Nitrogen-Substituted Derivatives of 2,5-Pyridinedicarboxylic Acid

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The N-methyl and N-oxide derivatives of 2,5-pyridinedicarboxylic acid were prepared. 2,5-Dicarboxy-N-methylpyridinium betaine reacted with potassium ferricyanide in a basic solution to yield 5-carboxy-N-methyl-2-pyridone. 2,5-Dicarboxypyridine-N-oxide reacted with benzoyl chloride to give 5-carboxy-2-pyridine and with acetic anhydride to give 3-carboxy-4-pyridone.

Many of the reactions of pyridine compounds are dependent on the presence of the nitrogen atom which exerts its influence as a center of electron attraction in the pyridine nucleus and as the site for the formation of reactive ammonium salts and N-oxides from which numerous transformations are possible. N-Alkyl pyridinium salts are prepared from alkyl iodides and pyridine by a vigorous exothermic reaction which is initiated at room temperature. The pyridine monocarboxylic acids are alkylated only under more severe conditions. N-Ethylnicotinium iodide was prepared by the reaction of potassium nicotinate with ethyl iodide at 150°.[1] 2-Methyl-6-phenylpyridine-3-carboxylic acid was not alkylated by alkyl halides, but its ethyl ester was alkylated by methyl sulfate.[2]

In our work, the pyridine dicarboxylic acid, 2,5-pyridinedicarboxylic acid (isocinchomeronic acid), was not alkylated by dimethyl sulfate in refluxing toluene or xylene solutions. However, the dimethyl ester of the acid was alkylated smoothly by dimethyl sulfate in a refluxing benzene solution to yield 2,5-dicarbomethoxy-N-methylpyridinium methosulfate (I). The dimethyl ester was not alkylated by methyl iodide at 130–140° in a chloroform solution.

2,5-Dicarbomethoxy-N-methylpyridinium methosulfate was hydrolyzed in a concentrated hydrochloric acid solution to give 2,5-dicarboxy-N-methylpyridinium betaine (II). The methyl betaine was insoluble in organic solvents but was slightly soluble in hot water, from which it was crystallized. The 5-carboxyl group could not be esterified by refluxing the betaine in a methanol solution with a sulfuric acid or a cation-exchange resin catalyst.

A characteristic reaction of N-alkyl pyridinium compounds is oxidation to pyridones by mild oxidizing agents, such as potassium ferricyanide, in basic solutions.[3]

2,5 - Dicarbomethoxy - N - methylpyridinium methosulfate reacted rapidly and exothermically with potassium ferricyanide in basic solution. The 2-carbomethoxy group of the pyridinium

methosulfate was eliminated as carbon dioxide and methanol, and the ester, 5-carbomethoxy-N-methyl-2-pyridone (III), and the acid, 5-carboxy-N-methyl-2-pyridone (IV), were formed. An exothermic reaction also occurred when the betaine, II, was oxidized by potassium ferricyanide in a basic solution, and 5-carboxy-N-methyl-2-pyridone was isolated as the sole product.
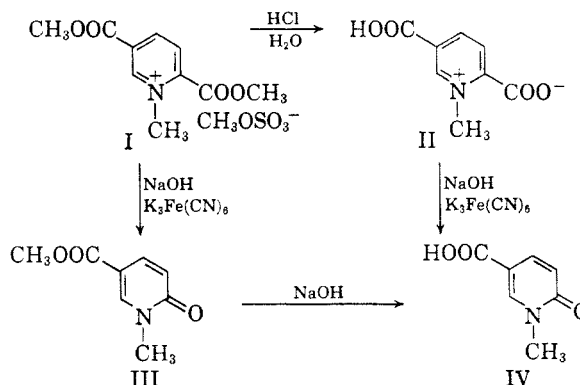
When zinc powder was added to an aqueous solution of 2,5-dicarbomethoxy-N-methylpyridinium methosulfate at room temperature, a yellow unstable solid was formed in a slightly exothermic reaction. The yellow crystalline product rapidly decomposed at room temperature and was not characterized.

