[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Pyridine Syntheses. II. A New Pyridine Synthesis Leading to Vitamin B_6

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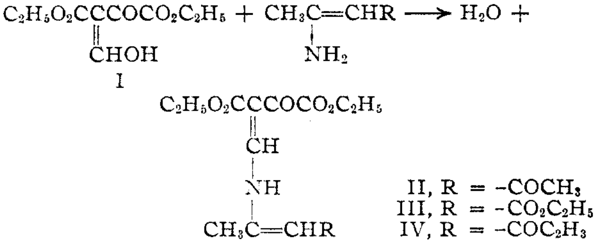
Reactions of ethyl hydroxymethyleneoxalacetate with iminoacetylacetone, ethyl β-aminocrotonate and methyl β-aminocrotonate gave diethyl [(1-methyl-3-oxo-1-butenylamino)-methylene]-oxalacetate, diethyl [(2-carbethoxy-1-methylvinylamino)-methylene]-oxalacetate and diethyl [(2-carbomethoxy-1-methylvinylamino)-methylene]-oxalacetate, respectively. However, the reaction with β-aminocrotononitrile gave diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate. In addition, some of the ammonium salt of ethyl hydroxymethyleneoxalacetate was isolated from each of the reactions. Treatment of diethyl [(1-methyl-3-oxo-1-butenylamino)-methylene]-oxalacetate, diethyl [(2-carbethoxy-1-methylvinylamino)-methylene]-oxalacetate and diethyl [(2-carbomethoxy-1-methylvinylamino)-methylene]-oxalacetate with concentrated sulfuric acid brought about ring closure to yield diethyl 5-acetyl-6-methyl-3,4-pyridinedicarboxylate, triethyl 2-methyl-3,4,5-pyridinetricarboxylate and diethyl 5-carbomethoxy-6-methyl-3,4-pyridinedicarboxylate, respectively. 5-Amino-6-methyl-3,4-pyridinedicarboxylic acid a key intermediate for the synthesis of vitamin B_6 was prepared from diethyl 5-acetyl-6-methyl-3,4-pyridinedicarboxylate or its partially hydrolyzed derivative, 5-acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic acid by treatment with hydrogen azide in concentrated sulfuric acid solution followed by acid hydrolysis.

The preceding paper of this series[1] has described reactions of ethyl ethoxymethyleneoxalacetate[2] with β-aminocrotononitrile, iminoacetylacetone and certain other "ene amines." It was hoped that these reactions would lead to pyridine compounds with substituents in the 2, 3, 4 and 5 positions, which would be useful intermediates for the synthesis of vitamin B_6. Indeed, pyridine compounds were formed in good yields but invariably the substituents appeared in the 2,3,5 and 6 positions of the ring. As an extension of this work the reactions of "ene amines" with ethyl hydroxymethyleneoxalacetate (I) have been investigated, and this has led to the synthesis of the desired 2,3,4,5-tetrasubstituted pyridines.

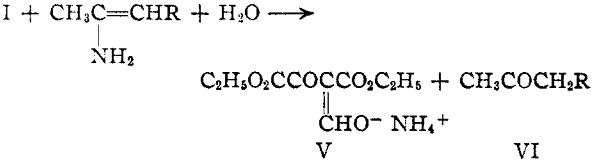
When ethyl hydroxymethyleneoxalacetate (I) and iminoacetylacetone were mixed in a dry solvent, a mild exothermic reaction took place, but, unexpectedly, no pyridine compound was formed. Two crystalline products were isolated from this reaction. One was a white powder, insoluble in ether or ethyl acetate but soluble in water. It proved to be the ammonium salt (V) of ethyl hydroxymethyleneoxalacetate. The other product was soluble in ethyl acetate or benzene, and insoluble in water. It was found to be diethyl [(1-methyl-3-oxo-1-butenylamino)-methylene]-oxalacetate[3] (II). Ethyl and methyl β-aminocrotonate each underwent reaction with I in the same manner as did iminoacetylacetone to yield V and compounds III and IV, respectively. The further transformations of II, III and IV as described below furnish unequivocal evidence for the structures as pictured.



