Experimental

α-Methyl-β-phenylsuccinic Acid (VII, R_1 = H, R_2 = Methyl).—To a solution of 106 g. (1.0 mole) of benzaldehyde and 113 g. (1.0 mole) of ethyl cyanoacetate in 300 ml. of 60% ethanol was added 3 ml. of piperidine. The temperature slowly increased to 60° and then, on standing, decreased to 25°. The mixture was diluted with 100 ml. of water and 49 g. (1.0 mole) of sodium cyanide was added portionwise over a period of 20 minutes. After stirring until a clear solution was obtained, 800 ml. of water was added. On acidification to congo red with 12 *N* hydrochloric acid, an orange-colored oil precipitated which solidified as the mixture was stirred.

The aqueous layer was decanted and the solid ethyl α,β-dicyano-β-phenylpropionate dissolved in a solution of 40 g. of sodium hydroxide in 200 ml. of water. While the solution was stirred 126 g. (1.0 mole) of methyl sulfate was added in 50-ml. portions over a period of one hour, basic conditions being maintained by the addition of alkali if necessary. When the temperature had decreased to 30°, 6 *N* hydrochloric acid was added until the mixture was acid to congo red.

The oily product was removed and refluxed with 1 l. of 12 *N* hydrochloric acid for 20 hours. The water layer was decanted from the cooled mixture and the residue dissolved in a solution of 60 g. of sodium hydroxide in 800 ml. of water. After adding a moderate amount of charcoal and filtering, the filtrate was made acid to congo red and 12 *N* hydrochloric acid. The mixture was cooled thoroughly, filtered and the solid washed with 200 ml. of water before being air-dried; yield 130 g. or 70%; m.p. 169–172°

α-Ethyl-β-phenylsuccinic Acid (VII, R_1 = H, R_2 = Ethyl).—A solution of 106 g. (1.0 mole) of benzaldehyde and 113 g. (1.0 mole) of ethyl cyanoacetate in 400 ml. of 95% ethanol was treated with 3 ml. of piperidine. When the solution had cooled to 30°, 54 g. (1.1 moles) of sodium cyanide was added. The solution obtained by stirring was heated on a steam-bath for 5 minutes and then cooled to 40°. After adding 109 g. (1.0 mole) of ethyl bromide in one portion, the mixture was refluxed for 10 hours, cooled and filtered to remove sodium bromide. The filtrate was concentrated on a steam-bath and the residue refluxed with 1.2 l. of 12 *N* hydrochloric acid for 20 hours. After cooling and decanting the aqueous layer, the oily material was dissolved in an excess of 10% aqueous sodium hydroxide and extracted with ether. The basic solution was mixed with a moderate amount of charcoal, filtered and the filtrate acidified with 6 *N* hydrochloric acid. Since the product remained an oil, it was refluxed with a mixture of 400 ml. of 12 *N* hydrochloric acid and 200 ml. of glacial acetic acid for 24 hours. On diluting with 400 ml. of water and cooling, a solid product was obtained which was filtered off and purified by precipitation from 10% aqueous sodium hydroxide with 6 *N* hydrochloric acid; yield 64 g. or 28%; m.p.[14] 160–166°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30. Found: C, 64.93; H, 6.54.

α-Methyl-β-phenylsuccinimide (II, R = R_1 = H, R_2 = Methyl).—This procedure is typical for the preparation of the succinimides listed in Table I. Occasionally the product was recrystallized from a suitable solvent.

Five hundred grams (2.4 moles) of α-methyl-β-phenylsuccinic acid was added portionwise to a flask containing 500 g. of concentrated ammonium hydroxide. The mixture was heated on a Glas–Col mantle until the temperature of the product reached 225°. A solution of the residue in absolute ethanol was filtered and concentrated on a steam bath. The product obtained by distillation of the residue *in vacuo* solidified on standing.

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[14] F. W. Upson and T. J. Thompson, THIS JOURNAL, **44**, 181 (1922). These authors reported that the substituted succinic acid obtained from the sodium salt of benzyl cyanide and ethyl α-bromobutyrate melted at 196°.

