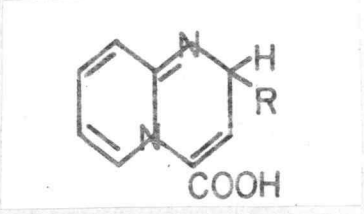


In 1940 and 1941, Mazza and Migliardi (10, p.438-444 and 11, p.548-551) stated that the use of 2-aminopyridine in the Doebner reaction gave 2-substituted 1,8-naphthyridine-4-carboxylic acids:

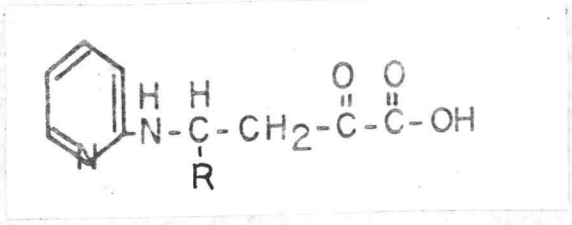


R= C_6H_5-, O-HOC_6H_4-, P-$CH_3OC_6H_4$-, P-$(CH_3)_2NC_6H_4$-, $C_6H_5CH_2$-CH_2-, C_6H_5CH=CH-

Because of the previous work done by Chichibabin, Seide, and Khitrik using 2-aminopyridine, an expected product of this reaction would be:



For this reason, Allen, Spangler, and Webster (2, p.17-20) repeated this work using anisaldehyde and pyruvic acid with 2-aminopyridine. Their results show that neither 1,8-naphthyridines nor 1,4a diazanaphthalenes were formed, but 2-aminopyridine addition products of benzal-pyruvic acids:



Likewise, Decker (4, p.5-11) tried to determine the course of ring closure of 2-aminopyridine in the Doebner reaction, using formaldehyde and benzaldehyde with pyruvic acid. No definite results were obtained from his work.

Previously, the synthesis of 1,8-naphthyridines had been accomplished by condensing certain 2-amino, 6-substituted pyridines with active carbonyl compounds. Examples are: 2,6-diaminopyridine with ethyl actoacetate, benzoylacetone, and ethyl ethoxymethlenemalonate, and 2,6-diamino; 2-amino, 6-methyl; and 2-amino, 6-ethoxy-pyridines with ethyl malonate(1, p.289-290). Two reviews on the synthesis and reactions of 1,8-naphthyridines are available (1, p.275-305 and 5, p.136-153).

The current work was to investigate the condensation reaction between 2-amino, 6-methylpyridine, benzaldehyde, and pyruvic acid. Although the work of Mazza and Migliardi was refuted by the later work of Allen, Spangler, and Webster, ring closure possibly would occur in the present reaction along with the formation of an open chain compound. The cyclization would be due to the presence of an activating group. The cyclized compound would be a substituted 1,8-naphthyridine similar to those reported by Mazza and Migliardi, while the open chain compound would be similar to those reported by Allen, Spangler, and Webster.

EXPERIMENTAL

Benzalpyruvic Acid (12, p.3147-3149)

In a 2-liter three-necked flask equipped with a stirrer, a thermometer, and a separatory funnel, 191 g. of fresh benzaldehyde (1.8 moles) and 158.4 g. of fresh pyruvic acid (1.8 moles) were mixed and cooled to about 5° C. in an ice bath. Then 495 cc of 25% potassium hydroxide in methanol was added with stirring at a rate to keep the temperature below 10° C. After about two-thirds of this solution was added, a white precipitate formed; it changed to a cream color as the rest of the base was added. The ice bath was replaced with a cold water bath. As the temperature of the reaction mixture rose to 20° C. the precipitate disappeared, and the reaction mixture became a red-brown color. The water bath was removed. After about five minutes at room temperature, a yellow precipitate of the potassium salt began to form. The reaction mixture was allowed to stand at room temperature for 11 hours. The yellow precipitate was filtered off and washed with small portions of methanol and ether and air dried.

The free acid was generated from the potassium salt in about 75% yield as needed. Iced 6N hydrochloric acid was added with stirring to a cooled, saturated water solution

of the potassium salt until no further precipitation occurred upon the addition of a drop of the acid. The pale yellow product was dried over P_2O_5 and was recrystallized twice from benzene. m.p. listed: 61-62° C., found: 59-61° C.

Preparation of γ-(phenyl)-γ-(6-methyl, 2-amino pyridyl)-α-oxobutyric acid (compound A) and compound B

In a 300 cc three-necked flask equipped with a stirrer, a condenser, and a $CaCl_2$ drying tube, 10.81 g. (0.1 mole) of 2-amino, 6-methyl pyridine (dried over P_2O_5 under vacuum) and 10.61 g. (0.1 mole) of fresh benzaldehyde were dissolved in 150 cc of commercial absolute ethanol. This mixture was stirred at room temperature for about 20 minutes. Then 8.8 g. (0.1 mole) of redistilled pyruvic acid was added with stirring. The final solution was refluxed for 6 hours.

