The addition of 2 ml. of alcohol and reheating the suspension to 85° gave a clear solution, which was treated with a solution of 0.200 g. of 2,4-dinitrophenylhydrazine in 1 ml. of sulfuric acid, 1.5 ml. of water and 5 ml. of ethanol. After one hour the crystalline precipitate was collected by filtration and washed with 50% ethanol, weight 0.290 g. (66%), m.p. 185–186°. Recrystallization from ethyl acetate–carbon tetrachloride raised the m.p. to 186.4–187.3°.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52.05; H, 4.13; N, 16.86. Found: C, 51.69; H, 4.24; N, 16.72.

CAMBRIDGE 39, MASSACHUSETTS RECEIVED MARCH 3, 1951

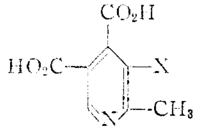
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Pyridine Syntheses. I. Some Reactions of "Ene Amines" with 1,3-Dicarbonyl Derivatives

BY EDMOND M. BOTTORFF, REUBEN G. JONES, EDMUND C. KORNFELD AND MARJORIE J. MANN

Condensations of certain "ene amines" such as β-aminocrotononitrile, ethyl β-aminocrotonate and iminoacetylacetone with ethyl ethoxymethyleneoxalacetate, ethyl ethoxymethyleneacetylpyruvate and related compounds have been carried out in an attempt to prepare 2,3,4,5-tetrasubstituted pyridines suitable for conversion to vitamin B_6. Instead of the desired compounds, the pyridines obtained were substituted invariably in the 2,3,5,6-positions. The following pyridine compounds and/or their derivatives were synthesized: 5-cyano-6-methyl-2,3-pyridinedicarboxylic acid, 6-methyl-2,3,5-pyridinetricarboxylic acid, 5-acetyl-6-methyl-2,3-pyridinedicarboxylic acid, 5-carboxanilido-6-methyl-2,3-pyridinedicarboxylic acid, 3-acetyl-5-cyano-6-methyl-2-pyridinecarboxylic acid, 3-acetyl-6-methyl-2,5-pyridinedicarboxylic acid, 3,5-diacetyl-6-methyl-2-pyridinecarboxylic acid and 2-methyl-6-trifluoromethyl-3,5-pyridinedicarboxylic acid. The condensation of ethyl β-aminocrotonate with ethyl ethoxymethyleneacetoacetate gave, in addition to diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate, two other crystalline compounds thought to be 3-acetyl-5-carbethoxy-6-methyl-2-pyridone and ethyl α-[(2-carbethoxy-1-methylvinylamino)-methylene]-acetoacetate. The condensation of iminoacetylacetone with ethyl ethoxymethyleneacetylpyruvate gave two products, ethyl 3,5-diacetyl-6-methyl-2-pyridinecarboxylate and ethyl β-[(1-methyl-3-oxo-1-butenylamino)-methylene]-α,γ-dioxovalerate.

A preceding paper from this Laboratory has described the synthesis of vitamin B_6 through reduction of the esters of 5-amino-6-methyl-3,4-pyridinedicarboxylic acid (I) and 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid (II) with lithium aluminum hydride.[1] The practical importance of this method is dependent upon the availability of the acids I and II. Itiba and Emoto[2] have described the preparation of I and II, but the yields are low, and the method is generally unsatisfactory. The other known ways[3] of obtaining the pyridine ring system suitably substituted, *i.e.*, in positions 2, 3, 4 and 5, for conversion to vitamin B_6 also are not entirely satisfactory. Therefore, some alternative methods have been sought.



I, X = NH_2
II, X = OH

This paper is concerned with an investigation of the reaction of some so-called "ene amines" such as ethyl β-aminocrotonate with certain 1,3-dicarbonyl or potential 1,3-dicarbonyl compounds. The first example of this type of reaction was that between ethyl β-aminocrotonate and ethyl ethoxymethyleneacetoacetate reported by Claisen[4] to yield diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (XI). Later workers have described similar reactions.[5] This condensation of "ene amines" with 1,3-dicarbonyl compounds sometimes is regarded as a special case of the well-known Hantzsch pyridine synthesis.[6] It differs from the latter, however, in that fully aromatic pyridine compounds are formed directly instead of dihydropyridines, as are obtained in the Hantzsch reaction.