DETROIT, MICHIGAN RECEIVED MAY 25, 1951

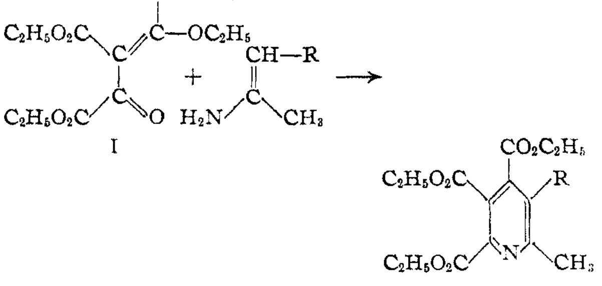
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Pyridine Syntheses. III. Preparation and Reactions of Some Penta-substituted Pyridines

BY REUBEN G. JONES

Condensation of triethyl α-ethoxy-γ-ketoaconitate with β-aminocrotononitrile, ethyl β-aminocrotonate and iminoacetylacetone gave triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate, tetraethyl 6-methyl-2,3,4,5-pyridinetetracarboxylate and triethyl 5-acetyl-6-methyl-2,3,4-pyridinetricarboxylate, respectively. Diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate underwent condensation with iminoacetylacetone to yield diethyl 3,5-diacetyl-6-methyl-2,4-pyridinedicarboxylate. Hydrolysis of triethyl 5-acetyl-6-methyl-2,3,4-pyridinetricarboxylate followed by decarboxylation gave 5-acetyl-6-methyl-3,4-pyridinedicarboxylic acid. Triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate has been converted to 5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid, 5-hydroxy-6-methyl-2,3,4-pyridinetricarbroxylic acid, 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid, 5-amino-6-methyl-2,4-pyridinedicarboxylic acid, 4-amino-6-methyl-2,5-pyridinedicarboxylic acid and related derivatives.

Preceding communications[1,2] from this Laboratory have been concerned with new methods of preparing 2,3,4,5-tetra-substituted pyridines suitable for conversion to vitamin B_6. One approach to the synthesis of these compounds appeared to be the elimination of a substituent such as carboxyl from the 6 position of appropriate penta-substituted pyridines. The purpose of this paper is to describe a new synthesis of such pentasubstituted pyridine compounds and their transformations into vitamin B_6 and related derivatives.



II, R = $-CN$
III, R = $-CO_2C_2H_5$
IV, R = $-COCH_3$

Triethyl α-ethoxy-γ-ketoaconitate (I)[3] has been found to undergo reaction readily with β-aminocrotononitrile, ethyl β-aminocrotonate, and iminoacetylacetone to form the pyridine compounds II, III and IV, respectively, in yields of 65 to 70%. One additional example of this reaction was the condensation of diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate[3] with iminoacetylacetone to yield

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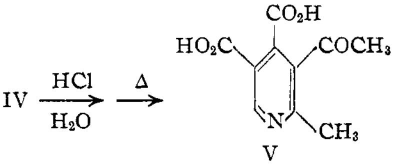
[1] E. M. Bottorff, R. G. Jones, E. C. Kornfeld and M. J. Mann, THIS JOURNAL, **73**, 4380 (1951)

[2] R. G. Jones, *ibid.*, **73**, 5168 (1951).

[3] R. G. Jones, *ibid.*, **73**, 5244 (1951).

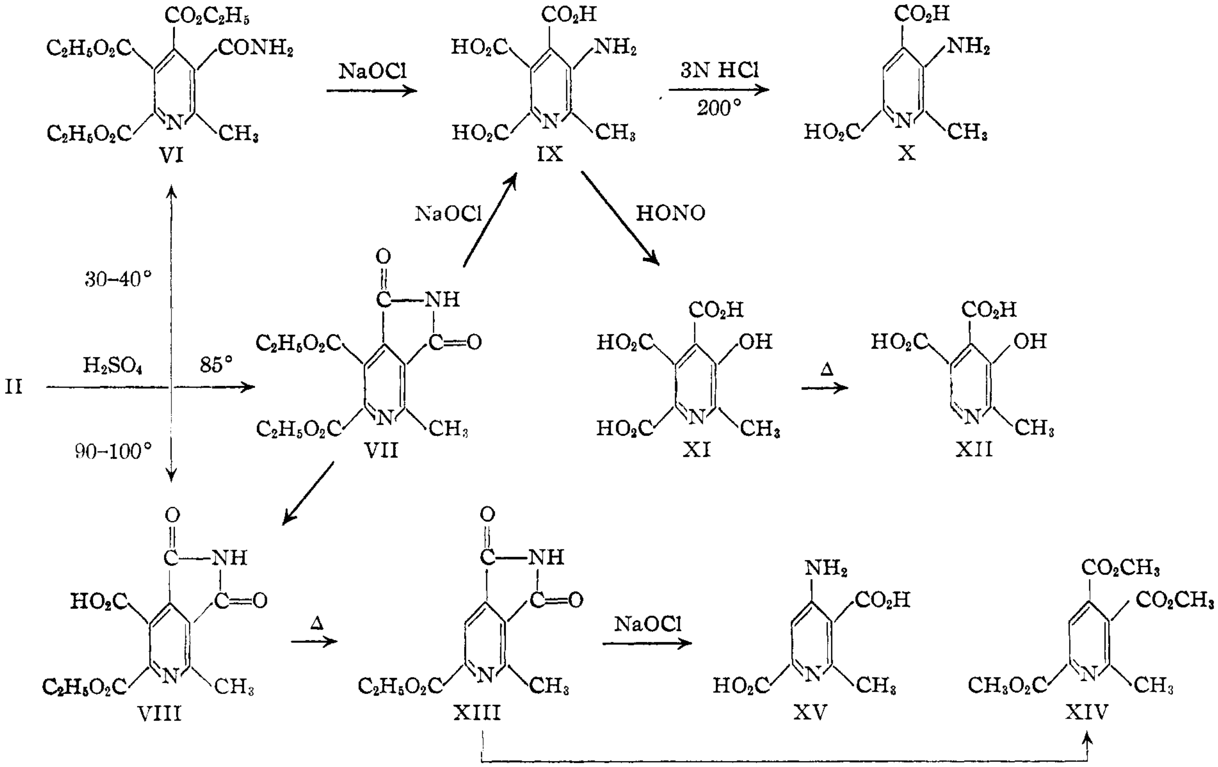
diethyl 3,5-diacetyl-6-methyl-2,4-pyridinedicarboxylate. In these reactions not any of the open-chain condensation products were found analogous to those obtained in similar reactions leading to tetra-substituted pyridines.[1,2]