The reaction volume was reduced to about 40-50 cc by vacuum distillation using either a water or steam bath. A thick deep-red syrup was obtained. After cooling in a refrigerator, it was stirred vigorously to complete precipitation. Although some precipitation occurred by reducing the reaction volume and cooling, vigorous stirring was necessary for complete precipitation, for a supersaturated solution was usually formed. Then it was filtered, and the

material was washed with small portions of cold 95% ethanol or acetone and air dried. The filtrate was reduced to about 10 cc by vacuum distillation, and the isolation procedure repeated to obtain the rest of the material. The final deep red tary solution was discarded. The combined material was extracted with three or four 15 cc portions of boiling acetone and filtered while hot. The filtrates were combined, and crude compound B was isolated from the evaporated acetone in about 1% yield. Usually, rather pure compound B precipitated from the cooled acetone and was filtered off before evaporation. Crude γ-(phenyl)-γ-(6-methy, 2-amino pyridyl)-α-oxo butyric acid (compound A) remained on the filter after the extractions in about 2% yield.

Compound B: small white crystals; recrystallized from acetone; m.p. 167-168° C. with decomposition; soluble in hot acetone, benzene, and ethanol and warmed 5% hydrochloric acid, slightly soluble in cold acetone; insoluble in ether, water, and cold 5% sodium hydroxide; reduces potassium permanganate solution and bromine in carbon tetrachloride. Analytical for $C_{16}H_{14}N_2O_2$: assigned molecular weight = 266. Calculated: C, 72.2; H, 5.31. Found: C, 72.64; H, 5.60; average of five analyses.

Compound A: fine yellow needles; recrystallized from a 2:1 water-ethanol mixture; m.p. 155-156° C. with decomposition. The crystals became light brown between 135-140° C.; soluble in hot ethanol and water, cold 5% sodium hydroxide and hydrochloric acid; very slightly soluble in hot acetone; insoluble in hot ether and benzene; reduces potassium permanganate solution and bromine in water. Analytical for $C_{16}H_{16}N_2O_3$: molecular weight = 284. Calculated: C, 67.7; H, 5.67. Found: C, 67.33; H, 5.52; average of five analyses.

Alternate Method of Preparation of Compounds A and B

In a 200 cc flask equipped with a condenser, 17.6 g. (0.1 mole) of 2-amino, 6-methyl pyridine (dried over P_2O_5 under vacuum) and 10.8 g. (0.1 mole) of benzalpyruvic acid were dissolved in 75 cc of commercial absolute ethanol. A yellow precipitate formed which dissolved as the temperature of the mixture increased. Four refluxing times were tried: 6 hours, 2 hours, 1 hour, and 40 minutes. The isolation procedure was the same as previously described for these compounds. The yields of the two compounds varied with the refluxing time and were greater than the previous synthesis. No weights were recorded for the 1 hour refluxing time.

The yields are based on 0.1 mole quantities.

Reaction time(hr.)	wt.A(g.)	% yield	wt.B(g.)	% yield
6	4.04	14.2	1.96	7.37
2	(a) 3.80	(a) 13.9	1.1	4.14
	(b) 6.93	(b) 24.4	-	-
2/3	13.65	48.1	0.3	1.1

Preparation of Compound B from Compound A

In a 500 cc flask equipped with a condenser, 10 g. (0.035 mole) of compound A was dissolved in 350 cc of commercial absolute ethanol. The reaction mixture was refluxed for 6 hours. Compound B was isolated as previously described in about 40% yield. Some compound A was recovered, but most of it had formed a deep-red tar. The formation of compound B was verified by a mixed m.p. and a comparison infrared analysis with another sample of compound B on hand.

Preparation of γ-(phenyl)-γ-(2-amino pyridyl)-α-oxo butyric acid (compound A') (2, p.18)

In a 100 cc flask equipped with a condenser, 2.35 g. (0.025 mole) of 2-amino pyridine and 4.4 g. (0.025 mole) of benzalpyruvic acid were dissolved in 50 cc of commercial absolute ethanol. A yellow precipitate formed which dissolved as the temperature of the mixture increased. The

mixture was refluxed for 1 hour. The reaction volume was reduced by two-thirds by vacuum distillation using a steam bath and then was cooled in a refrigerator. Ice and a few drops of acetic acid were added to the cooled solution, and a yellow precipitate formed when the solution was vigorously stirred. It was filtered, and the material was air dried. The filtrate was evaporated to dryness, and a pale yellow material was obtained.