Pyridine-N-oxides usually are prepared readily by the oxidation of pyridine compounds by 30% hydrogen peroxide in acetic acid solutions. The N-oxide of nicotinic acid has been prepared by this procedure.[4] 2,5-Pyridinedicarboxylic acid was not oxidized to the N-oxide by this method. However, its dimethyl ester was oxidized by 30% hydrogen peroxide in an exothermic reaction which was initiated at 100° to give 5-carbomethoxy-2-carboxypyridine-N-oxide (V). Only the monoester could be isolated from the reaction mixture. The monoester was saponified readily to 2,5-dicarboxypyridine-N-oxide. The facile hydrolysis of the 2-carbomethoxy group may be attributed to the inductive effect of the N-oxide function and to the stabilization of the acid by hydrogen bonding (Va) or by zwitterion formation (Vb).

(1) E. Winterstein and A. B. Weinhagen, Z. physiol Chem.; 100, 170 (1917).
(2) H. Nienberg, Chem. Ber., 68, 1474 (1935).
(3) R. C. Elderfield, Heterocyclic Compounds, John Wiley and Sons, New York, N. Y., 1950, Vol. I, p. 415.
(4) G. R. Clemo and H. Koenig, J. Chem. Soc., S231-2 (1949).

CH₃OOC structure (Va) and (Vb)

Va   Vb
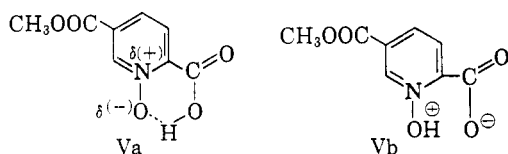
Substitution reactions, such as nitration, which are difficult to effect on the pyridine ring, have been carried out readily with the pyridine oxides.[5] 5 - Carbomethoxy - 2 - carboxypyridine - N - oxide was not nitrated in a mixture of sulfuric and nitric acids at 130°.

When benzoyl chloride was added to a dioxane solution of 5-carbomethoxy-2-carboxypyridine-N-oxide at 90°, a rapid exothermic reaction occurred in which carbon dioxide was evolved. After the reaction product had been hydrolyzed, 5-carboxy-2-pyridone (VI) was isolated. The 5-carboxy-2-pyridone was identical with a sample of 5-carboxy-2-pyridone which was prepared by the carboxylation of 2-pyridone by the method of Tschitschibabin.[6]

The carboxypyridone was not formed, however, when a benzene solution of 5-carbomethoxy-2-carboxypyridine-N-oxide and benzoyl chloride was refluxed. A polar solvent, therefore, appears to be necessary to effect the reaction. The formation of the pyridone may be rationalized by the following mechanism:

CH₃OOC reaction scheme structures: V + C₆H₅COCl ⇌ (dioxane) → intermediate → VII + CO₂ → VI

VII   VI
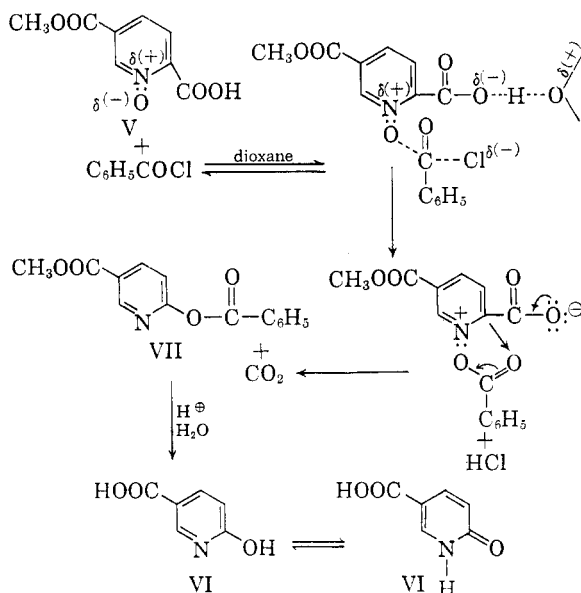
As the oxygen atom of the N-oxide function with its partial negative charge reacts with benzoyl chloride at the carbonyl function, dioxane solvates the acid hydrogen and an unstable intermediate zwitter ion is formed. Resonance of the positive charge in the ring places a partial positive charge

at the α-carbon. By an intramolecular rearrangement with simultaneous decarboxylation, carbon dioxide is eliminated and 2-benzoxy-5-carbomethoxypyridine (VII) is formed.