Compounds II and IV have afforded two new routes to the preparation of vitamin B_6. Triethyl 5-acetyl-6-methyl-2,3,4-pyridinetricarboxylate (IV) was converted to 5-acetyl-6-methyl-3,4-pyridinedicarboxylic acid (V) in reasonably good yield by hydrolysis followed by decarboxylation. The conversion of V to the vitamin has been described.[2,4]



V

A similar hydrolysis and decarboxylation of II was not realized, presumably, because of the liability of the cyano group under the conditions used. However, II appeared to offer a number of other possibilities, and, therefore, its transformations were studied in some detail as indicated in the accompanying series of reactions.



Treatment of II with concentrated sulfuric acid resulted in the formation of three different products depending upon the conditions under which the reaction was carried out. At 30–40° the only compound obtained (90% yield) was the amide, VI. When the mixture was heated to 85° for a few minutes the imide VII was formed in 70% yield. More vigorous conditions, *i.e.*, heating at 90–100° for one hour, gave, in addition to VII, about a 40% yield of the imide-ester-acid VIII.

Both the amide, VI and the imide VII were smoothly converted by treatment with hypochlorite to 5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid (IX) in yields of 80–90%. It was expected that IX would easily lose the carboxyl group at position 2 to furnish 5-amino-6-methyl-3,4-pyridinedicarboxylic acid. This was found not to be the case. Compound IX proved to be unusually resistant toward decarboxylation. Numerous experiments were carried out in which IX was heated in the dry state in suspension in inert solvents, or in solution in acetic acid and acetic anhydride. In every case the compound was recovered unchanged or was decomposed to such an extent that no pure products could be isolated. Eventually it was discovered that by heating a solution of IX in dilute hydrochloric acid at 200° for one hour a 15 to 20% yield of the dicarboxylic acid X could be isolated. The structure of X as 5-amino-6-methyl-2,4-pyridinedicarboxylic acid follows from the fact that its properties did not correspond with those of either the known 5-amino-6-methyl-2,3-pyridinedicarboxylic acid[10] or 5-amino-6-methyl-3,4-pyridinedicarboxylic acid.[2,5]

It is surprising that the carboxyl group at position 3 of IX should be lost in preference to either of those at positions 2 and 4. The high resistance of IX toward loss of the carboxyl at position 2 is undoubtedly due to the presence of the 5-amino group. The corresponding 5-hydroxy-6-methyl-2,3,4-pyridinetricarboxylic acid (XI) was obtained in 85% yield from IX by treatment with nitrous acid. When it was heated in acetic anhydride solution, the 2-carboxyl group was lost, and 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid[5]

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

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

(XII) was obtained in a very modest yield (18%). Compound XII is readily convertible to vitamin B_6 as previously described.[4]

The structure of 2-carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic acid (VIII) was proven by decarboxylating it to form ethyl 4,5-dicarboximido-6-methyl-2-pyridinecarboxylate (XIII). The structure of XIII in turn, was disclosed when it was hydrolyzed and the resulting tricarboxylic acid esterified with diazomethane. The properties of the methyl ester did not correspond with those of the known trimethyl 2-methyl-3,4,5-pyridinetricarboxylate,[2] and therefore the new ester must have been trimethyl 6-methyl-2,4,5-pyridinetricarboxylate (XIV). When XIII was treated with sodium hypochlorite it was converted to 4-amino-6-methyl-2,5-pyridinedicarboxylic acid (XV). The structure of XV was assigned on the basis of the fact that its properties, except melting point, differed from those of X. Furthermore, the methyl esters of X and XV were found to be distinctly different.