$$\underset{\text{I}}{C_2H_5O_2C\underset{\underset{\text{CHOH}}{\|}}{C}COCO_2C_2H_5} + CH_3\underset{\underset{NH_2}{|}}{C}{=}CHR \longrightarrow H_2O + C_2H_5O_2C\underset{\underset{\underset{\underset{\underset{\underset{CH_3C=CHR}{|}}{NH}}{|}}{CH}}{\|}}{C}COCO_2C_2H_5$$

$$\text{II},\ R = -COCH_3 \quad \text{III},\ R = -CO_2C_2H_5 \quad \text{IV},\ R = -COC_2H_3$$

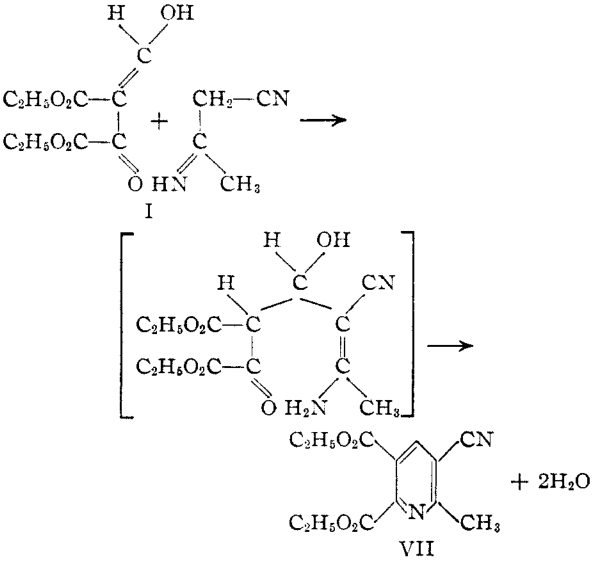
The primary reaction appears to be addition of the amino group of the "ene amine" to the hydroxymethylene group of I followed by elimination of water to give compounds II, III and IV. The liberated water in the presence of the strongly acidic I then brings about hydrolysis of part of the "ene amine" to form the ammonium salt V and the ketoester or diketone, VI.



$$\text{I} + CH_3\underset{\underset{NH_2}{|}}{C}{=}CHR + H_2O \longrightarrow \underset{\text{V}}{C_2H_5O_2CCO\underset{\underset{CHO^-\ NH_4^+}{\|}}{C}CO_2C_2H_5} + \underset{\text{VI}}{CH_3COCH_2R}$$

The yields of compounds II, III and IV ranged from about 40 to 60% and of the salt, V, about 30 to 50%.

In view of the results just described it was surprising to find that the reaction of I with β-aminocrotononitrile did not give an open-chain compound like II. Instead, diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate (VII) was obtained, together with the salt V. In this condensation ethyl hydroxymethyleneoxalacetate reacts in the same way as does ethyl ethoxymethyleneoxalacetate.[1]


I
VII

From inspection of structures II, III and IV it is evident that ring closure and elimination of one mole of water should give pyridine derivatives with substituents at positions 2, 3, 4 and 5. However,

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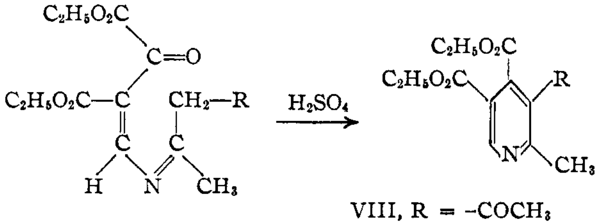
[1] E. M. Bottorff, R. G. Jones, E. C. Kornfeld and M. J. Mann, THIS JOURNAL, **73**, 4380 (1951).

[2] R. G. Jones, *ibid.*, **73**, 3684 (1951).

[3] This name was suggested by Dr. Leonard T. Capell, Associate Editor of *Chemical Abstracts*.

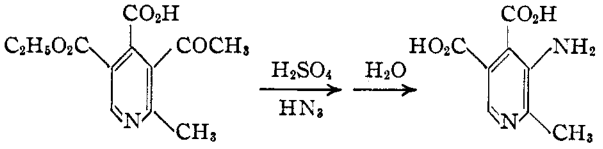
compounds II, III and IV appeared to be quite stable under ordinary conditions. Heating strongly resulted in the formation only of black, intractable tars. It was discovered, eventually, that ring closure of II, III and IV could be achieved by treatment with concentrated sulfuric acid to form the pyridine compounds VIII, IX and X, respectively. Yields up to 80 or 85% were obtained.



