amino-4-*p*-bromphenylthiazole and 2-aminobenzimidazole.

Experimental

2-Methyl-4-amino-6-hydroxypyrimidine (IV).—Acetamidine hydrochloride (9.5 g., 0.10 mole) and cyanoacetic ester (11.4 g., 0.10 mole) in 20 ml. of methanol cooled in an ice-bath was added to 22.0 g. (0.40 mole) of sodium methoxide dissolved in 100 ml. of methanol. The mixture was refluxed for 2 hours, taken down to dryness under reduced pressure, and dissolved in 80 ml. of warm water. The cooled solution was filtered from a trace of precipitate[7] and diluted to twice its volume with water. Upon acidification to *p*H 5 with glacial acetic acid, a voluminous white powdery precipitate appeared, which was filtered off the next day. The solid was washed with water, dried at 110°, and weighed 10.1 g. (81%). It melted at 295–297° and gave a mixed melting point of 294.5–296.5° with a sample, m.p. 294–296°, prepared according to Földi's procedure.

2-Methyl-4-amino-6-*p*-chloroanilinopyrimidine. Procedure A.—A mixture of 7.2 g. (0.05 mole) of 2-methyl-4-amino-6-chloropyrimidine,[2] 6.4 g. (0.05 mole) of *p*-chloroaniline, 50 ml. of water and 4.2 ml. of concd. hydrochloric acid was heated just to boiling on a hot-plate for 1 hour. Upon cooling the crystalline hydrochloride of 2-methyl-4-amino-6-*p*-chloroanilinopyrimidine precipitated. The contents were made basic with 5% ammonium hydroxide, and the resulting white crystalline solid was filtered off. After drying at 110° the yield was 10.5 g. (90%), m.p. 189–190°. Recrystallization from 50% ethanol raised the m.p. to 190–191°. *Anal.* Calcd. for $C_{11}H_{11}ClN_4$: N, 24.9. Found: N, 24.8.

2-Methyl-4-amino-6-piperidinopyrimidine. Procedure B.—A mixture of 12.7 g. (0.15 mole) of piperidine and 7.2 g. (0.05 mole) of 2-methyl-4-amino-6-chloropyrimidine was refluxed at 160° for 2 hours. The cooled contents were triturated with 100 ml. of water to give a gray-white crystalline residue, which was dissolved in dilute hydrochloric acid and was reprecipitated with 5% ammonia. Recrystallization from benzene–hexane gave 9.3 g. (100%) of white crystals; m.p. 206–207°. *Anal.* Calcd. for $C_{10}H_{16}N_4$: C, 62.5; H, 8.4. Found: C, 62.7; H, 8.2.

(7) Földi and Todd found ethyl β-amino-α-cyanocrotonate to be insoluble in water and aqueous base.

Acknowledgment.—We are indebted to Samuel W. Blackman and N. Martinez, Jr., for microanalyses and to Elizabeth Burgi for the preparation of intermediates.

Summary

A series of 2-methyl-4-amino-6-substituted aminopyrimidines have been prepared from the reaction of alkyl and arylamines with the corresponding chloropyrimidine.

Amino compounds in which the amino group is a portion of an amidine or guanidine system appeared to give no product with the chloropyrimidine under aqueous acid conditions.

A simple and improved procedure for the preparation of 2-methyl-4-amino-6-hydroxypyrimidine is described.

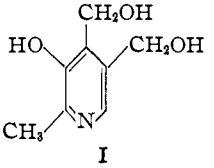
TUCKAHOE 7, N. Y. RECEIVED JUNE 22, 1950

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Lithium Aluminum Hydride Reduction of Pyridine Carboxylic Esters: Synthesis of Vitamin B_6

BY REUBEN G. JONES AND EDMUND C. KORNFELD

One of the major problems in the synthesis of vitamin B_6 (I) has been the reduction of carboxyl groups to hydroxymethyl groups in the 4- and 5-positions of the pyridine ring. Generally, in the