In the present work ethyl ethoxymethylene oxalacetate[7] (III) was allowed to condense with β-aminocrotononitrile,[8] ethyl β-aminocrotonate[9] and iminoacetylacetone.[10] These condensations took place with great ease simply by mixing the reactants in an inert solvent, and excellent yields of pyridine compounds were isolated. By *a priori* reasoning, it might have been expected that either or both structures IV or V would be formed.

Actually, the desired isomer IV was never obtained. The only products formed were V, VI and VII. Their structures were established by conversion to methyl and *p*-bromophenacyl esters of 2,3,5,6-pyridinetetracarboxylic acid and 6-methyl-2,3,5-pyridinetricarboxylic acid, which were compared with authentic samples.

The condensation of ethyl ethoxymethyleneacetylpyruvate[7] (VIII) with β-aminocrotononitrile gave ethyl 3-acetyl-5-cyano-6-methyl-2-pyridinecarboxylate, and with ethyl β-aminocrotonate gave diethyl 3-acetyl-6-methyl-2,5-pyridinedicarboxylate. Reaction of VIII with iminoacetylacetone,

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

[2] A. Itiba and S. Emoto, *Sci. Papers, Inst. Phys. Chem. Research* (*Tokyo*), **38**, 347 (1941) [*C. A.*, **35**, 6960 (1941)].

[3] See, for example: S. A. Harris and K. Folkers, THIS JOURNAL, **61**, 1245 (1939); R. Kuhn, K. Westphal, G. Wendt and O. Westphal, *Naturwissenschaften*, **27**, 469 (1939); F. Bergel and A. Cohen, U. S. Patents 2,440,218, 2,440,219, 2,493,520 [*C. A.*, **42**, 6381 (1948)]. W. Salzer and H. Henecka, U. S. Patent 2,345,633 [*C. A.*, **37**, 5419 (1943)].

[4] L. Claisen, *Ann.*, **297**, 1 (1897).

[5] (a) P. Rabe and E. Milarch, *Ber.*, **45**, 2169 (1912); (b) O. Mumm and H. Hüneke, *ibid.*, **50**, 1568 (1917); (c) O. Mumm and O. Böhme, *ibid.*, **54**, 726 (1921); (d) O. Mumm and E. Gottschaldt, *ibid.*, **55**, 2064 (1922); (e) E. Späth and G. Burger, *Monatsh.*, **49**, 265 (1928); (f) U. Basu, *Ann.*, **512**, 131 (1934); (g) U. Basu, *J. Indian. Chem. Soc.*, **12**, 289 (1935) [*C. A.*, **29**, 6891 (1935)]; (h) P. Baumgarten and A. Dornow, *Ber.*, **72**, 563 (1939); (i) A. Dornow, *ibid.*, **72**, 1548 (1939); (j) A. Dornow and E. Bormann, *ibid.*, **82**, 216 (1949).

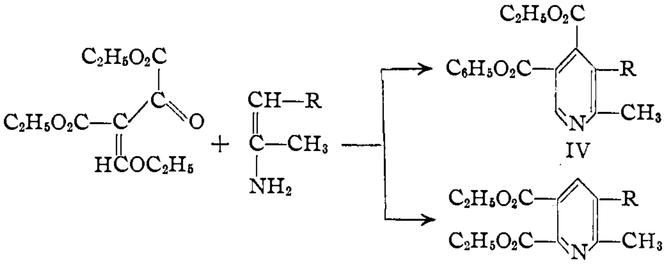
[6] H. S. Mosher in Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 468.

[7] R. G. Jones, THIS JOURNAL, **73**, 3684 (1951).

[8] J. Moir, *J. Chem. Soc.*, **81**, 101 (1902).

[9] A. Michaelis, *Ann.*, **366**, 337 (1909).

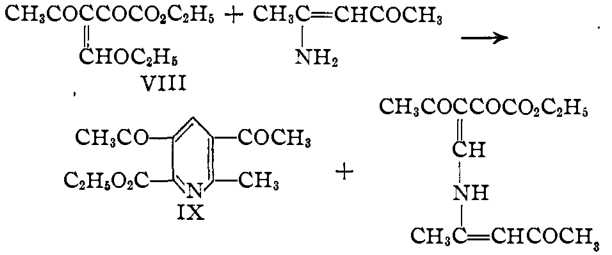
[10] A. Combs and C. Combs, *Bull. soc. chim.*, [3] **7**, 779 (1892).