VIII, R = $-COCH_3$
IX, R = $-CO_2C_2H_5$
X, R = $-CO_2CH_3$

The ring closure was carried out by dissolving the open-chain compound in about three or four times its weight of 97% sulfuric acid. An exothermic reaction took place, and usually it was necessary to cool the mixture. The solution was then poured onto ice, and, after partial neutralization with base, the product was extracted into ethyl acetate. Under these conditions the ester groups of VIII, IX and X were partially hydrolyzed. Actually, in the ring closure of II the chief product isolated was a mono-ester-acid which tentatively has been designated as 5-acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic acid (XI).[4] Hydrolysis of the esters largely could be avoided by first pouring the sulfuric acid solution into absolute ethanol and then adding ice and water.[4] A number of other reagents such as hydrogen chloride, boron trifluoride and phosphoric acid were tried in place of sulfuric acid to effect the ring closure, but the experiments were unsuccessful. The conversion of XI to the known 5-amino-6-methyl-3,4-pyridinedicarboxylic acid (XII) as described below leaves no doubt as to its structure as a 2,3,4,5-tetrasubstituted pyridine. The triethyl ester IX was converted to the trimethyl ester which melted at 61–62°. This differs appreciably from the melting point (88.5–89.5°) of the known trimethyl 6-methyl-2,3,5-pyridinetricarboxylate.[1] Therefore, the structure of IX must be that indicated.

Vitamin B_6 has an hydroxyl group in position 3 of the pyridine ring. In order to use compounds VIII, IX or X for the synthesis of the vitamin some method was necessary for degrading the group in position 3 to hydroxyl. The triesters, IX and X appeared to be useless for this purpose since there is no way of transforming the ester function at position 3 without, at the same time, affecting the groups at positions 4 and 5. However, VIII and its derivative XI offered attractive possibilities. The obvious thing to try with VIII and XI was the Schmidt reaction.[5] There was good reason to believe that hydrogen azide would react with the methyl ketone group in preference to the ester or acid groups.[5] Compound XI did react smoothly with hydrogen azide in sulfuric acid solution, and yields in the range of 70% of 5-amino-6-methyl-3,4-pyridinedicarboxylic acid (XII) were obtained subsequent to hydrolysis of the reaction mixture.



XI XII

In practice, it was not necessary to isolate VIII or XI. The open-chain compound II was treated with sulfuric acid, and, after the initial reaction, powdered sodium azide was added directly to the sulfuric acid solution. By this procedure II was converted to XII in about 50% yield.

The use of azide on a large scale in this reaction probably would not be very hazardous. When sodium azide is added to the sulfuric acid solution of VIII in small quantities reaction takes place rapidly so that in no time is there more than a small concentration of hydrogen azide present. Furthermore, hydrogen azide is held strongly in solution in 95–97% sulfuric acid, and none escapes even when air is bubbled through.

The transformation of XII to vitamin B_6 by converting the amino group to hydroxyl, and reducing the carboxyl groups with lithium aluminum hydride has been reported previously.[6]

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Experimental

Reaction of Ethyl Hydroxymethyleneoxalacetate with Iminoacetylacetone.—A solution made by dissolving 43 g. (0.20 mole) of ethyl hydroxymethyleneoxalacetate[2] and 25 g. (0.25 mole) of iminoacetylacetone[7] in 200 ml. of dry ether was allowed to stand at room temperature. After about one hour a white crystalline precipitate began to separate, and after about two to three hours a second crystalline precipitate appeared. After standing overnight the mixture had set to an almost solid crystalline mass. The mixture was treated with 200 ml. of warm ethyl acetate which dissolved one of the precipitates. The insoluble product was collected on a filter, washed with ethyl acetate, then with dry ether and air-dried. It was identified as the ammonium salt of ethyl hydroxymethyleneoxalacetate (V). The yield was 14 g. (30%), and in several similar experiments the yields were about the same. A sample recrystallized from absolute ethanol melted at 134–135° dec.