The effect of substituents on the direction of opening of the imide ring during the Hoffmann reaction on VII and XIII is quite apparent. In the case of VII both the 3-carbethoxy group and the pyridine-ring nitrogen would be expected to favor an opening leading to IX whereas the 2-carbethoxy group would tend to have the opposite effect.[6] In compound XIII the effect of the 2-carbethoxy group overshadows that of the ring nitrogen so that the imide ring is opened on the side opposite to that occurring in VII.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses.

Experimental

Triethyl 5-Cyano-6-methyl-2,3,4-pyridinetricarboxylate (II).—To 64 g. (0.20 mole) of triethyl α-ethoxy-γ-ketoaconitate[3] was added 20 g. (0.24 mole) of β-aminocrotononitrile.[7] The mixture was thoroughly stirred and warmed to about 30°, and a mild exothermic reaction began. The temperature of the mixture was kept at 40–60° by occasionally cooling in an ice-bath. After about 15 minutes the exothermic reaction had subsided. The mixture was heated on the steam-bath for one hour, cooled, then taken up in 200 ml. of ether. The ether solution was filtered, washed with 200 ml. of saturated sodium carbonate solution then with 100 ml. of water. After drying with magnesium sulfate the ether solution was evaporated and the residual dark liquid distilled under reduced pressure. There was obtained 47.5 g. (71% yield) of almost colorless, very viscous liquid; b.p. 177–179° (1 mm.), 161° (0.2 mm.); $n^{25}{}_{D}$ 1.5028; $d^{25}{}_{25}$ 1.1863.

Anal. Calcd. for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.20; H, 5.81; N, 8.23.

Several similar experiments were carried out using larger quantities of reactants, and the yields ranged from 68 to 72%. The product darkened a little after standing.

Tetraethyl 6-Methyl-2,3,4,5-pyridinetetracarboxylate (III).—A mixture of 40 g. (0.125 mole) of triethyl α-ethoxy-γ-ketoaconitate[3] and 20 g. (0.155 mole) of ethyl β-aminocrotonate[8] was allowed to react, and the reaction mixture was worked up as described above for the preparation of triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate to yield 31 g. (65%) of nearly colorless, viscous liquid; b.p. 197–202° (1.5 mm.), 180–185° (0.8 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_8$: N, 3.67. Found: N, 3.62.

Triethyl 5-Acetyl-6-methyl-2,3,4-pyridinetricarboxylate (IV).—This was prepared from 64 g. (0.20 mole) of triethyl α-ethoxy-γ-ketoaconitate[3] and 25 g. (0.25 mole) of iminoacetylacetone[9] in the same manner as described above for the preparation of triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate. The yield was 48 g. (69%) of pale yellow, viscous liquid; b.p. 190–192° (1 mm.); $n^{25}{}_{D}$ 1.4973; $d^{25}{}_{25}$ 1.178.

Anal. Calcd. for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.03; N, 3.99. Found: C, 57.67; H, 6.24; N, 3.85.

Diethyl 3,5-Diacetyl-6-methyl-2,4-pyridinedicarboxylate.—A mixture of 28.6 g. (0.10 mole) of diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate[3] and 11 g. (0.11 mole) of iminoacetylacetone was allowed to react and the reaction mixture worked up in the same way as described above for the preparation of triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate. The product was a crystalline solid. It was not distilled but was recrystallized from ether and obtained as colorless prisms; m.p. 96–97°. The yield was 8.5 g. (35%).

Anal. Calcd. for $C_{16}H_{19}NO_6$: C, 59.70; H, 5.92; N, 4.36. Found: C, 59.70; H, 6.13; N, 4.69.