Yellow material: recrystallized twice from 95% ethanol and once from H_2O; m.p. 135-136° C. with some decomposition.

γ-(phenyl)- γ-(2-amino pyridyl)- α-oxobutyric acid: pale yellow material from the filtrate; recrystallized once from 95% ethanol and twice from H_2O; m.p. 154-157° C. with decomposition. Allen, et al gave a m.p. of 148-160° C. with decomposition for the pale yellow compound.

Infrared and ultraviolet analysis of the two fractions indicated they were different compounds. Allen, et al reported only one compound from this reaction. No further work was attempted on the yellow material which melted at 135-136° C.

Preparation of the p-nitrophenylhydrazone of compound A (13, p.219).

1.20 g. of P-nitrophenylhydrazine hydrochloride was added to 30 cc of water. The solution was heated to boiling and filtered hot. 1 g. of compound A was added to a mixture of 25 cc of 95% ethanol and 10 cc of water, and the mixture was heated until the compound dissolved. The two solutions were combined, and four drops of glacial acetic acid were added. The final solution was heated to boiling with stirring and digested for 1 hour on a hot plate. Then it was cooled in a refrigerator and filtered. The crude material was air dried.

P-nitrophenylhydrazone of compound A: recrystallized four times from ethanol by adding water at the boiling point until the cloud point was reached; m.p. 191-193° C. with some previous melting beginning at 189° C. Analytical for $C_{22}H_{21}N_5O_4$: molecular weight = 419. Calculated: C, 63.0; H, 5.02. Found: C, 62.9; H, 4.49; average of three analyses.

Quantitative microhydrogenation of Compound B to Form Compound C

In a 50 cc flask, 0.1152 g. of compound B and 0.03 g. of 10% Palladium on charcoal were added to 10 cc of glacial acetic acid. The solution was stirred by a magnetic stirrer bar. The hydrogenation was carried out at room temperature and

at atmospheric pressure. The reduction was complete in about 25 minutes. A blank was run on the catalyst and solvent. 0.1152 g. of compound B required 19.38 cc of hydrogen for the reduction.

The reaction mixture was filtered, and ice was added with vigorous stirring to the filtrate. A white precipitate slowly formed when the ice had melted, 6 N sodium hydroxide was added dropwise until further precipitation stopped at a pH 5-6. The solution was filtered, and the product air dried.

Compound C: small white crystals; recrystallized from ethanol-acetone mixture; m.p. 180-181° C.; soluble in warm ethanol and water, hot acetone, and 5% sodium hydroxide and hydrochloric acid; slightly soluble in hot benzene; reduces potassium permanganate solution slowly over a long period of time, but did not reduce bromine in water; gave a positive test for elemental nitrogen by a sodium fusion.

Analytical for $C_{16}H_{18}N_2O_2$: assigned molecular weight = 270. Calculated: C, 71.2; H, 6.68. Found: C, 71.4, H, 7.27; average of three analyses.

Preparation of the 2-nitro, 1,3-indandione derivative of Compound B

0.20 g. of compound B was dissolved in 10 cc of acetone by heating slightly. 0.20 g. of 2-nitro, 1,3-indandione was dissolved in another 10 cc of acetone. The two solutions were combined and stirred. A pale yellow precipitate formed and was collected on a filter. The material was air dried and then further dried in an abderhalden over P_2O_5.

2-nitro, 1,3-indandione derivative of compound B: pale yellow; recrystallized from an ethanol-acetone mixture; m.p. 149-150° C. with slight decomposition; no carbon and hydrogen analysis attempted.

Prepration of the picrate of Compound A (13, p.229)

0.28 g. of Compound A was added to 10 cc of 95% ethanol, and the solution was heated to boiling and filtered hot. The filtrate was added to 10 cc of a saturated solution of picric acid in 95% ethanol. The final solution was heated to boiling and allowed to cool slowly to room temperature. A bright yellow precipitate formed and was collected on a filter. The picrate was air dried and gave a m.p. 189-191° C. with decomposition. No carbon and hydrogen analysis was attempted due to lack of time.

Development of ultraviolet and infrared Spectra

Because of the need for obtaining more information about the structure of compounds A, B, and C, it was necessary to develop their ultraviolet and infrared spectra. Also compound A' and benzalpyruvic acid were analyzed by ultraviolet and infrared absorption. Potassium benzalpyruvate was analyzed by infrared absorption. The solvents used for the ultraviolet work were distilled water and 95% ethanol. All infrared spectra were developed from nujol malls, except for compound C, which was also developed from a KBr pellet. The following table lists the $m\mu_{max}$ and E_{max} for the compounds analyzed by ultraviolet absorption.