Anal. Calcd. for $C_9H_{15}O_6$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.43; H, 6.88; N, 6.35.

This ammonium salt was insoluble in ether, ethyl acetate or benzene, sparingly soluble in absolute ethanol, readily soluble in water. At room temperature it completely decomposed after standing for several weeks, but samples have been kept at ice-box temperatures for many months without any deterioration. Acidification of an aqueous solution of the salt with hydrochloric acid and extraction with ether yielded ethyl hydroxymethyleneoxalacetate identified by boiling point, refractive index and infrared absorption spectrum.

The ethyl acetate–ether filtrate from the above salt was washed successively with dilute hydrochloric acid, aqueous sodium carbonate solution, and water, and, after drying with

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(4) The structure XI appears to be the most likely for this compound because, under the experimental conditions used, the most sterically hindered ester group of VIII would be expected to hydrolyze; see, M. S. Newman and C. D. McCleary, THIS JOURNAL, **63**, 1539 (1941); M. S. Newman, *ibid.*, **63**, 2431 (1941).

(5) H. Wolff in Adams, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 307.

(6) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951).

(7) A. Combs and C. Combs, *Bull. soc. chim.*, [3] **7**, 779 (1892).

magnesium sulfate it was evaporated under reduced pressure on the steam-bath. A crystalline residue remained. To this was added 100 ml. of dry ether and 100 ml. of petroleum ether (b.p. 60–68°), and after mixing well it was stored in the refrigerator at 0° for two days. The product, 30 g., was collected and air-dried, and by working up the filtrate an additional 3 g. was obtained making the total yield 33 g. (53%). In several similar experiments the yields ranged from 48 to 58%. A sample was recrystallized from an ether–petroleum ether mixture and obtained as fine, pale yellow needles; m.p. 119–120°. The compound was readily soluble in ethyl acetate or benzene, somewhat soluble in ether, very sparingly soluble in petroleum ether.

Anal. Calcd. for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.56; H, 6.50; N, 4.63.

This compound was identified as diethyl [(1-methyl-3-oxo-1-butenylamino)-methylene]-oxalacetate[3] (II) by ring closure to diethyl 5-acetyl-6-methyl-3,4-pyridinedicarboxylate (VIII) as described below.

The above experiment was carried out in benzene and in ethyl acetate as solvents in place of ether with about the same results. Absolute ethanol was less satisfactory as a solvent.

Reaction of Ethyl Hydroxymethyleneoxalacetate with Ethyl β-Aminocrotonate.—To a solution of 65 g. (0.30 mole) of ethyl hydroxymethyleneoxalacetate[2] in 300 ml. of dry ether was added 45 g. (0.35 mole) of ethyl β-aminocrotonate.[8] After a few minutes the solution became cloudy, a little heat was evolved, and a white crystalline precipitate separated. The reaction appeared to be complete within one-half hour, but the mixture was allowed to stand overnight. The white precipitate was collected on a filter, washed with anhydrous ether and air-dried. It was identified as the ammonium salt of ethyl hydroxymethyleneoxalacetate (see above) by its m.p., 134–135°, mixed m.p. and infrared absorption spectrum. The yield was 32 g. (46%).

The ether filtrate, 350 ml., was diluted with 100 ml. of ethyl acetate, and the resulting solution was washed successively with dilute hydrochloric acid, aqueous sodium carbonate solution, and water and dried with magnesium sulfate. Evaporation of the solvent by heating under reduced pressure on the steam-bath left a partially crystalline residue. This was heated in a distilling apparatus at 100° under 2 mm. pressure and 10 g. of colorless liquid was collected. The distillate was identified as ethyl acetoacetate by conversion to its copper salt (m.p. and mixed m.p. with an authentic sample, 189–190°).