5-Acetyl-6-methyl-3,4-pyridinedicarboxylic Acid (V).——Triethyl 5-acetyl-6-methyl-2,3,4-pyridinetricarboxylate, 17.5 g. (0.05 mole) was dissolved in 20 ml. of 12 *N* hydrochloric acid, and the resulting solution was heated on the steam-bath for three hours. To the solution was added 20 ml. of water, and heating was continued for three hours after which the solution was evaporated in vacuum to a sirup. The sirup was taken up in 40 ml. of diethylene glycol diethyl ether, and the solution was heated slowly up to 150° where it was held for one hour. Gas was evolved, rapidly at first. The solution was evaporated in vacuum to remove the solvent, and to the residue was added 50 ml. of water followed by 10 g. of sodium carbonate added in small portions with stirring. The resulting solution was heated to boiling, decolorized with carbon and carefully acidified with excess hydrochloric acid. After standing a crystalline precipitate separated. The yield was 6.2 g. (56%), and the yield in a similar experiment was 57%. The compound was obtained as fine white needles by recrystallization from water. It was identified as 5-acetyl-6-methyl-3,4-pyridinedicarboxylic acid by its melting point (230–232° dec.) and mixed melting point with an authentic sample.[2] Also, its infrared absorption spectrum was identical with that of an authentic sample.[2]

Triethyl 5-Carbamyl-6-methyl-2,3,4-pyridinetricarboxylate (VI).—To 50 g. (0.15 mole) of triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate in a small flask cooled in an ice-bath was added 100 ml. of 97% sulfuric acid precooled to 10°. The mixture was well stirred while cooling in the ice-bath, but the temperature spontaneously went up to 35–37°. The flask was removed from the cooling bath, and the temperature of the mixture was maintained at 35–40° by occasionally cooling. After one hour the red-brown liquid was poured slowly and with stirring onto 400 g. of chipped ice. The mixture was extracted with two 200-ml. portions of ethyl acetate, and the combined extract was washed with aqueous sodium bicarbonate solution, dried and evaporated under reduced pressure leaving a white crystalline solid. This was washed with petroleum ether and air-dried. The crude product, 47 g. (89% yield), m.p. 110–112°, was recrystallized from a mixture of ethyl acetate and petroleum ether yielding shiny white platelets, m.p. 117–117.5°.

Anal. Calcd. for $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.72; N, 7.95. Found: C, 54.54; H, 5.48; N, 8.12.

The above procedure gave the best and most consistent yields (89–95%). When less sulfuric acid was used, or when the reaction was carried out at lower or higher temperatures, the yields of the desired product were lower.

Diethyl 4,5-Dicarboximido-6-methyl-2,3-pyridinedicarboxylate (VII).—To 13.5 g. (0.04 mole) of triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate was added 35 ml. of concentrated (97%) sulfuric acid. The mixture was stirred and the temperature rapidly went up to 60–65°. The resulting solution was heated on the steam-bath at 85–90° for 20 minutes, then cooled to 25° and poured slowly, with stirring, over 250 g. of chipped ice. Two 150-ml. portions of ethyl acetate were used to extract the mixture. The com-

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(6) E. S. Wallis and J. F. Lane in Adams, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 277.

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

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

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

bined ethyl acetate extract was washed with sodium carbonate solution, dried and evaporated leaving 8.5 g. (70% yield) of white crystalline solid; m.p. 143–144°. A sample was recrystallized from a benzene–petroleum ether mixture and obtained as a white crystalline powder, m.p. 145–146°.

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.95; H, 4.76; N, 9.53.

When the above reaction was carried out at 80° for five minutes or at 60° for one hour, mixtures of diethyl 4,5-dicarboximido-6-methyl-2,3-pyridinedicarboxylate and triethyl 5-carbamyl-6-methyl-2,3,4-pyridinetricarboxylate were obtained melting from 95 to 125°.

2-Carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic Acid (VIII).—Ten grams of triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate was mixed with 25 ml. of 97% sulfuric acid and the solution was heated on the steam-bath at 90–95° for one hour. It was then cooled, poured onto 200 g. of chipped ice, and the mixture extracted with two 100-ml. portions of ethyl acetate. The ethyl acetate solution was extracted with 100 ml. of saturated aqueous sodium bicarbonate solution, dried and evaporated leaving 3.1 g. (33% yield) of diethyl 4,5-dicarboximido-6-methyl-2,3-pyridinedicarboxylate, m.p. 143–144°.

The sodium bicarbonate extract was combined with the original aqueous acid solution and the whole was extracted with four 100-ml. portions of ethyl acetate. This ethyl acetate extract was dried and evaporated leaving 2-carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic acid as a white crystalline solid or a gum which quickly crystallized when a little ether was added. It was washed with 25 ml. of ice-cold, dry ether and air-dried. The yield was 3.0 g. (36%), and, after recrystallization from an ethyl acetate petroleum ether mixture, it melted at 227–228° dec. (uncor.).