Compound	Solvent	$m\mu_{max}$	E_{max}
Compound A	Distilled water	235	10,410
		282	5,350
		355	4,600
Compound A'	Distilled water	285	4,570
		350	3,545
Compound B	95% ethanol	234	11,780
		285	15,020
		303	16,140
Compound C	95% ethanol	243	11,920
		311	5,425
benzalpyruvic acid	Distilled water	225	9,770
		300	21,100

The following table lists the important peaks in wave numbers

(cm^{-1}) for the compounds analyzed by infrared absorption.

Compound	peak (cm^{-1})
Compound A	3,420
	3,120
	1,635
	1,620
	1,585
	1,545
	1,435
	1,395
	1,310
	900
	860
	820
	800
	705
Compound A'	3,480
	3,180
	1,632
	1,617
	1,585
	1,550
	1,432
	1,385
	1,307
	1,147
	895
	862
	805
	792
	770
	707
Compound B	3,390
	1,755
	1,660
	1,610
	1,590
	1,543
	1,325
	1,135
	1,045
	790
	695

Compound	peak (cm^{-1})
Compound C	2,800
	2,730
	1,688
	1,618
	1,454
	1,386
	1,324
	1,290
	1,186
	1,124
	782
	751
	723
	710
benzalpyruvic acid	1,735
	1,698
	1,620
	1,580
	1,260
	1,097
	1,080
	1,007
	995
	742
	723
	695
potassium benzalpyruvate	1,726
	1,686
	1,623
	1,608
	1,378
	1,277
	758
	737
	680

Determination of the Molecular Weights of Compounds A, B, and C

To aid in the interpretation of structure indicated by the ultraviolet and infrared absorption data for

compounds A, B, and C, the determination of their molecular weights was attempted.

Although compound A would dissolve in base, a neutralization equivalent could not be determined because the molecule apparently exists as a zwitter ion. Instead, a procedure (3, p. 163), utilizing the absorption of the picrate and the molecular extinction coefficient of picric acid at 380 mμ, was used. Two analyses gave values of 216 and 220 for the molecular weight of compound A. The molecular weight was assumed to be 284. The low values must result from compound A absorping too greatly at 380 mμ.

The molecular weight of compound B could not be determined by the Rast method, for no suitable solvent could be found. However, a method recently investigated by Ellested[1] employing the 2-nitro, 1,3-indandione derivative was used. Utilizing the molecular extinction coefficient of 2-nitro, 1,3-indandione and the absorption of the nitro indandione derivative at 341 mμ, a value of 261 was obtained for the molecular weight of compound B. The compound had been assigned a molecular weight of 266.

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[1]Ellestad, George. Unpublished research for a Master's thesis in Organic Chemistry, Corvallis, Oregon State College, Dept. of Chemistry, 1958. Now being typed. Title: Determination of Molecular Weights of Certain Organic Bases by the Ultraviolet Absorption Spectra of their 2-Nitro, 1,3-Indandionates.

Since compound C was soluble in base, its neutralization equivalent was determined in alcohol (14, p.225-229). The determination gave values of 271.5 and 272.2. Because the compound was thought to have only one carboxyl group, the neutralization equivalent would equal the molecular weight. The compound had been assigned a molecular weight of 270.

Attempted reactions with Compound B

Because the infrared spectrum gave a sharp peak at 3390cm^{-1}, which is in the N-H stretching region, an attempt was made to acylate compound B. However, acylation was unsuccessful by four different methods. These methods included the Schotten-Baumann reaction and the use of acetic anhydride with pyridine. In all the attempts, either the starting material was recovered or decomposition occurred.

Likewise, decarboxylation of compound B was attempted by two methods. One method, refluxing in 50% sulfuric acid, resulted in decomposition of compound B, and the other method, heating to a temperature slightly above the melting point to lose CO_2, gave a brown amorphous material which melted 140-145° C. with decomposition. No analysis was made of this material, for it was thought to be a decomposition product.

Also, the methyl ester formation of compound B using diazomethane was attempted. This was unsuccessful, for only the starting material was recovered from the reaction. A check was made to see if diazomethane was generated by the use of benzoic acid.

In addition, dehydrogenation of compound B was attempted by two methods. In the first method, it was dissolved in nitrobenzene, and the solution was heated to boiling. Decomposition occurred after the solution refluxed for about five minutes. In the second method, phenyl ether and 10% Palladium on charcoal were used. A large amount of bubbling, which was thought to be hydrogen gas, was observed from 160-190° C. A brown material, which turned to a liquid upon standing in the open, was isolated. This material was thought to be a free 1,8-naphthyridine base, but an attempt to make the picrate was unsuccessful. This was shown by a mixed m.p. and a comparison infrared analysis of the recovered material and picric acid.

An attempt to make the p-nitrophenylhydrazone of compound B was also unsuccessful.