The reaction of pyridine-N-oxide with acetic anhydride to give 2-pyridone was demonstrated by Katada.[7]

The reaction of 5-carbomethoxy-2-carboxypyridine-N-oxide with acetic anhydride was initiated at 45° and was exothermic. Carbon dioxide was evolved from the reaction mixture. A crystalline ester whose elemental analysis corresponded to that of an acetoxycarbomethoxypyridine (VIII) was isolated. The acetoxycarbomethoxypyridine was hydrolyzed by water at room temperature to give a compound (IX), m.p. 82–84°, whose elemental analysis corresponded to that of a carbomethoxypyridone. The acetoxycarbomethoxypyridone was hydrolyzed in a hydrochloric acid solution to give an acid (X), m.p. 245–247° dec., whose elemental analysis corresponded to that of a carboxypyridone. However, this acid was not the same as the 5-carboxy-2-pyridone, m.p. 303.4–303.7° dec., produced by the reaction of the N-oxide (V) with benzoyl chloride.

A consideration of the possible structures for the product of the reaction of the N-oxide (V) with acetic anhydride (Table I) led to the conclusion that the product was 3-carboxy-4-pyridone, rather than the expected 5-carboxy-2-pyridone.

TABLE I

MELTING POINTS OF CARBOXYPYRIDONES AND THEIR ESTERS

Carboxypyridone	M.P. of Acid	M.P. of Methyl Ester
3-Carboxy-2-pyridone	225°	153°
5-Carboxy-2-pyridone	301–302°	164°
6-Carboxy-2-pyridone	282°	—
3-Carboxy-4-pyridone	250°	—
Reaction product	245–247°	82–84°

The ultraviolet spectra of the products obtained from the reaction of the N-oxide (V) with acetic anhydride and with benzoyl chloride provided additional evidence for the proposed structures. The spectra of 3-carboxy-4-pyridone, 3-carbomethoxy-4-pyridone, and 3-carbomethoxy-4-acetoxypyridine were very similar to the spectrum recorded for 1 - methyl - 3 - carboxy - 5,6,7,8 - tetrahydroquinolone,[8] whereas the spectra of 5-carboxy-2-pyridone and N-methyl-5-carboxy-2-pyridone were very similar to the spectra recorded for 5-carboxy-6-methyl-2-pyridone[9] and 1-methyl-5-carbamyl-2-

(5) F. E. Cislak, Ind. Eng. Chem., 47, 800 (1955). E. Ochiai, J. Org. Chem., 18, 534 (1953).

(6) E. A. Tschitschibabin and A. W. Kirssanow, Ber., 57, 1161 (1924).

(7) M. Katada, J. Pharm. Soc. Japan, 67, 51 (1947).

(8) R. D. Brown and F. N. Lahey, Austral. J. Sci. Research, A3, 623 (1950).

(9) F. Ramirez and A. P. Paul, J. Am. Chem. Soc., 77, 1035 (1955).

pyridone[10] (Table II). The two maximum intensity absorption bands in the spectra of the 3-carboxy-4-pyridone derivatives occur at shorter wave lengths than do the maximum absorptions of the 5-carboxy-2-pyridone derivatives. The intensities of the bands of the spectra of 4-pyridone[11] and of the 3-carboxy-4-pyridone derivatives were much greater than the intensities of the bands in the spectra of 2-pyridone[11] and its carboxylated derivatives.

TABLE II

ULTRAVIOLET SPECTRA OF PYRIDONES[a]

Compound	λ_{max} (mμ)	ϵ_{max}
3-Carboxy-4-pyridone	267; 220	13,320; 26,800
3-Carbomethoxy-4-pyridone	268; 223	13,540; 27,850
3-Carbomethoxy-4-acetoxy-pyridine	271; 224	19,240; 43,400
1-Methyl-3-carboxy-5,6,7,8-tetrahydro-4-quinolone[b,c]	262; 220	9,120; 28,800
N-Methyl-4-hydroxypyridine[d]	262	18,200
4-Pyridone[d]	256	14,100
5-Carboxy-2-pyridone	298; 256	4,170; 14,500
N-Methyl-5-carboxy-2-pyridone	300; 255	5,370; 15,800
5-Carboxy-6-methyl-2-pyridone[b,e]	300; 268	6,000; 14,500
1-Methyl-5-carbamyl-2-pyridone[f]	300; 260	—
2-Pyridone[d]	297; 227	9,000; 10,000

[a] All spectra taken in neutral methanol solution except as marked. [b] In ethanol. [c] See ref. 8. [d] See ref. 11. [e] See ref. 9. [f] See ref. 10.