The residue in the distilling flask partly crystallized on cooling. It was dissolved in a minimum quantity of warm dry ether and the solution was diluted to cloudiness with petroleum ether. The crystalline precipitate which separated was collected on a filter, and the filtrate was diluted with more petroleum ether and cooled to give a second crop of crystalline product, identified as diethyl [(2-carbethoxy-1-methylvinylamino)-methylene]-oxalacetate[3] (III) by ring closure to triethyl 2-methyl-3,4,5-pyridinetricarboxylate (IX) (see below). The yield was 40 g. (41%). A sample, recrystallized from ether–petroleum ether, was obtained as fine white needles, m.p. 110–110.5°.

Anal. Calcd. for $C_{16}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28. Found: C, 54.84; H, 6.59; N, 4.55.

Reaction of Ethyl Hydroxymethyleneoxalacetate with Methyl β-Aminocrotonate.—This reaction was carried out exactly as described above except that methyl β-aminocrotonate[9] was used in place of ethyl β-aminocrotonate. There were obtained 47–49% yields of the ammonium salt of ethyl hydroxymethyleneoxalacetate and 38–40% yields of diethyl [(2-carbomethoxy-1-methylvinylamino)-methylene]-oxalacetate[3] (IV); m.p. 114–115°.

Anal. Calcd. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.58; H, 6.15; N, 4.50.

Reaction of Ethyl Hydroxymethyleneoxalacetate with β-Aminocrotononitrile.—To a solution of 43.2 g. (0.20 mole) of ethyl hydroxymethyleneoxalacetate in 200 ml. of dry ether was added 19 g. (0.23 mole) of β-aminocrotononitrile.[10] Soon an exothermic reaction began; the ether boiled, and a precipitate separated, first as a liquid which slowly crystallized. After about one-half hour another 250 ml. of dry ether was added, and the white crystalline precipitate mixed with a little orange gum was collected on a filter and washed with ether. It was recrystallized from absolute ethanol and identified as the ammonium salt of ethyl hydroxymethyleneoxalacetate by its melting point (134–135° dec.), mixed melting point with an authentic sample, and infrared absorption spectrum. The yield of crude product was 17.5 g. (37%).

The ether filtrate was washed successively with dilute hydrochloric acid, aqueous sodium carbonate solution and water. It was dried and distilled to yield 20 g. (38%) of diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate; b.p. 140–145° (0.5 mm.). This was identified by its infrared absorption spectrum which was identical with that of an authentic sample.[1] The experiment was repeated, and the same results were obtained.

5-Acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic Acid (XI).—In a small flask was placed 30 g. (0.10 mole) of diethyl [(1-methyl-3-oxo-1-butenylamino)-methylene]-oxalacetate (II), and to it was added 50 ml. of 97% sulfuric acid. The solid dissolved with evolution of heat, and the flask was cooled in an ice-bath to keep the temperature at about 50–55°. After the exothermic reaction had subsided, the solution was allowed to stand at room temperature for two hours. It was then poured with stirring onto 350 g. of chipped ice. The resulting solution was partially neutralized by adding slowly and with stirring 70 g. of sodium carbonate monohydrate. The solution was extracted with three 200-ml. portions of ethyl acetate, and the combined ethyl acetate solution was extracted with a solution of 30 g. of sodium bicarbonate in 500 ml. of water. This bicarbonate solution was acidified with concentrated hydrochloric acid and extracted with three 100-ml. portions of ethyl acetate. The ethyl acetate extract was dried and evaporated under reduced pressure leaving a sirup which slowly crystallized to a hard cake. The yield of this product, 5-acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic acid (XI), was 17.7 g. (70%). A sample was recrystallized by dissolving in a minimum quantity of hot benzene, adding an equal volume of ether, filtering, and diluting with three volumes of petroleum ether. It separated very slowly, m.p. 138–139°.

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.21; N, 5.58. Found: C, 57.18; H, 5.42; N, 5.76.

The original aqueous sulfuric acid solution which had been partially neutralized with sodium carbonate and extracted with ethyl acetate (see above) was allowed to stand at room temperature for two days during which time it deposited 1.0 g. (4.5% yield) of 5-acetyl-6-methyl-3,4-pyridinedicarboxylic acid (see below).

The first ethyl acetate extract (above) which had been washed with sodium bicarbonate solution was evaporated under reduced pressure leaving 4 g. of brown oil. This oil consisted largely of diethyl 5-acetyl-6-methyl-3,4-pyridinedicarboxylate (see below). It was hydrolyzed with sodium hydroxide solution which, upon acidification, yielded 2 g. (9%) of 5-acetyl-6-methyl-3,4-pyridinedicarboxylic acid.