DISCUSSION

Results of the current work on the condensation reaction of 2-amino, 6-methyl pyridine, benzaldehyde, and pyruvic acid indicate that it is of a more complex nature than was previously assumed. Although the experimental data compiled for compound A indicates that the originally proposed structure is probably correct, a complete structure cannot be proposed for compounds B and C at this time. As was originally thought, the open chain compound, compound A, was similar to those reported by Allen, Spangler, and Webster. However, the failure to obtain a compound which would correspond to a substituted 1,8-naphthyridine would seem to indicate that the 6-methyl group played little or no role in the condensation.

The work of Chichibabin, Seide, and Khitrik with 2-amino pyridine would suggest that the failure to effect ring closure at the 3-position of this pyridine was due not only to the inductive effect of the ring nitrogen atom and the α-amino group decreasing the electron density at this position, but also to the nuclear nitrogen atom not being sterically hindered to ring closure. However, the substitution of an ortho, para directing group in the 6-position of 2-amino pyridine would increase the electron density at the 3-position and also increase the steric hinderance to

ring closure through the nuclear nitrogen atom. The fact that the synthesis of substituted 1,8-naphthyridines had been accomplished employing a 2-amino pyridine with an ortho, para directing group in the 6-position was mentioned in the Introduction. This was the basis for assuming that ring closure would possibly occur in the condensation reaction between 2-amino, 6-methyl pyridine, benzaldehyde, and pyruvic acid. If this occurred, the cyclized compound would not be a true 1,8-napthyridine, for a material balance showed that only one double bond could form in the second ring with the elimination of two moles of water. The reaction would probably proceed through the following steps as shown in figure 1.

The yield of each compound would depend upon the activating strength of the 6-methyl group to effect ring closure.

The reaction between 2-amino, 6-methyl pyridine, benzaldehyde, and pyruvic acid did produce two compounds in very low yield. Preliminary carbon and hydrogen analysis indicated that they were probably the two compounds shown by the reaction scheme. In an attempt to improve yields and establish the role of benzalpyruvic acid as a intermediate in the reaction, benzalpyruvic acid and 2-amino, 6-methyl pyridine were condensed together employ-