Anal. Calcd. for $C_{12}H_{10}N_2O_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.74; H, 3.98; N, 10.05, 10.23.

The above experiment was repeated on a larger scale. The yield of diethyl 4,5-dicarboximido-6-methyl-2,3-pyridinecarboxylate was 41%, and the yield of the desired 2-carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic acid was 40%. When the reaction time was increased to two hours at 90° the yields of both products were lower.

A solution of 20 g. of diethyl 4,5-dicarboximido-6-methyl-2,3-pyridinedicarboxylate in 100 g. of 97% sulfuric acid was heated at 90–95° for 1.5 hours. The mixture was worked up as above to yield 6.5 g. (36%) of 2-carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic acid and 3 g. (15%) of the starting material was recovered.

5-Amino-6-methyl-2,3,4-pyridinetricarboxylic Acid (IX).—To a cold solution of 40 g. (1.0 mole) of sodium hydroxide in 40 ml. of water was added 90 g. of chipped ice and then chlorine gas was bubbled in until the weight had increased 10.3 g. (0.145 mole of Cl_2). Chipped ice, 150 g., was added followed by 45 g. (0.128 mole) of triethyl 5-carbamyl-6-methyl-2,3,4-pyridinetricarboxylate. The mixture was stirred and the solid slowly dissolved. After one hour the solution had reached room temperature, and it was clear and light orange in color. It was heated for one-half hour on the steam-bath, and then 58 ml. (0.70 mole) of 12 *N* hydrochloric acid was added slowly with stirring so that the evolved carbon dioxide did not cause the solution to foam over. After a few minutes a yellow crystalline precipitate began to separate. The mixture which should be at about *p*H 2 was kept at 0° for about 60 hours, and then the solid was collected on a filter. It was stirred to a paste with 50 ml. of ice-water, again collected on the filter, washed with a little cold acetone followed by ether and air-dried. The yield of yellow, crystalline powder was 32.0 g. (90%) and the yields in five similar experiments ranged from 87 to 91%. The compound had no sharp melting point but began to darken at about 185°, turned brown at 189–191° and finally liquefied with extensive decomposition at 235–240°. A sample for analysis was recrystallized from water and dried at 60° under reduced pressure for one hour.

Anal. Calcd. for $C_9H_8N_2O_6 \cdot 2H_2O$: C, 39.15; H, 4.35; N, 10.14. Found: C, 39.49; H, 4.60; N, 9.82. After drying at 100° under reduced pressure for four hours, *Anal.* Calcd. for $C_9H_8N_2O_6$: N, 11.67. Found: N, 11.22.

5-Amino-6-methyl-2,3,4-pyridinetricarboxylic acid dihydrate was soluble in water to the extent of about 40 g. per liter at 100° and 10 g. per liter at 0°. It was slightly soluble in acetone, very sparingly soluble in ether.

The above experiment was repeated except that 39 g. (0.128 mole) of diethyl 4,5-dicarboximido-6-methyl-2,3-pyridinedicarboxylate was used in place of the triethyl 5-carbamyl-6-methyl-2,3,4-pyridinetricarboxylate. The product, obtained in 82% yield, was shown to be 5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid dihydrate by comparison of the X-ray diffraction pattern with that of the compound described above.

5-Amino-6-methyl-2,4-pyridinedicarboxylic Acid (X).—A solution of 5 g. of 5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid in 25 ml. of 6 *N* hydrochloric acid in a sealed tube was heated at 200° for about one hour. After the tube had been cooled and opened the contents were evaporated to dryness. The residue was taken up in 50 ml. of hot water. This solution was decolorized with carbon, filtered and evaporated in vacuum to 15 ml. and cooled in an ice-bath for several hours. A brown crystalline precipitate (0.6 g., 17% yield) was deposited, m.p. 267–268° dec. (uncor.). After recrystallization from a large volume of water the compound was obtained as light tan crystals, m.p. 270–271° dec. (uncor.).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.33; H, 4.56; N, 14.45.

The filtrate was brought to *p*H 2 and kept cold for several days, and it deposited 1.5 g. (30%) of the starting material (5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid). The experiment repeated on a larger scale gave essentially the same results. Also, the same results were obtained when 3 *N* hydrochloric acid was used in place of 6 *N* acid.