IV

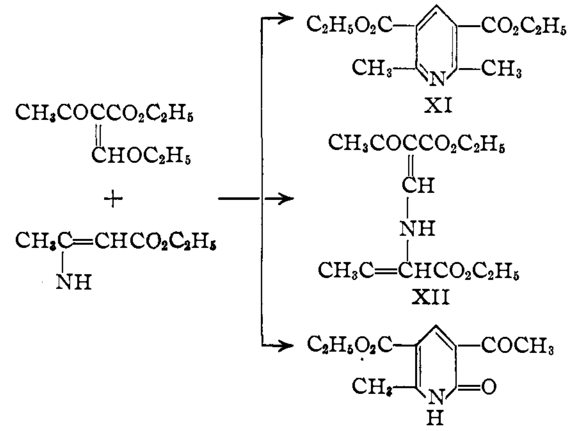
V, R = -CN
VI, R = $-CO_2C_2H_5$
VII, R = $-COCH_3$

on the other hand, gave two products. In addition to ethyl 3,5-diacetyl-6-methyl-2-pyridine carboxylate (IX), another crystalline compound containing the elements of one molecule of water more than IX was isolated. On the basis of the empirical formula, $C_{13}H_{17}NO_5$, and by analogy with some similar compounds which will be reported later, this substance tentatively has been assigned the structure X.



VIII IX X

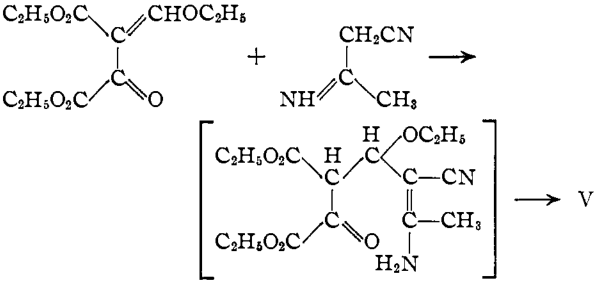
In connection with the present work, the reaction between ethyl β-aminocrotonate and ethyl ethoxymethyleneacetoacetate was reinvestigated. Three crystalline products were isolated. The compound obtained in greatest yield (40–50%) was diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (XI) reported by Claisen.[4] Its structure (XI) was established definitely by saponification and decarboxylation to form 2,6-lutidine. A second crystalline compound, obtained in 8–10% yield, had the empirical formula $C_{13}H_{19}NO_5$. It is believed to be ethyl α - [(2 - carbethoxy - 1 - methylvinylamino) - methylene]-acetoacetate[11] (XII), and this structure is based on the analysis and on analogy with other similar compounds to be reported later. The third compound, isolated in low yield, had the properties and analysis characteristic of a pyridone. It tentatively has been designated as 3-acetyl-5-carbethoxy-6-methyl-2-pyridone (XIII).



XI XII XIII

The yield of XII was increased to 25% and the yield of XI decreased to 30% when ethyl hydroxymethyleneacetoacetate was used in the reaction in place of ethyl ethoxymethyleneacetoacetate.

The mechanism of the reactions between "ene amines" and 1,3-dicarbonyl derivatives in which pyridine compounds are formed very likely involves first a Michael addition followed by ring closure as indicated in the accompanying reaction.[12]



The fact that the only pyridine compounds formed in these reactions were substituted in the 2, 3, 5 and 6 positions is consistent with the above mechanism. Furthermore, the several analogous reactions which have been previously reported[5a,e,g,i] have invariably given pyridine derivatives unsubstituted in position 4. Compounds like X and XII have not been reported heretofore. Their formation involves addition of the amino instead of the methylene group of the "ene amine" to the ethoxymethylene group of the 1,3-dicarbonyl derivative. Once formed, these compounds appear to be stable and do not undergo cyclization to give pyridines.

Acknowledgment.—The authors are grateful to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here.

Experimental

Reaction of Ethyl Ethoxymethyleneacetoacetate with Ethyl β-Aminocrotonate.[4]—A mixture of 89 g. (0.48 mole) of ethyl ethoxymethyleneacetoacetate and 62 g. (0.48 mole) of ethyl β-aminocrotonate was heated on the steam-bath for several hours until bubbling ceased. The product was distilled under reduced pressure, and a fraction boiling from 60 to 160° (4 mm.) was collected. This crystallized in the receiver and was recrystallized to yield 26 g. of diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate,[4] m.p. 70–71°.