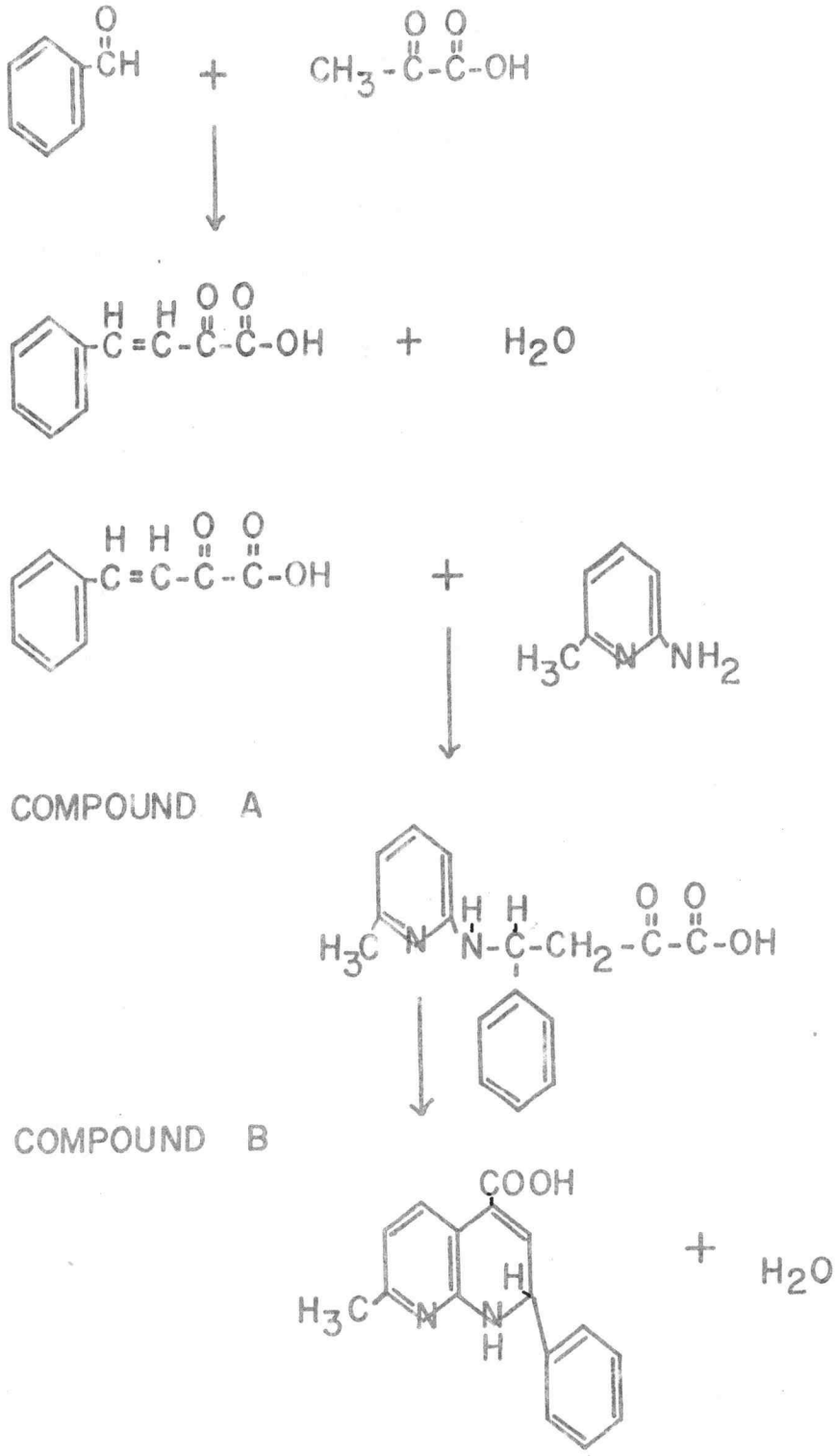


Figure I

ing four different reaction times. Again, the two compounds A and B were obtained, and the yields were improved. To complete the investigation of the proposed reaction scheme, compound A was successfully converted to compound B. This was verified by a mixed m.p. and a comparison infrared analysis with other compound B on hand. At this point, investigation of the reaction scheme was discontinued, and an attempt to verify the proposed structures of compounds A and B was undertaken.

Compound A

Although the carbon and hydrogen analysis was somewhat low for the assigned empirical formula for compound A (see Experimental), the assigned formula was still thought to be correct.

The solubility of the compound in both 5% sodium hydroxide and hydrochloric acid would indicate the presence of a carboxyl group and an amine group. In addition, the solubility of the compound in hot water and insolubility in hot benzene would suggest the molecule existed as a zwitter ion. The compound reduced both potassium permanganate solution and bromine in water. The former could be explained by the ease of oxidizing an α-keto acid, while the latter could be explained by the formation of a perbromide with

the pyridine portion of the molecule or by the bromination of an aromatic amine. The presence of a keto group was indicated by the formation of the p-nitro phenylhydrazone. However, the carbon and hydrogen analysis of the derivative was low for hydrogen.

At this point, compound A', γ-(phenyl)-γ-(2-amino pyridyl)-α-oxo butyric acid, was prepared by condensing 2-aminopyridine with benzalpyruvic acid. This compound had been made previously by Allen, Spangler, and Webster (2, p.19). Since compound A differed from compound A' only by a methyl group on the pyridine nucleus, their respective ultraviolet and infrared spectra should be very similar. This was found to be true.

For example, their ultraviolet spectra exhibited similar maxima and E_{max} around 280 and 350 mμ in the ultraviolet. The presence of a maximum at 235 mμ for compound A is the major difference between the two spectra. However, compound A' gave the largest value for its optical density at 220 mμ, and it most likely exhibits a maximum near this reading. The reason for the difference may be due to the presence of the methyl group in compound A. The maximum exhibited by compound A at 235 mμ may be due to the 2-amino pyridyl portion of the molecule, for 2-amino pyridine exhibits the following maxima and E_{max} (6, plate 111):

$m\mu_{max}$	E_{max}
230	10,000
290	3,800

But, if this were the cause of the absorption, compound A' should exhibit a maximum around 230 mμ also. More likely the maximum at 235 mμ for compound A is due to the conjugation of the α keto group with the carboxyl group. The spectra of compounds A and A' exhibit a maximum and E_{max} similar to tryptophane around 280 mμ (7, p.191). This amino acid possesses a benzene nucleus which makes it similar to these two compounds. The maximum around 350 mμ cannot be assigned to any particular structural grouping at this time.

These two compounds also gave very similar infrared spectra (see Experimental section) which indicate they are amino acids in the zwitter ion form (9, p.5098-5101). Certain peaks of Compound A in the infrared are tentatively given the following structural assignment (9, p.5098-5101 and 16, p.247-563).

peak (cm^{-1})	structural assignment
3,420	NH
3,120	NH_2^+ or NH^+
1,635 broad	COO^-
1,620	NH_2^+
1,585	C_6H_5

peak (cm^{-1})	structural assignment
1,545	NH_2^+ or COO^-
1,500	NH_2^+ or C_6H_5
1,475	CH_2
1,435	CH_2CO
1,395	COO^-
1,373	CH_3
780	2-NH, 6-CH_3 pyridyl
752	C_6H_5
705	C_6H_5