The infrared spectra of 3-carboxy-4-pyridone and of 5-carboxy-2-pyridone show marked differences. Broad absorbances in the 4.0 μ and 5.0–5.7 μ regions of the spectrum of 3-carboxy-4-pyridone, which are not found in the spectrum of 5-carboxy-2-pyridone, indicate strong intramolecular hydrogen bonding between hydroxyl and carboxyl functions. Such bonding is possible if the hydroxyl and carboxyl functions are attached to adjacent carbons. The disappearance in the spectrum of 3-carboxy-4-pyridone of the strong absorptions found at 6.05 and 6.2 μ in the spectrum of 5-carboxy-2-pyridone also suggests that the former exists largely in the form of the hydroxy-pyridine.

When the N-oxide (V) was treated with an equimolar quantity of acetic anhydride in a dioxane solution, 3-carboxy-4-pyridone again was formed. Even the reaction of the N-oxide (V) with acetyl chloride in a dioxane solution produced 3-carboxy-4-pyridone instead of the product, 5-carboxy-2-pyridone, produced by the reaction of the N-oxide with benzoyl chloride.

2,5-Bis(N,N-diethylcarboxamido)pyridine-N-

(10) W. E. Knox and W. I. Grossman, J. Biol. Chem., 168, 1363 (1947).

(11) H. Specker and H. Gawrosch, Chem. Ber., 75, 1338 (1942).

oxide was prepared by the oxidation of 2,5-bis-(N,N-diethylcarboxamido)pyridine by hydrogen peroxide in a glacial acetic acid solution. This N-oxide, from which carbon dioxide can not be eliminated readily, did not react with acetic anhydride.

EXPERIMENTAL

Dimethyl 2,5-pyridinedicarboxylate. A solution of 501 g. (3.0 moles) of 2,5-pyridinedicarboxylic acid, 3200 ml. of methanol, and 480 ml. of concd. sulfuric acid was refluxed for 6 hr. After the reaction mixture had been neutralized with 4500 ml. of a 25% aqueous sodium carbonate solution, it was extracted with two 1000-ml. portions of chloroform. The chloroform extracts yielded 430 g. (69% yield) of dimethyl 2,5-pyridinedicarboxylate, m.p. 162–163°.

2,5-Dicarbomethoxy-N-methylpyridinium methosulfate (I). A mixture of 19.5 g. (0.1 mole) of dimethyl 2,5-pyridinedicarboxylate, 100 ml. of benzene, and 20 g. (0.16 mole) of dimethyl sulfate was refluxed for 3 hr. An oil separated from the benzene solution as the reaction mixture was refluxed; this oil formed a solid crystalline mass when it was cooled. When this material was crystallized from acetone, 26 g. of white crystals, m.p. 88–89°, was obtained.

Anal. Calcd. for $C_{11}H_{15}O_8NS$: C, 41.12; H, 4.71; N, 4.36. Found: C, 41.06, 41.24; H, 4.29, 4.41; N, 4.35, 4.18.

Quaternization of the dimethyl 2,5-pyridinedicarboxylate did not occur when a mixture of 19.5 g. (0.1 mole) of the ester, 60 ml. of chloroform, and 20 g. (0.14 mole) of methyl iodide was heated at 130–140° for 4 hr. in a glass-lined bomb.

2,5-Dicarboxy-N-methylpyridinium betaine (II). I, which had been obtained by refluxing a solution of 39.0 g. (0.20 mole) of dimethyl 2,5-pyridinedicarboxylate, 200 ml. of xylene, and 30.0 g. (0.24 mole) of dimethyl sulfate for 2 hr., was refluxed with 100 ml. of concentrated hydrochloric acid for 3 hr. When the hydrochloric acid solution was cooled, 20 g. (55% yield) of 2,5-dicarboxy-N-methylpyridinium betaine precipitated from the solution. II was insoluble in organic solvents and cold water and sparingly soluble in hot water. When II was crystallized from hot water, white crystals which melted at 170° dec. were obtained.

Anal. Calcd. for $C_8H_7O_4N$: C, 53.02; H, 3.90; N, 7.73; neut. equiv., 181. Found: C, 53.50, 53.52; H, 3.95, 3.94; N, 7.51, 7.55; neut. equiv., 177, 179.