The residue in the distilling flask solidified after cooling. It was extracted with hot petroleum ether (b.p. 60–68°), leaving 2.5 g. of white crystalline solid, m.p. 210–213°. The petroleum ether filtrate, after cooling, deposited a crystalline solid, m.p. 101–102°. All of the filtrates were combined, evaporated, and the residue was again worked up as described above. Eventually, there was obtained a total of 51 g. (42% yield) of diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate, 2.5 g. of the compound melting at 210–213°, and 10.5 g. of the compound melting at 101–102°.

The compound melting at 210–213° was recrystallized from methanol, and the melting point remained unchanged. It was insoluble in sodium bicarbonate solution, and from its

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

[12] A similar mechanism was suggested by Mumm and Böhme for the condensation of ethyl β-aminocrotonate with ethyl acetylpyruvate, see ref. 5c.

analysis and properties it is believed to be 3-acetyl-5-carbethoxy-6-methyl-2-pyridone (XIII).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.17; H, 5.70; N, 6.56.

The compound melting at 101–102° was recrystallized several times from petroleum ether. It melted at 102.5–103.5°. On the basis of the analysis and by analogy with other similar compounds to be reported later, this compound is most probably ethyl α-[(2-carbethoxy-1-methylvinylamino)-methylene]-acetoacetate (XII). The yield, 10.5 g., is 8%.

Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.01; H, 7.03; N, 5.49.

The above experiment was repeated using 13 g. (0.10 mole) of ethyl β-aminocrotonate and 16 g. (0.10 mole) of ethyl hydroxymethyleneacetoacetate[4] in place of the ethyl ethoxymethyleneacetoacetate. Instead of being heated, the mixture was allowed to stand at room temperature for 12 days. There was obtained 7.5 g. (30% yield) of diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (XI) and 6.7 g. (25% yield) of ethyl α-[(2-carbethoxy-1-methylvinylamino)-methylene]-acetoacetate (XII).

Structure of Diethyl 2,6-Dimethyl-3,5-pyridinedicarboxylate.—A solution of 35 g. of the diester (XI) prepared in the above experiment and 18 g. of potassium hydroxide in 500 ml. of absolute alcohol was heated under reflux for 45 minutes and then filtered. After evaporation of the filtrate, the solid residue was dried at 110°. It weighed 24 g. This was mixed with 47 g. of calcium oxide and 40 ml. of water, and the mixture in a small flask with a condenser set for distillation was heated with a free flame until nothing more came over. The distillate was extracted with ether, and, after drying with potassium hydroxide pellets, the ether was removed and the residual liquid distilled. The boiling point, 139–141°, corresponded almost exactly with the reported value for 2,6-lutidine[13] and differed appreciably from the reported value for 2,4-lutidine.[13]

A sample of the compound was converted to the picrate, which melted at 100.5–102° and did not depress the melting point of an authentic sample of 2,6-lutidine picrate.

Tetramethyl 2,3,5,6-Pyridinetetracarboxylate.—A solution of 10 g. of the dipotassium salt of 2,6-dimethyl-3,5-pyridinedicarboxylic acid (see above) and 30 g. of potassium permanganate in 500 ml. of water was heated on the steam-bath for four hours. The mixture was filtered, and the filtrate was evaporated under reduced pressure to dryness. The dry residue was suspended in 300 ml. of methanol saturated with hydrogen chloride. After standing for 24 hours the mixture was worked up in the usual way to yield tetramethyl 2,3,5,6-pyridinetetracarboxylate. It was recrystallized from ether–acetone mixture, m.p. 118–119°.

Anal. Calcd. for $C_{13}H_{13}NO_8$: C, 50.17; H, 4.21; N, 4.50. Found: C, 50.38; H, 4.53; N, 4.56.

Diethyl 5-Cyano-6-methyl-2,3-pyridinedicarboxylate (V).—Twenty grams (0.24 mole) of β-aminocrotononitrile[8] was added to a solution of 49 g. (0.20 mole) of ethyl ethoxymethyleneoxalacetate[7] in 50 ml. of dry ether. The mixture was agitated until all the solid dissolved, and then an exothermic reaction took place, causing the ether to boil. After the spontaneous reaction had subsided, the mixture was heated on the steam-bath for about one-half hour. The light red-brown liquid was taken up in 100 ml. of ether, and the solution was washed with dilute aqueous sodium carbonate solution, then with water and dried with magnesium sulfate. After removal of the ether by evaporation the residual liquid was distilled under greatly reduced pressure, and 36 g. (70% yield) of diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate was obtained as a viscous, almost colorless liquid; b.p. 150° (0.8 mm.), 155° (1 mm.); n^{25}_D 1.5123; d^{25}_{25} 1.1708. The yield in each of three similar experiments was 70%.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.29; H, 5.91; N, 10.89.