When the tricarboxylic acid in 3 *N* hydrochloric acid solution was heated in a sealed tube at 165–170° for two hours only unchanged starting material (83%) was obtained. Numerous experiments were carried out in which the acid was heated in boiling decalin. Red, amorphous products were obtained from which no pure products could be isolated. Likewise, heating in acetic acid or acetic anhydride solution gave black mixtures from which it was not possible to isolate pure products.

Dimethyl 5-Amino-6-methyl-2,4-pyridinedicarboxylate.—The above acid was esterified with diazomethane to yield the dimethyl ester which was recrystallized from petroleum ether and obtained as long white needles; m.p. 110–110.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40; N, 12.50. Found: C, 53.49; H, 5.78; N, 12.49.

The melting point of this ester is distinctly different from that of the known dimethyl 5-amino-6-methyl-3,4-pyridinedicarboxylate[4] (m.p. 94–95°) or dimethyl 5-amino-6-methyl-2,3-pyridinedicarboxylate[10] (m.p. 88–88.5°). When it was mixed with either of them the m.p. was greatly depressed.

5-Hydroxy-6-methyl-2,3,4-pyridinetricarboxylic Acid (XI).—A solution of 20 g. (0.072 mole) of 5-amino-6-methyl-2,3,-4-pyridinetricarboxylic acid dihydrate in 200 ml. of 3 *N* hydrochloric acid was heated to 70° and 15 g. of sodium nitrite crystals were added in small portions with stirring. After the addition was complete (about one-half hour) the solution was heated for an additional one-half hour and then evaporated to dryness in vacuum. The residue was extracted with three 200-ml. portions of hot acetone, and the combined extract was evaporated to a volume of 50 ml. To this was added slowly 200 ml. of benzene, and the mixture was evaporated on the steam-bath to a volume of 150 ml. The white crystalline solid, 11.5 g., was collected on a filter and air-dried, m.p. 204–206° dec. (uncor.).

Anal. Calcd. for $C_9H_7NO_7$: N, 5.80. Found: N, 5.98.

Further evaporation of the filtrate gave an additional 3.5 g. of less pure product. The total yield was 15 g. (86%).

5-Hydroxy-6-methyl-3,4-pyridinedicarboxylic Acid (XII).—A solution of 27.6 g. (0.10 mole) of 5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid dihydrate in 250 ml. of 3 *N* hydrochloric acid was treated with 20 g. of sodium nitrite as described above. After the reaction mixture had been evaporated to dryness the residue was treated with 150 ml. of acetic anhydride, and the mixture was heated under reflux for 1.5 hours. During this time 1300 ml. of gas (CO_2) was evolved. The mixture was filtered and the dark filtrate was evaporated under reduced pressure to a sirup. This was taken up in 200 ml. of water, and the solution was heated to boiling then evaporated under reduced pressure to a volume of about 100 ml. After standing, a crystalline

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(10) Unpublished studies by the author.

precipitate was deposited. A sample was recrystallized from water and identified as 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid by its infrared absorption spectrum which was identical with that of an authentic sample.[5] The yield was 3.5 g. (18%).

Ethyl 4,5-Dicarboximido-6-methyl-2-pyridinecarboxylate (XIII).—In 25 ml. of carbitol acetate was suspended 7.0 g. (0.026 mole) of 2-carbethoxy-4,5-dicarboximido-6-methyl-3-pyridinecarboxylic acid (VIII). The mixture was heated up to the boiling point (210–215°) and the resulting solution was held under reflux for about ten minutes. About one-half of the solvent was removed by evaporation in vacuum, and the residue was taken up in 200 ml. of ethyl acetate. The solution was washed well with aqueous sodium bicarbonate solution, decolorized with carbon, dried with magnesium sulfate and evaporated to remove the ethyl acetate. Petroleum ether, 200 ml., was added, and an oily precipitate separated which soon crystallized. The yield was 4.0 g. (68%), and the yield in a duplicate experiment was 78%. The product was recrystallized from a mixture of ethyl acetate and petroleum ether and obtained as a white crystalline powder, m.p. 176–177°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.35; H, 4.49; N, 11.64.

Trimethyl 6-Methyl-2,4,5-pyridinetricarboxylate (XIV).—A sample of 1.0 g. of the above ethyl 4,5-dicarboximido-6-methyl-2-pyridinecarboxylate in 10 ml. of 10% sodium hydroxide solution was heated on the steam-bath for three hours. The solution was acidified with 5 ml. of 12 *N* hydrochloric acid and evaporated to dryness by heating on the steam-bath under reduced pressure. After thorough drying in air the solid was suspended in 25 ml. of methanol and treated with excess diazomethane in ether. The mixture was worked up in the usual way leaving a sirup which soon crystallized. The ester was recrystallized twice from petroleum ether and obtained as a white powder; m.p. 83–84°.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.25. Found: C, 54.15; H, 5.27; N, 5.49.