Only a trace of II was formed when a mixture of 33.4 g. (0.20 mole) of 2,5-pyridinedicarboxylic acid, 28 g. (0.22 mole) of dimethyl sulfate, and 200 ml. of toluene was refluxed for 28 hr. Most of the 2,5-pyridinedicarboxylic acid was recovered.

Attempted esterification of II. When II was refluxed in a methanol solution in the presence of sulfuric acid or a Dowex 50-X12 cation exchange resin for 5–7 hr., no esterification occurred and II was recovered.

Oxidation of I *by potassium ferricyanide.* When 16.1 g. (0.05 mole) of I was added gradually to a stirred solution of 33.0 g. (0.10 mole) of potassium ferricyanide, 6.02 (0.15 mole) of sodium hydroxide, and 100 ml. of water, an exothermic reaction occurred. The temperature of the reaction mixture was maintained at 35–40°. After the reaction was completed, the aqueous solution was extracted with four 40-ml. portions of chloroform. One gram of 5-carbomethoxy-N-methyl-2-pyridone (III) was obtained from the chloroform extracts. After III was crystallized from hot water three times, it melted at 138.3–139.2°.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.46; H, 5.33; N, 8.39. Found: C, 57.56, 57.82; H, 5.25, 5.47; N, 8.42, 8.35.

When the extracted aqueous reaction mixture was acidified, carbon dioxide was evolved and the acid, 5-carboxy-N-methyl-2-pyridone (IV) precipitated. After IV was recrystallized from water and from ethanol, white crystals, m.p. 241–243°, were obtained.

Anal. Calcd. for C₇H₇O₃N: C, 54.91; H, 4.61; N, 9.15. Found: C, 55.21, 55.33; H, 4.56, 4.63; N, 8.92, 9.04.

III and IV are reported to melt at 139° and 237–238°, respectively.[12]

An exothermic reaction occurred also when a solution of 3.4 g. (0.085 mole) of sodium hydroxide and 10 ml. of water was added to a solution of 3.8 g. (0.021 mole) of II, 13.9 g. (0.042 mole) of potassium ferricyanide, and 50 ml. of water. The sodium hydroxide solution was added at a rate such that the temperature of the reaction mixture did not exceed 43°. When the basic solution was acidified, carbon dioxide was evolved and IV, m.p. 240.5–241.5°, precipitated.

III and IV were not formed by the oxidation of I by 30% hydrogen peroxide in aqueous basic solutions. Instead, black tars were obtained.

Reduction of I by zinc dust. When 25 g. of zinc dust was slowly added to a solution of 21.3 g. (0.066 mole) of I in 50 ml. of water, a slightly exothermic reaction took place and a yellow solid precipitated. The yellow solid was extracted with chloroform. After the chloroform solution was distilled, a black tar containing crystalline material remained. The yellow crystalline material was recovered by crystallizing the residues from ethanol. When the crystals stood over-night in a closed vial at room temperature, they decomposed to a black tar.

5-Carbomethoxy-2-carboxypyridine-N-oxide (V). When the temperature of a solution of 117 g. (0.60 mole) of dimethyl 2,5-pyridinedicarboxylate, 300 ml. of glacial acetic acid, and 150 ml. of 30% hydrogen peroxide was raised to 100°, an exothermic reaction was initiated which maintained the temperature of the reaction mixture at 105° for 15 min. without the application of outside heat. The solution was heated at 100° for 1.5 hr. after the exothermic reaction ceased. When the reaction mixture was chilled, 96.5 g. (80% yield) of V precipitated. After V had been recrystallized from 95% ethanol, it melted at 151° dec.

Anal. Calcd. for C₈H₇O₅N: C, 48.72; H, 3.58; N, 7.10. Found: C, 48.72, 48.94; H, 3.37, 3.56; N, 7.00, 7.11.

When an aqueous solution of V was titrated with a sodium hydroxide solution, one equivalent of base was rapidly neutralized. A second equivalent of base was neutralized as the ester group was saponified.

Anal. Calcd. for C₈H₇O₅N: sapon. equiv., 98.6. Found: sapon. equiv., 98.4, 98.5.

When a mixture of 16.7 g. (0.10 mole) of 2,5-pyridinedicarboxylic acid, 50 ml. of glacial acetic acid, and 50 ml. of 30% hydrogen peroxide was refluxed for 8 hr., no N-oxide was formed.