The above experiment was repeated except that 50 ml. of glacial acetic acid was used in place of ether as the solvent. After the exothermic reaction had subsided, the acetic acid was removed by evaporation under reduced pressure, and the product was worked up and distilled as described above. There was obtained 38 g. (72% yield) of diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate. The infrared absorption spectrum of this sample was identical with that of the product described above.

The experiment was again repeated using as a solvent 50 g. of absolute ethanol in which had been dissolved 0.5 g. of sodium. Again diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate was obtained in 70% yield and identified by its boiling point, 145–146° (0.4 mm.), and infrared absorption spectrum.

Diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate, 6.2 g., and 4 g. of sodium hydroxide were dissolved in a mixture of 25 ml. of water and 10 ml. of ethanol. The solution was heated under reflux for three hours. More ethanol (about 200 ml.) was added, and the sirup was digested until it changed to a granular crystalline solid. This solid, which was the sodium salt of 6-methyl-2,3,5-pyridinetricarboxylic acid, was collected on a filter, washed with ethanol and ether and air dried. The yield was 6.0 g.

Five and eight-tenths grams of the sodium salt was dissolved in 150 ml. of water and to the solution was added 6.32 g. of potassium permanganate in 100 ml. of hot water. The solution was heated on the steam-bath overnight, then filtered and evaporated to dryness under reduced pressure. The residue was esterified with methanol and hydrogen chloride, and there was obtained 2 g. of tetramethyl 2,3,5,6-pyridinetetracarboxylate, m.p. 118–119°. A mixed m.p. with an authentic sample (see above) showed no depression. The X-ray diffraction pattern was identical with that of the authentic sample.

Trimethyl 6-Methyl-2,3,5-pyridinetricarboxylate.—Three grams of the sodium salt of 6-methyl-2,3,5-pyridinetricarboxylic acid prepared from diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate (see above) was suspended in 100 ml. of methanol saturated with hydrogen chloride. After 24 hours the mixture was worked up as usual. The crystalline trimethyl 6-methyl-2,3,5-pyridinetricarboxylate was recrystallized from ether; m.p. 78.5–79.5°.

Anal. Calcd. for $C_{12}H_{13}NO_6$: N, 5.24. Found: N, 5.32.

Tri-*p*-bromophenacyl Ester of 6-Methyl-2,3,5-pyridinetricarboxylate.—This was prepared from the sodium salt of 6-methyl-2,3,5-pyridinetricarboxylic acid (obtained from diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate—see above) and *p*-bromophenacyl bromide in the usual way.[14] The compound was recrystallized from a dioxane–ethanol–water mixture; m.p. 190–192°.

Anal. Calcd. for $C_{33}H_{22}Br_3NO_9$: Br, 29.37; N, 1.72. Found: Br, 28.89; N, 1.85.

Triethyl 6-Methyl-2,3,5-pyridinetricarboxylate.—To a solution of 32 g. (0.136 mole) of ethyl ethoxymethyleneoxalacetate[7] in 25 ml. of anhydrous ether was added 18 g. (0.14 mole) of ethyl β-aminocrotonate.[9] Almost at once an exothermic reaction began, and the ether boiled vigorously. This reaction appeared to be complete within a few minutes. The pale orange colored reaction mixture was heated on the steam-bath for one-half hour, but no further change took place. The liquid was distilled under greatly reduced pressure, and, after a small forerun, 36 g. (86% yield) of triethyl 6-methyl-2,3,5-pyridinetricarboxylate was obtained; b.p. 158–161° (0.5 mm.). This almost colorless, viscous liquid was redistilled, and the sample for analysis was taken at 160° (0.5 mm.); n^{25}_D 1.5000; d^{25}_{25} 1.168.

Anal. Calcd. for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.18. Found: C, 58.29; H, 6.10.