Part of the evidence against the proposed structure of compound A from the infrared analysis is the absence of a peak around 2130cm^{-1} which was exhibited by the other amino acids investigated by Leifer and Lippincott. The other evidence is the absence of a definite carbonyl peak in the spectrum. The tentative assignment of the α-carbonyl group to the broad peak at 1635cm^{-1} appears to be too low, for the peak which is given the same assignment for benzal-pyruvic acid appears at 1698cm^{-1} and only shifts to 1686cm^{-1} for potassium benzalpyruvate (see Experimental). But the formation of the *p*-nitro phenylhydrazone of compound A would somewhat strengthen the assignment of the broad peak at 1635cm^{-1}.

The low values of 216 and 220 obtained in the molecular weight determination of compound A, as against an

assigned value of 284, must result from compound A absorping too greatly at 380 mμ. The procedure used is applicable only to compounds which will form a picrate and do not themselves have any absorption at 380 mμ.

Compound B

The carbon and hydrogen analysis was somewhat high for the assigned empirical formula for compound B, but the analysis indicated that the assigned formula was probably correct. The differences in solubility between compounds A and B indicated a different structure for compound B. The insolubility of compound B in cold 5% sodium hydroxide and hot water would suggest that the strength of the carboxyl group present in compound A was weakened or that it had disappeared with the formation of compound B. The solubility of compound B in warm 5% hydrochloric acid would indicate a hindered amine or an amide. Also, compound B was soluble in hot acetone and benzene; compound A did not exhibit these solubilities. Compound B reduced both potassium permanganate solution and bromine in CCl_4 which indicated unsaturation.

Because compound B was thought to be a substituted 1,2-dihydro 1,8-naphthyridine, a series of reactions were attempted to prove this structure.

The infrared spectra for this compound gave a peak at 3390cm^{-1}, indicating the presence of the NH group. So an attempt was made to acylate compound B to prove the position of the double bond in the second ring. This attempt was unsuccessful. The failure to acylate compound B was probably due to steric hinderance of the phenyl group in the α position to the NH group. Then, the unsuccessful attempts to decarboxylate, to prepare the methyl ester, and to dehydrogenate compound B were made. The failure of these attempts indicated that the proposed structure of a substituted 1,2-dihydro 1,8-naphthyridine for compound B was incorrect, for these reactions should have been successful with this type of structure.

The ultraviolet absorption spectrum of compound B exhibited three maxima with a position and E_{max} which would suggest a highly conjugated system similar to that found in benzalpyruvic acid or cinnamic acid. This is illustrated by the following data:

Compound	$m\mu_{max}$	E_{max}
Compound B	234	11,780
	285	15,020
	303	16,140
benzalpyruvic acid (from Experimental)	225	9,770
	300	21,100
cinnamic acid (15, p.597)	220	17,500
	267	20,200

The only similarity in the ultraviolet spectra of compounds A and B is the maximum around 230 mμ with an E_{max} of approximately 10,000. As was mentioned before, this maximum is possibly due to the 2-amino pyridyl group (see Discussion of compound A). The ultraviolet spectrum of compound B does not support the proposed substituted 1,2-dihydro 1,8-naphthyridine structure, for this structure would not possess the necessary highly conjugated system. Moreover, the infrared spectrum of compound B does not support the originally proposed structure. The peak of main interest occurs at 1755cm^{-1}, which is too high for a normal carboxyl group. This frequency has been assigned to the carbonyl of a 5-membered α,β unsaturated lactone (8, p.880). The other peak of interest occurs at 1660cm^{-1} which is possibly due to the carbonyl of an amide. Certain peaks of compound B in the infrared are tentatively given the following structural assignment (8, p.880 and 16, p. 247-563):

peak (cm^{-1})	Structural Assignment
3,390	NH
1,755	C = O, 5-member α,β unsaturated lactone
1,660	amide or C = C
1,610	C = C
1,590	C_6H_5

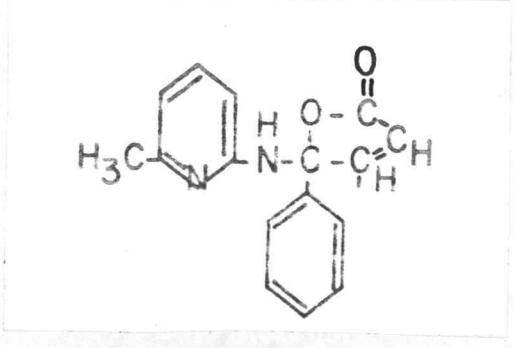
peak (cm^{-1})	Structural Assignment
1,543	Secondary amine
1,135	2-NH, 6-CH_3 pyridyl
1,045	C_6H_5
790	2-NH, 6-CH_3 pyridyl
695	C_6H_5

The presence of a methyl group was not definite, for a nujol mall of the compound was used to obtain the spectrum.