I

synthesis of I, carboxyl groups have been converted *via* amides to nitriles and the nitriles reduced catalytically to aminomethyl side chains.[1] A further step, *viz.*, treatment with nitrous acid, is then necessary to convert the aminomethyl to hydroxymethyl groups.[1] It occurred to us that this awkward process might be avoided, and the desired hydroxymethyl functions at positions 4 and 5 might be obtained directly by reducing an appropriately substituted 4,5-pyridinedicarboxylic acid ester with lithium aluminum hydride. Previous work in this Laboratory has shown that esters of imidazole,[2] pyrazole,[3] pyrrole,[4] furan,[4] indole[4] and other heterocyclic carboxylic acids are smoothly reduced with lithium aluminum hydride to the corresponding hydroxymethyl compounds. On the other hand, esters of pyrazine carboxylic acid,[4] oxazole carboxylic acid[4] and certain others appear to undergo extensive decomposition when treated with lithium aluminum hydride. Furthermore, Hochstein[5] has reported that pyridine itself is attacked by lithium aluminum hydride.

A variety of pyridinecarboxylic acid esters has now been reduced with lithium aluminum hydride, and in most cases good to excellent yields of the corresponding hydroxymethyl compounds have been obtained. In no case was reduction of the pyridine ring observed. 3-Hydroxymethylpyridine[6] was obtained in 80% yield from ethyl nicotinate.[7] The reduction of diethyl 2-methyl-4,5-pyridinedicarboxylate[8] gave a satisfactory yield of 2-methyl-4,5-dihydroxymethylpyridine (II). Reduction of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate[9] gave a 50% yield of 2,6-dimethyl-3,4-dihydroxymethyl-

(1) See, for example, Szabo, U. S. Patent 2,410,531, Nov. 6, 1946; Mowatt, Pilgrim and Carlson, THIS JOURNAL, **65**, 954 (1943); Harris and Folkers, *ibid.*, **61**, 1245, 3307 (1939).

(2) Jones and McLaughlin, *ibid.*, **71**, 2444 (1949).

(3) Jones, *ibid.*, **71**, 3994 (1949).

(4) Unpublished studies by the authors.

(5) Hochstein, THIS JOURNAL, **71**, 305 (1949).

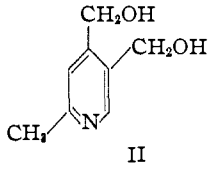
(6) Panizzon, *Helv. Chim. Acta*, **24E**, 24 (1941).

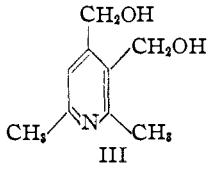
(7) Since this paper was submitted for publication a similar reduction has been reported in British Patent 631,078 [*C. A.*, **44**, 5397[e] (1950)].

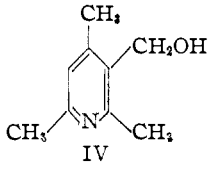
(8) The intermediate 2-methyl-4,5-pyridinedicarboxylic acid used in this experiment was obtained by permanganate oxidation of 3-methylisoquinoline (see Experimental).

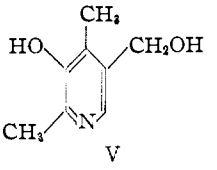
(9) Mumm and Hüneke, *Ber.*, **50**, 1573 (1917).

pyridine (III). When this latter reduction was carried out under more vigorous conditions, there was obtained, among other products, a trimethylhydroxymethylpyridine. We have formulated this as the 2,4,6-trimethyl compound (IV).


II

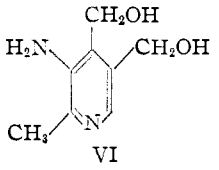

III


IV


V

The basis for structure IV rests on analogy with desoxypyridoxin (V), which is formed by catalytic hydrogenolysis of I.[10]

After having thus established that simple mono- and dicarboxylic acid esters of pyridine are readily reduced to hydroxymethyl derivatives, attention was turned to the reduction of compounds which might directly yield vitamin B_6 or which might yield products readily convertible to the vitamin. For this purpose, esters of the known 2-methyl-3-hydroxy-4,5-pyridinedicarboxylic acid[11] and 2-methyl-3-amino-4,5-pyridinedicarboxylic acid[11] were prepared. These esters underwent smooth reduction with lithium aluminum hydride in ether to give excellent yields of the hydroxymethyl compounds I and VI, respectively. In addition, di-


VI

methyl 2-methyl-3-acetoxy-4,5-pyridinedicarboxylate was reduced with lithium aluminum hydride to give vitamin B_6 (I) in a yield of more than 80%. The amino compound VI was readily converted to I by treatment with nitrous acid.

