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2-AMINOPYRIDINE AND THE DOEBNER REACTION

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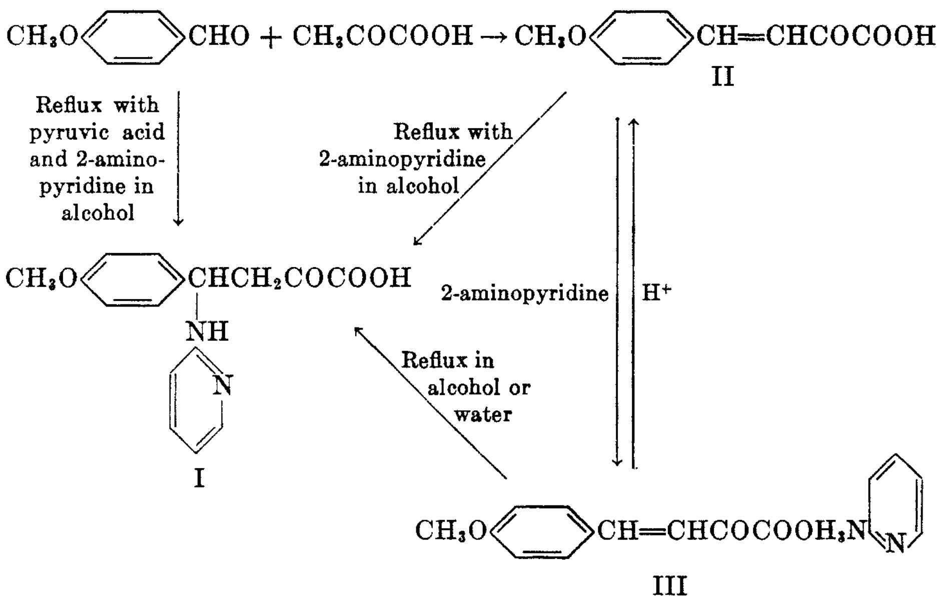
About twenty-five years ago Chichibabin (1, 2, 3) showed that when 2-aminopyridine and its simple derivatives react with other substances ring closure takes place through the ring nitrogen, to give bicyclic compounds having a nitrogen atom common to both rings. Certain previous investigators had represented the reaction products as 1,8-naphthyridines; this structure was shown to be untenable by Seide (4, 5, 6) and Khitrik (7). In view of these numerous instances, it is somewhat surprising to note in recent publications (8, 9) the statement that in the Doebner reaction 2-aminopyridine gives derivatives of 1,8-naphthyridine.

Attempts to repeat this work have been unsuccessful. Although the substances which were obtained had decomposition points in the ranges stated, they appear to be 2-aminopyridine addition products of the benzalpyruvic acids. The reaction was most carefully examined using anisaldehyde, pyruvic acid, and 2-aminopyridine. Upon refluxing an alcoholic solution of these three components, γ-(4-methoxyphenyl)-γ-(2-pyridylamino)-α-oxobutyric acid (I) was obtained. When anisalpyruvic acid and 2-aminopyridine were refluxed in alcoholic solution, the acid (I) again resulted. Upon refluxing the 2-aminopyridine salt of anisalpyruvic acid in either alcoholic or aqueous solution, the acid (I) was obtained in nearly quantitative yield. No other substances were obtained, in numerous attempts, except sticky brown tars. These results are summarized in the diagram.



It may be concluded, therefore, that this case is not an exception and that 1,8-naphthyridines are not formed. This view is concurred with independently by Petrow (10). Very recently, Lappin (11, 12) has also shown that 1,8-naphthyridines are not formed from 2-aminopyridine derivatives, except in instances where there is an electron-releasing group in the 6-position.

Evidence for the structure of I is furnished by its properties. It dissolves in dilute hydrochloric acid or sodium hydroxide solution, and can be recovered without change by careful neutralization. There is no change when an aqueous solution is boiled for six hours, but when refluxed with a 5% sodium hydroxide solution it gives 2-aminopyridine, anisaldehyde, and anisic acid. When heated at 5 to 10 degrees above its melting point *in vacuo* or at 760 mm., 2-aminopyridine distils, leaving a tarry residue. It is well known that arylamino addition products of α,β-unsaturated ketones are dissociated by heat. The ultraviolet absorption curve (Figure 1) shows the absence of a conjugated system of double bonds which is present in II and in III.

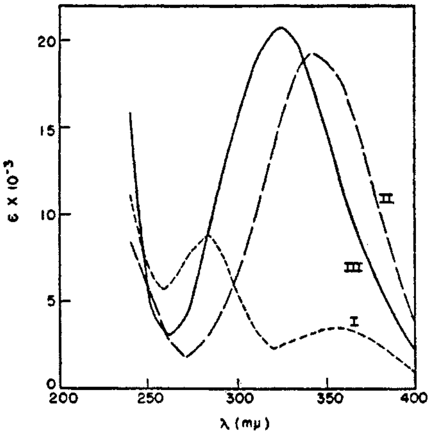


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA IN ETHANOL

I, reaction product; II, anisalpyruvic acid; and III, 2-aminopyridine salt of anisalpyruvic acid.