A sample of this compound was saponified with sodium hydroxide and then re-esterified with methanol and hydrogen chloride to yield trimethyl 6-methyl-2,3,5-pyridinetricarboxylate, m.p. 78.5–79.5°, and mixed with an authentic sample of this ester, the m.p. was unchanged. Another sample was saponified and converted to the tri-*p*-bromophenacyl ester of 6-methyl-2,3,5-pyridinetricarboxylic acid; m.p. and mixed m.p. with an authentic sample (see above), 191–192°.

Diethyl 5-Acetyl-6-methyl-2,3-pyridinedicarboxylate.—This was prepared from ethyl ethoxymethyleneoxalacetate[7] and iminoacetylacetone.[10] The reaction was carried out in ether or benzene solution and was worked up as described above for the preparation of diethyl 2-methyl-3-cyano-5,6-pyridinedicarboxylate. The product was distilled; b.p.

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[13] "Beilstein," Vol. 20, p. 244.

[14] Shriner and Fuson, "Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 132.

165–167° (0.5 mm.), and after standing it crystallized; m.p. 62–63°. The yield was 65–70%.

Anal. Calcd. for $C_{14}H_{17}NO_5$: H, 5.02. Found: N, 5.27.

5-Acetyl-6-methyl-2,3-pyridinedicarboxylic Acid.—About 1 g. of the above diester was moistened with alcohol and treated with 3 ml. of 12 *N* sodium hydroxide solution. The mixture was warmed for a short time, then 10 ml. of water was added. The clear solution was acidified with hydrochloric acid. After cooling and scratching, a white crystalline precipitate separated. It was recrystallized from water; m.p. 165–166° (dec.).

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.07; N, 6.28. Found: C, 53.95; H, 4.24; N, 6.10.

The structure of this acid was determined as follows: A sample, 1.0 g., was added to a hypochlorite solution made by absorbing 1.0 g. of chlorine in 25 ml. of cold 5 *N* sodium hydroxide solution. After standing for one hour the solution was heated on the steam-bath for one hour, evaporated to dryness in vacuum, and the thoroughly dry residue was treated with 100 ml. of methanol saturated with hydrogen chloride. Trimethyl 6-methyl-2,3,5-pyridinetricarboxylate was isolated in the usual way and identified by mixed m.p. with an authentic sample.

Diethyl 5-Carboxanilido-6-methyl-2,3-pyridinedicarboxylate.[15]—A solution of 24.5 g. (0.10 mole) of ethyl ethoxymethyleneoxalacetate in 100 ml. of dry ether was treated with 18 g. (0.10 mole) of β-aminocrotonanilide.[16] As soon as all the solid had dissolved, an exothermic reaction took place. The yellow-orange solution was allowed to stand overnight, during which time a white crystalline precipitate was deposited. Petroleum ether, 200 ml., was added, and, after chilling, the crystalline solid was collected on a filter and washed with a little ice-cold ether. The yield was 23 g. (69%). A sample was recrystallized from a benzene–petroleum ether mixture; m.p. 121–122°.

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.88. Found: C, 64.31; H, 5.46; N, 7.78.

Ethyl 3-Acetyl-5-cyano-6-methyl-2-pyridinecarboxylate.—Ethyl ethoxymethyleneacetylpyruvate,[7] 21.3 g. (0.10 mole) and 10 g. (0.12 mole) of β-aminocrotononitrile[8] in 50 ml. of dry ether were allowed to react, and the mixture was worked up as described above for the preparation of diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate. There was obtained 11 g. (47% yield) of viscous liquid, b.p. 132–137° (0.8 mm.), which crystallized after standing. A sample recrystallized from an ether–petroleum ether mixture melted at 94.5–95°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07. Found: C, 62.56; H, 5.77; N, 12.95.

3-Acetyl-5-cyano-6-methyl-2-pyridinecarboxylic Acid.—A sample of the above ester was saponified by shaking with 5 *N* sodium hydroxide solution. The resulting solution was acidified with hydrochloric acid, and the product separated as a white crystalline solid. It was recrystallized from water; m.p. 154–156° (dec.).

Anal. Calcd. for $C_{10}H_8N_2O_3$: N, 13.72. Found: N, 13.43.

The structure of this acid was proven by oxidation in alkaline hypochlorite solution followed by hydrolysis of the cyano group and esterification with methanol and hydrogen chloride to yield trimethyl 6-methyl-2,3,5-pyridinetricarboxylate.