Preliminary tests using *Neurospora sitophilia* have indicated that VI is a reversible antagonist for vitamin B_6.

Acknowledgment.—The authors are grateful to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported; to F. Streightoff for the microbiological tests, and to K. C. McLaughlin for valuable assistance.

Experimental

Diethyl 2-Methyl-4,5-pyridinedicarboxylate.—To 215 g. (1.5 moles) of 3-methylisoquinoline in 4 liters of water at 90° was added with stirring a hot solution of 1422 g. (9.0 moles) of potassium permanganate dissolved in the minimum quantity of hot water. The addition required about two hours, after which the manganese dioxide was filtered off and washed with 1 liter of hot water. The total filtrate was evaporated to dryness in vacuum, and the residue was extracted with three 500-ml. portions of absolute alcohol. Evaporation of the alcohol solution left a red gum. This was again taken up in hot absolute alcohol, and the solution was evaporated to dryness *in vacuo*. The residue was dissolved in 2 liters of absolute alcohol, saturated with hydrogen chloride, and the solution was allowed to stand for four days. It was then evaporated *in vacuo* to about 500 ml., poured into excess sodium carbonate solution and the mixture extracted with ether. Evaporation of the ether solution and distillation of the residual liquid gave 140–160 g. of distillate, b.p. 141–142° (1 mm.). This was a mixture of diethyl phthalate and diethyl 2-methyl-4,5-pyridinedicarboxylate. The compounds were separated by dissolving the mixture in ether and precipitating the pyridine compound with dry hydrogen chloride. The yield was 57 g. (11%); m.p. 90–93°.

Anal. Calcd. for $C_{12}H_{15}NO_4 \cdot HCl$: C, 52.65; H, 5.89; N, 5.12. Found: C, 52.84; H, 5.80; N, 5.28.

The hydrochloride was converted to the free ester; b.p. 119–121° (0.5 mm.); $n^{25}D$ 1.5001.

Dimethyl 2-Methyl-3-amino-4,5-pyridinedicarboxylate.—2-Methyl-3-amino-4,5-pyridinedicarboxylic acid monohydrate was prepared according to the directions of Itiba and Emoto.[11] A suspension of 17 g. of the acid monohydrate in 200 ml. of methanol was treated with 500 ml. of a methylene chloride solution of diazomethane made from 42 g. of nitrosomethylurea. After the evolution of nitrogen had stopped the solution was filtered and evaporated *in vacuo* to a sirup. The residue was taken up in 500 ml. of ethyl acetate, a little insoluble material was removed by filtration, and the filtrate was evaporated again to a sirup. This was covered with petroleum ether, and it crystallized slowly. The yield was 16 g. (90%). A sample was recrystallized from an ethyl acetate–ether–petroleum ether mixture; m.p. 94–95°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40; N, 12.50. Found: C, 53.67; H, 5.62; N, 12.45.

Attempted esterification of the diacid monohydrate[11] with methanol and dry hydrogen chloride in the usual way gave low yields of the desired diester.

Dimethyl 2-Methyl-3-hydroxy-4,5-pyridinedicarboxylate.—A solution of 2.8 g. of 2-methyl-3-hydroxy-4,5-pyridinedicarboxylic acid[11] in 100 ml. of methanol saturated with dry hydrogen chloride was heated under reflux for 18 hours. The solution was then evaporated *in vacuo* to small volume, treated with 30 ml. of water and 10 g. of sodium bicarbonate, and the resulting mixture thoroughly extracted with ethyl acetate. There was obtained 1.0 g. (33% yield) of the dimethyl ester by evaporation of the ethyl acetate extract; m.p. 138.5–139° (after recrystallization from ethyl acetate–petroleum ether).