V was saponified to the disodium salt of 2,5-dicarboxypyridine-N-oxide when it was heated for 15 min. in 40 ml. of 10% sodium hydroxide solution. When the basic solution was acidified with concd. hydrochloric acid, the free acid, 2,5-dicarboxypyridine-N-oxide precipitated. The 2,5-dicarboxypyridine-N-oxide melted at 242–244° dec.

Anal. Calcd. for C₇H₅O₅N: neut. equiv., 91.6. Found: neut. equiv., 92.2, 92.1.

Reaction of V with benzoyl chloride. Eight grams (0.57 mole) of benzoyl chloride was added in one portion to a solution of 10 g. (0.51 mole) of V and 50 ml. of dioxane at 90°. The rapid reaction which resulted raised the temperature of the reaction mixture to reflux (100°), and carbon dioxide was evolved rapidly. After the dioxane had been distilled from the reaction mixture, a heavy oil was left. Benzoic acid was extracted from the oily mixture with an aqueous 10% sodium carbonate solution. The brown oil remaining after the extraction was refluxed for 1 hr. with a 15% hydrochloric acid solution. When the hydrochloric acid solution was

chilled, 5-carboxy-2-pyridone (VI) precipitated as a crystalline solid which melted at 303.4–303.7° dec. after recrystallization from water.

Anal. Calcd. for C₆H₅O₃N: C, 51.80; H, 3.62; N, 10.07. Found: C, 52.36, 52.58; H, 3.63, 3.70; N, 9.44, 9.65.

An authentic sample of VI was prepared by the carboxylation of 2-pyridone by the method of Tschitschibabin.[6] A mixture of 10 g. (0.105 mole) of 2-pyridone and 40 g. of dry, powdered potassium carbonate was heated in a bomb at 200° under a carbon dioxide pressure of 400 p.s.i.g. for 4 hr. When an aqueous solution of the contents of the bomb was acidified with hydrochloric acid, 6.9 g. of VI precipitated from the solution. After VI had been crystallized from water, it melted at 302–303° dec. and was identical with the VI produced by the reaction of V with benzoyl chloride.

When a solution of V, benzoyl chloride, and benzene was refluxed, there was no evidence of the occurrence of a reaction.

Reaction of V with acetic anhydride. When a mixture of 30 g. (0.152 mole) of V and 90 ml. of acetic anhydride was heated to 45°, a reaction started, and carbon dioxide was evolved. The exothermic reaction carried the temperature of the reaction mixture to 70°. The reaction was complete after 10 min. A crystalline solid (VIII) whose elemental analysis corresponded to that of an acetoxycarbomethoxy-pyridine was left after the acetic anhydride had been distilled under high vacuum. After the solid had been crystallized from benzene, it melted at 100–101.5°.

Anal. Calcd. for C₉H₉O₄N: C, 55.37; H, 4.65. Found: C, 55.71, 55.92; H, 4.70, 4.56.

When an acetic anhydride solution of VIII evaporated at room temperature and was exposed to the atmosphere for a week, it hydrolyzed to give a carbomethoxypyridine (IX), m.p. 82–84°. IX was crystallized from a benzene–petroleum ether mixture.

Anal. Calcd. for C₇H₇O₃N: C, 54.91; H, 4.61; N, 9.15. Found: C, 55.10, 55.22; H, 4.57, 4.65; N, 8.78, 8.88.

IX was hydrolyzed to 3-carboxy-4-pyridone (X) when it was refluxed for 1.5 hr. in a concd. hydrochloric acid solution. When the hydrochloric acid solution was partly neutralized with sodium carbonate, X precipitated as a white solid, which melted at 245–247° dec. after it was recrystallized from water.

Anal. Calcd. for C₆H₅O₃N: C, 51.80; H, 3.62; N, 10.06. neut. equiv., 139. Found: C, 51.92, 52.13; H, 3.51, 3.54; N, 9.36, 9.39; neut. equiv., 137.2, 136.7.

A solution of 10 g. (0.05 mole) of V, 50 ml. of dioxane, and 5.3 g. (0.05 mole) of acetic anhydride was heated at 85°. Carbon dioxide was evolved as the exothermic reaction proceeded. After the dioxane had been distilled under reduced pressure, the residue was hydrolyzed in a 15% aqueous hydrochloric acid solution. The product (4.5 g., 70% yield) melted at 243–245° after recrystallization from water.