Since compound B reduced both potassium permanganate solution and bromine in CCl_4, a quantitative microhydrogenation was run. For an assigned molecular weight of 266 for compound B, two moles of hydrogen per mole of compound were used in the reduction. The reaction conditions were room temperature and atmospheric pressure. The result of this hydrogenation also does not support the originally proposed structure of compound B, for, under the reaction conditions employed, only one mole of hydrogen per mole of compound should have been used. The product isolated from the reduction was now soluble in cold 5% sodium hydroxide.

To check on the assumed empirical formula for compound B, its molecular weight was determined employing an ultraviolet absorption method with 2-nitro, 1,3-indandione. A value of 261 was obtained. This value verified the assigned molecular weight of 266.

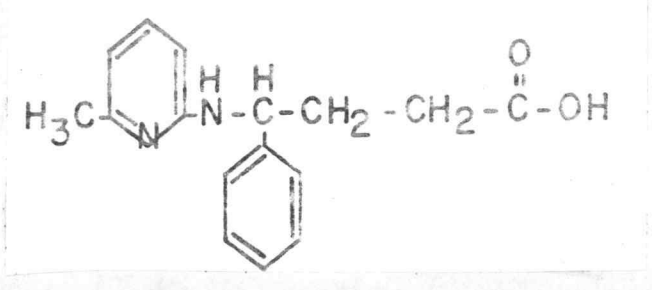
From all this evidence, the originally proposed structure of compound B was discarded, and the compound was assumed to have a structure similar to the following:



However, the ultraviolet spectrum would not support this structure over the previously proposed one, for there is no increase in conjugation. Further work with the isolated product from the micro hydrogenation indicates that this newly proposed structure is not completely correct.

Compound C

If the proposed lactone structure existed, hydrogenation of compound B would probably yield an open chain amino acid very similar to that of compound A:



The reaction would require two moles of hydrogen, one mole for the double bond and one mole for cleaving the lactone ring, to form compound C. The carbon and hydrogen analysis of compound C for an assigned molecular weight of 270 was somewhat high. The molecular weight of this compound was determined by a neutralization equivalent; values of 271.5 and 272.2 were obtained.

The solubility of compound C in both cold 5% sodium hydroxide and hydrochloric acid would indicate the presence of a carboxyl group and an amine group. Moreover, the compound was soluble in warm water. The compound reduced potassium permanganate solution slowly over a long period of time, but not bromine in water.

If compound C were an amino acid similar to compound A, as illustrated above, their infrared and ultraviolet spectra should be analogous. The infrared spectrum of compound C was very different from that of compound A, which indicated compound C was not an amino acid in the zwitter ion form. The peak at 1688cm^{-1} in the spectrum of compound C suggests a carboxyl group on an aromatic ring. Also, the peak at 3390cm^{-1} in the spectrum of compound B, which was assigned to the NH group, was not present in the spectrum of compound C. Certain peaks of compound C in the infrared are tentatively given the following structural

assignment (16, p.247-563):

peak (cm^{-1})	Structural Assignment
1,688	aromatic COOH
1,618	C_6H_5
1,452	CH_2
1,386	CH_3
1,324	COOH
1,290	COOH
1,186	tertiary amine
782, 751	2-N, 6-CH_3 pyridyl
723	C_6H_5
710	C_6H_5

Because of the disappearance of the peak in the NH stretch region in the spectrum of compound C, a qualitative test for nitrogen was made by a sodium fusion and was positive. Moreover, the ultraviolet spectrum of compound C was very different from that of compound A. The position of the maxima in the ultraviolet for compound C suggests the possibility of an aromatic acid as illustrated by the following data:

Compound	$m\mu_{max}$	E_{max}
Compound C	243	11,920
	311	5,425
1-napthoic acid	220	50,200
(6, plate 250)	290	7,950

However, the E_{max} of the maximum around 220-250 mμ for compound C appears to be too low for compound C to be of a napthoic acid-type structure.

In conclusion, the structure for compound A seems to be similar to those reported by Allen, Spangler, and Webster. However, no definite structure can be proposed for either compound B or compound C at this time.

SUMMARY

The condensation reaction between 2-amino, 6-methyl pyridine was investigated. An alternate condensation employing 2-amino, 6-methyl pyridine and benzalpyruvic acid was performed. One product, γ-(phenyl)- γ -(6-methyl,2-aminopyridyl)- α -oxo butyric acid, was found to be similar to those reported by Allen, Spangler, and Webster and was assigned a structure. The other product, compound B, and its hydrogenated product, compound C, were not assigned a complete structure because of insufficient evidence.

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