Diethyl 3-Acetyl-6-methyl-2,5-pyridinedicarboxylate.—A reaction between 21.4 g. (0.10 mole) of ethyl ethoxymethyleneacetylpyruvate[7] and 13 g. (0.10 mole) of ethyl β-aminocrotonate was carried out and worked up in the same way as described above for the preparation of ethyl 3-acetyl-5-cyano-6-methyl-2-pyridinecarboxylate. The yield was 23 g. (82.5%) of colorless, viscous liquid, b.p. 180–185° (2.5 mm.), which crystallized after standing; m.p. 67–68°.

Anal. Calcd. for $C_{14}H_{17}NO_5$: N, 5.02. Found: N, 5.03.

3-Acetyl-6-methyl-2,5-pyridinedicarboxylic Acid.—This was prepared by saponification of the above ester with sodium hydroxide solution, followed by acidification with hydrochloric acid. The product was recrystallized from water; m.p. 210–213° (dec.).

Anal. Calcd. for $C_{10}H_9NO_5$: N, 6.27. Found: N, 6.30.

The structure of this acid was determined by oxidation with hypochlorite, followed by esterification of the product with methanolic hydrogen chloride to yield trimethyl 6-methyl-2,3,5-pyridinetricarboxylate.

Reaction of Ethyl Ethoxymethyleneacetylpyruvate with Iminoacetylacetone.—To a solution of 125 g. (0.585 mole) of ethyl ethoxymethyleneacetylpyruvate[7] in 275 ml. of dry ether was added 58.5 g. (0.585 mole) of iminoacetylacetone.[10] An exothermic reaction took place, and after a few minutes a large quantity of crystalline precipitate had separated. After standing overnight, the solid was collected on a filter and washed with a little ether. It was then suspended in 100 ml. of ethyl acetate, heated to boiling, chilled, and the pale yellow crystalline product collected and air dried; m.p. 161–162°. There was obtained 37.5 g. (24% yield). On the basis of the analysis and other considerations (see above), this product is believed to be ethyl β-[(1-methyl-3-oxo-1-butenylamino)-methylene]-α,γ-dioxovalerate[11] (X). A sample recrystallized from ethyl acetate and again from benzene–petroleum ether melted at 164–165°.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.41; H, 6.36; N, 5.24. Found: C, 58.76; H, 6.57; N, 5.16.

All ether and ethyl acetate filtrates in the above preparation were combined and evaporated to dryness under reduced pressure. The residue was taken up in ether, and the warm solution diluted with petroleum ether until cloudy. After chilling, a crystalline precipitate of ethyl 3,5-diacetyl-6-methyl-2-pyridinecarboxylate (IX) was obtained. It melted at 96–97° after recrystallization from ether–petroleum ether. The yield was 38.5 g. (27%).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.93; H, 6.23; N, 5.66.

3,5-Diacetyl-6-methyl-2-pyridinecarboxylic Acid.—The above ester was saponified with sodium hydroxide and the solution acidified with hydrochloric acid to precipitate the product as a crystalline solid. It was recrystallized from water; m.p. 139–140° (dec.).

Anal. Calcd. for $C_{11}H_{11}NO_4$: N, 6.33. Found: N, 6.47.

The structure of this acid was established by oxidation with six equivalents of hypochlorite followed by esterification with methanol and hydrogen chloride to yield trimethyl 6-methyl-2,3,5-pyridinetricarboxylate.

Diethyl 2-Methyl-6-trifluoromethyl-3,5-pyridinedicarboxylate.[15]—The reaction between 18 g. (0.075 mole) of ethyl ethoxymethylenetrifluoroacetoacetate[7] and 11 g. (0.085 mole) of ethyl β-aminocrotonate[9] was carried out and the mixture worked up as described above for the preparation of diethyl 5-cyano-6-methyl-2,3-pyridinedicarboxylate. The yield was 19 g. (83%) of colorless liquid, b.p. 115–117° (1 mm.); n_D^{25} 1.4647, d^{25}_{25} 1.261.

Anal. Calcd. for $C_{13}H_{14}F_3NO_4$: C, 51.15; H, 4.62; N, 4.59. Found: C, 51.28; H, 4.88; N, 4.81.

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(15) The structure of this compound was not proven, but by analogy with the other compounds reported here, it is assumed to have the structure indicated.

(16) L. Knorr, *Ber.*, **25**, 776 (1892).