Anal. Calcd. for $C_{10}H_{11}NO_5$: N, 6.22. Found: N, 6.22.

From the aqueous solution in the above preparation there was recovered, after acidification, 1.1 g. (40%) of the unchanged diacid.

Dimethyl 2-Methyl-3-acetoxy-4,5-pyridinedicarboxylate.—The above diester, 0.70 g., was treated with about 10 ml. of acetic anhydride. After heating at 70–80° for four hours the solution was evaporated *in vacuo*. The residual brown sirup was covered with petroleum ether and kept in a refrigerator. After several hours it crystallized. The product was recrystallized from an ether–petroleum ether mixture; m.p. 61–62°.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.09; H, 5.16; N, 5.31.

3-Hydroxymethylpyridine (General Reduction Procedure).—A solution of 14.8 g. (0.4 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether was placed in a flask provided with a dropping funnel, reflux condenser and stirrer. The solution was stirred, and during a period of one-half hour a solution of 30.2 g. (0.2 mole) of ethyl nicotinate in 200 ml. of dry ether was added. To the reaction mixture was added dropwise with stirring 50 ml. of water to destroy excess lithium aluminum hydride. The mixture was filtered. The solid was suspended in 300 ml. of methanol; this mixture was saturated with carbon dioxide, heated to boiling and filtered. Again the solid was extracted with 300 ml. of hot methanol. The combined ether and methanol filtrates were evaporated *in vacuo*. The residual liquid was taken up in ether, the solution dried with anhydrous potassium carbonate and distilled to yield 17 g. (82%) of 3-hydroxymethylpyridine, b.p. 144–145° (20 mm.).

(10) Harris, THIS JOURNAL, **62**, 3203 (1940).

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

Anal. Calcd. for C_6H_7NO: N, 12.84. Found: N, 12.92.

2,6-Dimethyl-3,4-dihydroxymethylpyridine (III).—One-half mole of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate[9] was reduced in similar fashion using 0.7 mole of lithium aluminum hydride. The product was isolated in this case by extraction with hot water and was recrystallized from either water or ethanol, m.p. 182–183°.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.38. Found: C, 63.90; H, 7.83; N, 8.41.

2,4,6-Trimethyl-3-hydroxymethylpyridine (IV).—When diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate was reduced using four moles of lithium aluminum hydride for each mole of the ester during a 24-hour reflux period, the product was isolated by methanol extraction as in the general procedure. The mixture was fractionated *in vacuo*, and the fraction, b.p. 125–145° at 4 mm., crystallized on standing, (20%). It was recrystallized from acetone, m.p. 133–134°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.27. Found: C, 70.90; H, 8.42; N, 9.21. C, 70.95; H, 8.30.

2-Methyl-4,5-dihydroxymethylpyridine (II).[12]—Ethyl 2-methyl-4,5-pyridinedicarboxylate, 41 g., was reduced in ether solution using 11 g. of lithium aluminum hydride. The crude product obtained as usual was fractionated *in vacuo*. The fraction, b.p. 170–190° (7 mm.), 16 g., (60%) crystallized on standing. It was recrystallized twice from ethyl acetate, m.p. 95–97°.

Anal. Calcd. for $C_8H_{11}NO_2$: N, 9.15. Found: N, 9.24.

2-Methyl-3-amino-4,5-dihydroxymethylpyridine (VI).—Dimethyl 2-methyl-3-amino-4,5-pyridinedicarboxylate, 15 g. (0.067 mole) was added *via* Soxhlet extractor to a refluxing solution of 9.0 g. (0.23 mole) of lithium aluminum hydride in 600 ml. of anhydrous ether. This process required about one-half hour. The mixture was allowed to stand overnight and then 30 ml. of methanol was added dropwise followed by 30 ml. of water. The mixture was filtered and the solid was extracted with three 500-ml. portions of boiling methanol. After saturation with carbon dioxide the combined filtrates were evaporated to dryness *in vacuo*. The residue was taken up in 500 ml. of hot absolute ethanol, and this solution was filtered and evaporated leaving a sirup which quickly crystallized. Again the product was taken up in hot absolute ethanol, 200 ml., the solution decolorized with carbon, and evaporated to dryness leaving 10.0 g. (89% yield) of 2-methyl-3-amino-4,5-dihydroxymethylpyridine. A sample for analysis was recrystallized from ethyl acetate containing a little ethanol; m. p. 141.5–142°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 56.95; H, 7.21; N, 16.28.