Diethyl 5-Acetyl-6-methyl-3,4-pyridinedicarboxylate (VIII).—5-Acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic acid (XI), 12.5 g., was dissolved in 25 ml. of concentrated sulfuric acid, and the solution was poured into 100 ml. of absolute ethanol. After standing overnight the ethanol solution was poured with stirring onto 300 g. of chipped ice, and the mixture was extracted with two 100-ml. portions of ethyl acetate. The ethyl acetate extract was washed with sodium bicarbonate solution, dried and evaporated. A brown oil remained, and this was distilled under reduced pressure to yield 9 g. (65%) of the diester as a colorless liquid; b.p. 147–148° (1 mm.); $n^{25}\text{D}$ 1.5040; d^{25}_{25} 1.164.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.07; H, 6.82; N, 5.09.

From the sodium bicarbonate wash was recovered 2.3 g. (18%) of the starting material.

5-Acetyl-6-methyl-3,4-pyridinedicarboxylic Acid.—A sample of 5-acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic acid was dissolved in 3 *N* aqueous sodium hydroxide solution and heated on the steam-bath. The solution was acidified with hydrochloric acid and cooled whereupon the dicarboxylic acid separated as a crystalline solid. It was readily recrystallized from water. The solubility in water was 1.0 g. per 100 ml. at the boiling point and 0.17 g. per 100 ml. at 0°. 5-Acetyl-6-methyl-3,4-pyridinedicarboxylic acid melted at 230–232° dec. (uncor.).

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(8) A. Michaelis, *Ann.*, **366**, 337 (1909).

(9) M. Conrad and W. Epstein, *Ber.*, **20**, 3054 (1887).

(10) J. Moir, *J. Chem. Soc.*, **81**, 101 (1902).

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.07; N, 6.28. Found: C, 53.80; H, 4.19; N, 6.09.

Triethyl 2-Methyl-3,4,5-pyridinetricarboxylate (IX).—To 34 g. (0.10 mole) of diethyl [(2-carbethoxy-1-methylvinylamino)-methylene]-oxalacetate (III) in a small flask was added 75 ml. of 97% sulfuric acid. Heat was evolved, and the temperature went up to 55°. After standing for one hour the solution was poured onto 400 g. of chipped ice, and 100 g. of sodium carbonate was added in small portions with stirring. The mixture was extracted with three 200-ml. portions of ethyl acetate, and the ethyl acetate extract was washed with sodium bicarbonate solution. The dried ethyl acetate solution was evaporated, and the residual liquid was distilled under reduced pressure to yield 18 g. (61%) of triethyl 2-methyl-3,4,5-pyridinetricarboxylate (IX) as an almost colorless liquid; b.p. 157–160° (0.5 mm.); $n^{25}{}_D$ 1.4965; $d^{25}{}_{25}$ 1.163.

Anal. Calcd. for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.61; H, 6.56; N, 4.83.

The infrared absorption spectrum of this compound was distinctly different from that of triethyl 6-methyl-2,3,5-pyridinetricarboxylate.[1]

The sodium bicarbonate extract of the above ethyl acetate solution was acidified with hydrochloric acid and extracted with ethyl acetate. Evaporation of this solution left a sirup which crystallized. This product was thought to be 6-methyl-3,5-dicarbethoxy-4-pyridinecarboxylic acid. The yield was 3.2 g. (12%). It was not further investigated.

Trimethyl 2-Methyl-3,4,5-pyridinetricarboxylate.—A 1-g. sample of the above triethyl ester was mixed with 5 ml. of alcohol, 10 ml. of water and 1 g. of sodium hydroxide and heated on the steam-bath for a few minutes. The solution was evaporated to dryness, and the residue treated with 5 ml. of concentrated hydrochloric acid. Again the mixture was evaporated to dryness. The residue was suspended in methanol and treated with an excess of ethereal diazomethane. There was isolated 0.7 g. of trimethyl 2-methyl-3,4,5-pyridinetricarboxylate which, after recrystallization twice from petroleum ether melted at 61–62°.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.25. Found: C, 53.99; H, 5.04; N, 5.44.