EXPERIMENTAL

γ-*(4-Methoxyphenyl)*-γ-*(2-pyridylamino)*-α-*oxobutyric acid* (I). The reaction was carried out according to the procedure of Migliardi (9). 2-Aminopyridine (9.4 g., 0.1 mole) and 13.6 g. (0.1 mole) of freshly distilled anisaldehyde were dissolved in 75 ml. of absolute ethanol. After about a minute 8.8 g. (0.1 mole) of freshly distilled pyruvic acid was added and the resulting solution was heated under reflux for six hours. The reaction mixture was concentrated to about one-half its volume and then poured into a large volume of water with vigorous stirring. The yellow crystals, which were sometimes very slow to separate, were washed and dried. The yield was usually less than 50%, but additional product could be obtained when the filtrates were allowed to stand at room temperature for several days. The material was recrystallized from water or ethanol; m.p. 149–150° (decomp.).

The reaction product also could be obtained in almost quantitative yield by heating under reflux a solution of the 2-aminopyridine salt of anisalpyruvic acid in either ethanol or water.

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: C, 64.2; H, 5.4; N, 9.4.
Found: C, 64.3; H, 5.3; N, 9.4.

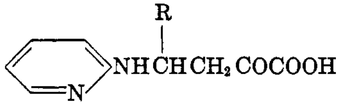
The *p-nitrophenylhydrazone* of the reaction product melted at 172–174°.

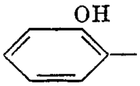
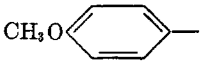
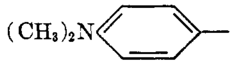
Anal. Calc'd for $C_{22}H_{21}N_5O_5$: C, 60.7; H, 4.8; N, 16.1.
Found: C, 60.8; H, 4.6; N, 15.8.

The reaction product is soluble in either aqueous hydrochloric acid or sodium hydroxide and can be recovered from such solutions by careful neutralization. It can be recrystallized from 10% aqueous sodium carbonate solution without change. An aqueous solution of the material was heated under reflux for six hours without change. The substance, as well as its solutions, fluoresces yellow when exposed to ultraviolet light.

TABLE I

REACTION PRODUCTS



R	COLOR	M.P., °C.	MAZZA AND MIGLIARDI'S DATA	
			COLOR	M.P., °C.
C_6H_5—	Pale yellow	148–160° (decomp.)	Light yellow crystals	145° (decomp.)
	Pale yellow	201–204° (decomp.)	Rose yellow crystals	201° (decomp.)
	Yellow crystals	149–150° (decomp.)	Reddish-yellow needles	150° (decomp.)
	Yellow crystals	189° (decomp.)	Yellow leaflets	182–183° (decomp.)
$C_6H_5CH_2$—			Light yellow needles	155° (decomp.)
$C_6H_5CH{=}CH$—	Tan	154–170° (decomp.)	Reddish-maroon needles	186° (decomp.)

Treatment of I with alkali. A solution of 3 g. of the reaction product in 300 ml. of 5% aqueous sodium hydroxide was heated under reflux overnight. There was obtained 0.3 g. of 2-aminopyridine, 0.2 g. of anisaldehyde in the form of its 2,4-dinitrophenylhydrazone, and 0.1 g. of anisic acid.

The effect of heat on I. When heated at 5 to 10 degrees above its melting point at either atmospheric or reduced pressure, the reaction product decomposed to give 2-aminopyridine and a dark, viscous residue.

Oxidation of I. A solution of 1 g. of the reaction product in 25 ml. of glacial acetic acid was heated on a steam-bath as 2 g. of chromic oxide was added in small portions. After heating 30 minutes longer, the reaction mixture was cooled and poured into water. Colorless needles separated on standing overnight and were recrystallized from water, m.p. 182–184°. A mixed melting point with an authentic sample of anisic acid showed no depression.

Oxidation of 1 g. of the reaction product with 30% hydrogen peroxide gave no *p*-methoxycinnamic acid, but only a trace of anisic acid.

Anisalpyruvic acid was prepared according to the method of Reimer (13). The bright yellow acid, recrystallized from water, melted at 130–131°.

The *methyl ester*, recrystallized from methanol, melted at 105–106°.

The *2-aminopyridine salt*, after recrystallization from water, melted at 135–136° (decomp.).

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: C, 64.2; H, 5.4; N, 9.4.
Found: C, 64.2; H, 5.0; N, 9.2.

Acidification of an aqueous solution of the salt with hydrochloric acid regenerates anisalpyruvic acid. Oxidation of either the acid or its salt with 30% hydrogen peroxide gives *p*-methoxycinnamic acid.

The *p-nitrophenylhydrazone* of anisalpyruvic acid melted at 184–185°.

Anal. Calc'd for $C_{17}H_{15}N_3O_5$: C, 60.0; H, 4.4; N, 12.3.
Found: C, 59.6; H, 4.3; N, 12.4.

The reaction of 2-aminopyridine and pyruvic acid with other aldehydes likewise was carried out according to the procedure of Mazza and Migliardi (8, 9). The products were isolated with some difficulty from brown tars. The results are summarized in Table I.

SUMMARY

The Doebner reaction, applied to 2-aminopyridine, does not give derivatives of 1,8-naphthyridine, but open-chain substances which are formed by the addition of the 2-aminopyridine to benzalpyruvic acids.

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