When the above ester was mixed with an authentic sample of trimethyl 2-methyl-3,4,5-pyridinetricarboxylate[2] (m.p. 61–62°), the m.p. was depressed to 48–55°.

4-Amino-6-methyl-2,5-pyridinedicarboxylic Acid (XV).—To a solution of 4 g. of sodium hydroxide in 4 ml. of water was added 10 g. of chipped ice, and chlorine gas was bubbled into the mixture until the weight had increased 1.30 g. Twenty grams of chipped ice was added followed by 4.0 g. of ethyl 4,5-dicarboximido-6-methyl-2-pyridinecarboxylate. After the mixture had stood for one hour it was heated on the steam-bath for ten minutes, cooled, and acidified to *p*H 2 with hydrochloric acid. The crystalline precipitate which soon separated was collected, washed with a little water, acetone, ether and air-dried. The yield was 2.3 g. (69%). A sample recrystallized from a large volume of water melted at 270–271° dec. (uncor.).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.30; H, 4.24; N, 14.18.

The X-ray diffraction pattern and the infrared absorption spectrum of this acid differed from those of the above 5-amino-6-methyl-2,4-pyridinedicarboxylic acid.

Dimethyl 4-Amino-6-methyl-2,5-pyridinedicarboxylate.—The dicarboxylic acid was esterified with diazomethane in the usual manner to yield the dimethyl ester, m.p. 136.5–137° from ethyl acetate–petroleum ether.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40; N, 12.50. Found: C, 53.97; H, 5.80; N, 12.77.

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The Relative Reactivities of the Isomeric Methyl Pyridinecarboxylates in the Acylation of Certain Ketones. The Synthesis of β-Diketones Containing Pyridine Rings

BY ROBERT LEVINE AND JAMES K. SNEED[1,2]

Using sodium methoxide to effect the condensations, the relative reactivities of the three methyl pyridinecarboxylates and methyl benzoate in the Claisen acylation of acetone, acetophenone and pinacolone have been found to be methyl picolinate > isonicotinate > nicotinate and/or benzoate. An explanation for this order of reactivity is given and certain comments on the factors influencing the Claisen acylation of methyl ketones are made.

In a recent communication[3] from this Laboratory the relative reactivities of a number of aliphatic and aromatic esters, in their condensations with methyl 2-thienyl ketone, have been determined. The reactivities of these esters have been found to parallel those reported in the literature for the ammonolysis[4] and alkaline hydrolysis[5] of the same compounds.

In the present paper, we report the results of the acylation of acetone, acetophenone and pinacolone with the three isomeric methyl pyridinecarboxylates and methyl benzoate. These reactions were carried out in refluxing anhydrous ether using one equivalent each of sodium methoxide and ester and two equivalents of ketone. The following equations, which show the preparation of picolinoylacetone, illustrate the method used.

$$CH_3COCH_3 + OCH_3^- \longrightarrow \underset{\text{I}}{(CH_2COCH_3)^-} + CH_3OH \quad (1)$$

$$2\text{-}C_5H_4NCO_2CH_3 + \text{I} \longrightarrow \underset{\text{II}}{2\text{-}C_5H_4NCOCH_2COCH_3} + OCH_3^- \quad (2)$$

$$\text{II} + OCH_3^- \longrightarrow (2\text{-}C_5H_4COCHCOCH_3)^- + CH_3OH \quad (3)$$

The results of our study are found in Table I. It may be seen that with the three ketones, the order of reactivity of the esters is methyl picolinate > isonicotinate > nicotinate and/or benzoate. Since the rate-controlling step in these condensations is probably the condensation of the ketone anion with the polarized form of the ester molecule (equation 2), that ester which has the most electrophilic carbonyl carbon atom should condense most readily with ketone anions. Consideration of the following resonance forms of methyl picolinate are of help in explaining the results. Form C represents the structure of the ester which is important in condensations with ketone anions (nucleophilic reagents). Also activating the carbonyl carbon atom of the ester is form A, which involves nuclear reso-

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[1] This paper is based on a portion of the thesis presented by James K. Sneed to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

[2] The Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del.

[3] Sneed and Levine, THIS JOURNAL, **72**, 5219 (1950).

[4] Gordon, Miller and Day, *ibid.*, **70**, 1946 (1948).

[5] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., pp. 121, 211, 212.