When the above ester was mixed with an authentic sample of trimethyl 6-methyl-2,3,5-pyridinetricarboxylate[1] (m.p. 78.5–79.5°) the mixture melted over the range 45–55°.

Diethyl 5-Carbomethoxy-6-methyl-3,4-pyridinedicarboxylate.—This was prepared from diethyl [(2-carbomethoxy-1-methylvinylamino)-methylene]-oxalacetate (IV) by treatment with sulfuric acid in the same way as described above for the preparation of triethyl 2-methyl-3,4,5-pyridinetricarboxylate. The yield was 41%; b.p. 140–143° (0.5 mm.); $n^{25}{}_D$ 1.5004; $d^{25}{}_{25}$ 1.188.

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.38; H, 5.95; N, 4.92.

There was also obtained about a 20% yield of an acidic fraction thought to be a diester of 2-methyl-3,4,5-pyridinetricarboxylic acid. It was not further investigated.

5-Amino-6-methyl-3,4-pyridinedicarboxylic Acid.—To 250 g. of 97% sulfuric acid was added with stirring 63 g. (0.25 mole) of crude 5-acetyl-3-carbethoxy-6-methyl-4-pyridinecarboxylic acid (XI). The solid dissolved with evolution of heat, the temperature going up to 55°. After cooling to 40°, finely powdered sodium azide was added with stirring in portions of about 0.5 g. every five minutes until a total of 17.5 g. (0.27 mole) has been added. This required about 2.5 hours. After each addition of sodium azide the solution foamed vigorously, but frequent tests with moistened ferric chloride paper[11] held closely over the surface of the mixture indicated that no trace of hydrogen azide was being evolved. The temperature tended to rise slowly, and it was maintained at about 45° by occasionally cooling the mixture in a bath of cold water.

After all sodium azide had been added the mixture was allowed to stand overnight. It was then poured with stirring onto 500 g. of chipped ice. The resulting solution was heated on the steam-bath for 15 hours. Ice, about 400 g., was added to bring the volume of the solution back to about 500–600 ml., and then concentrated ammonium hydroxide was added carefully and with stirring until the solution was brought to *p*H 2.1. The 5-amino-6-methyl-3,4-pyridinedicarboxylic acid monohydrate separated as a tan crystalline solid. After several days the product was collected, washed with water, acetone and ether and air dried. The yield was 37.8 g. (70%). It was identified by m.p. 230–232° dec. and mixed m.p. with an authentic sample.[6] The infrared absorption spectrum was identical with that of a known sample. Finally, the acid was converted to the dimethyl ester by treatment with diazomethane, and the melting point of the ester, 94–95°, was not depressed when mixed with an authentic sample.[6]

The above experiment was repeated starting with the open-chain compound, diethyl [(1-methyl-3-oxo-1-butenylamino)-methylene]-oxalacetate (II). To 250 g. of 97% sulfuric acid was added 75 g. (0.25 mole) of (II) with stirring and cooling so that the temperature did not exceed 70–75°. After standing for one hour the solution was brought to 40°, treated with 17 g. (0.26 mole) of sodium azide, and the reaction worked up as described above to yield 26.6 g. (50%) of 5-amino-6-methyl-3,4-pyridinedicarboxylic acid monohydrate.

In order to roughly determine the volatility of hydrogen azide from sulfuric acid solution the following experiment was carried out. To 100 g. of concentrated sulfuric acid (about 97%) was added with stirring 1.0 g. of sodium azide. A slow current of air was drawn through the sulfuric acid solution and then through a dilute ferric chloride solution.[11] The latter darkened but very slightly during two hours, indicating that hardly a trace of hydrogen azide was being swept out of the sulfuric acid solution. When the experiment was repeated using 90% sulfuric acid, the ferric chloride solution had darkened perceptibly after about one-half hour, indicating that a trace of hydrogen azide was being swept out.

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[11] L. F. Audrieth, *Chem. Revs.*, **15**, 194 (1934); Curtius and Rissom, *J. prakt. Chem.*, [2] **58**, 261 (1898).