Reaction of V with acetyl chloride. A mixture of 10 g. (0.05 mole) of V, 50 ml. of dioxane, and 5 g. (0.065 mole) of acetyl chloride reacted vigorously with evolution of carbon dioxide. The heavy oil which was left after dioxane had been distilled under reduced pressure was heated at 100° for 1 hr. in a 15% hydrochloric acid solution. The volume of the solution was reduced to 15 ml. When the solution was cooled, 4 g. (64% yield) of a crystalline product, m.p. 241–243°, was obtained.

Attempted nitration of V. V was not nitrated when 5.0 g. of V was heated at 110–130° for 3 hr. with 15 ml. of concentrated sulfuric acid and 15 ml. of nitric acid. Instead, hydrolysis of V to 2,5-dicarboxypyridine-N-oxide occurred.

2,5-Bis(N,N-diethylcarboxamido)pyridine-N-oxide (XI). A mixture of 62.5 g. (0.225 mole) of 2,5-bis(N,N-diethylcarboxamido)pyridine (which was prepared by the reaction of diethylamine and the dichloride of 2,5-pyridinedicarboxylic acid), 200 ml. of glacial acetic acid, and 100 ml. of 30% hydrogen peroxide was refluxed for 3 hr. After the

(12) H. V. Pechmann and W. Welsh, *Ber.*, **17**, 2395 (1884).

solvents had been distilled under reduced pressure, a white solid, m.p. 166.5–167.4°, remained.

Anal. Calcd. for $C_{15}H_{23}O_3N_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.46, 61.60; H, 7.83, 7.86; N, 13.86, 13.89.

XI did not react in a refluxing solution of acetic anhydride. The starting material was recovered after 4 hr. of heating in the acetic anhydride solution.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY]

3-Indolepropionic Acid

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3-Indolepropionic acid has been prepared in 56% yield by the reaction of indole with acrylic acid in the presence of acetic anhydride.

3-Indolepropionic acid has, over a period of years, been the subject of many investigations concerning its plant growth regulating properties. More recently, its use as a starting material for the synthesis of lysergic acid has been described.[1] There are various procedures by which 3-indolepropionic acid may be synthesized, and, until the present investigation, the most convenient of these consisted of the hydrolysis of 3-indolepropionitrile obtained from the reaction of indole and acrylonitrile.[2]

The reaction of acrylic acid with indole at 130° is reported to give a quantitative yield of 1-indolepropionic acid.[2] α-Acetamidoacrylic acid, however, reacts with indole in the presence of acetic anhydride to give acetyltryptophan.[3]

remains uncertain. Snyder and MacDonald[3] suggested that α-acetamidoacrylic acid is possibly converted by the anhydride present into an intermediate azlactone (I), oxazoline (II), or diacetylserine (III). On the basis of model experiments, these intermediates were rejected as unlikely, and no other explanations were presented. I and II are not possible intermediates in the present synthesis of 3-indolepropionic acid. III is considered improbable, as acetic acid would not be expected to add to acrylic acid under the reaction conditions.

A mechanism consistent with the addition of both acrylic acid and α-acetamidoacrylic acid to the 3-position of indole places the anhydride in the role of forming a mixed anhydride with the acrylic

When acrylic acid and indole were allowed to react in acetic acid solution containing acetic anhydride, 3-indolepropionic acid could be isolated in 56% yield from the reaction mixture. The quantity of anhydride necessary for the reaction to take place was not critically investigated, but it was found that 0.20 equivalent (based on indole) was not sufficient. For convenience, at least two equivalents were usually employed, one equivalent being somewhat less satisfactory.

The role of acetic anhydride in the reaction still

acid. This mixed anhydride, or an acryloyl cation produced by its dissociation, is the reactive species that adds to the 3-position (Equations A–D).

(1) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956). E. C. Kornfeld, G. B. Kline, and E. J. Fornefeld, U. S. Patent **2,796,419**.

(2) W. Reppe and H. Ufer, German Patent **698,273**; French Patent **48,570**, addition to French Patent **742,358**.

(3) H. R. Snyder and J. A. MacDonald, *J. Am. Chem. Soc.*, **77**, 1257 (1955); U. S. Patent **2,810,727**.