The compound was readily soluble in water or alcohol, sparingly soluble in cold acetone or ether. The dihydrochloride, m.p. 176–177°, was very sparingly soluble in ethanol.

2-Methyl-3-amino-4,5-pyridinedicarboxylic acid, 0.5 g., was esterified in dry ether with phenyldiazomethane,[13] and the crude dibenzyl ester so obtained was treated with 1.3 g. of lithium aluminum hydride in 50 ml. of ether. After the mixture had stood for 15 minutes, the excess reagent was decomposed with water (6 ml.), and the product was isolated as above. 2-Methyl-3-amino-4,5-dihydroxymethylpyridine was obtained, m.p. 141–142°; 0.15 g. (35%). A mixed m.p. with a sample obtained above showed no depression.

Crude di-*n*-butyl 2-methyl-3-amino-4,5-pyridinedicarboxylate, m.p. 112–114°, was obtained in 18% yield by esterification of the diacid with boiling *n*-butanol saturated with hydrogen chloride. The ester, 1.3 g. was reduced with 1.0 g. of lithium aluminum hydride in 400 ml. of ether. The reaction was worked up as described above to yield 0.40 g. (56%) of 2-methyl-3-amino-4,5-dihydroxymethylpyridine identified by a mixed melting point with an authentic sample.

2-Methyl-3-hydroxy-4,5-dihydroxymethylpyridine (Vitamin B_6).—Dimethyl 2-methyl-3-hydroxy-4,5-pyridinedicarboxylate 1.0 g., was added *via* Soxhlet extractor over a period of eight hours to a solution of 1.0 g. of lithium aluminum hydride in 200 ml. of ether. The reaction mixture was treated with 100 ml. of water, added dropwise at first. The mixture was filtered with the aid of filter-cel, and the aqueous filtrate, after saturation with carbon dioxide, was evaporated to dryness *in vacuo*. The residue was extracted with two 100-ml. portions of hot absolute alcohol. The filtered alcohol extract was saturated with dry hydrogen chloride and then evaporated *in vacuo* to a volume of about 5 ml. and chilled to yield 0.7 g. of white crystalline hydrochloride of vitamin B_6, m.p. 203–204° (dec.). When mixed with authentic vitamin B_6 hydrochloride, the m.p. was unchanged. The product was further characterized by the infrared absorption spectrum, which was identical with that of vitamin B_6 hydrochloride.

Dimethyl 2-methyl-3-acetoxy-4,5-pyridine dicarboxylate 0.20 g. was reduced with 0.30 g. of lithium aluminum hydride in 25 ml. of ether. The reaction was worked up as described above to yield 0.13 g. (84%) of vitamin B_6 hydrochloride identified by melting point, mixed melting point and infrared absorption spectrum.

A solution of 2.0 g. of 2-methyl-3-amino-4,5-dihydroxymethylpyridine in 40 ml. of 2 *N* H_2SO_4 was heated to 70–80° and to it was added dropwise with stirring a solution of 2 g. of sodium nitrite in 10 ml. of water. The resulting solution was kept at 70–80° for an additional 15 minutes, then cooled and brought to *p*H 7 with sodium hydroxide solution and evaporated to dryness *in vacuo*. The residue was extracted with 100 ml. of hot absolute alcohol. This solution was evaporated *in vacuo* to a sirup, which was dissolved in 200 ml. of hot acetone. Evaporation of the filtered acetone solution left a sirup which soon crystallized. The yield was 1.9 g. (95%) of 2-methyl-3-hydroxy-4,5-dihydroxymethylpyridine. This product was dissolved in 200 ml. of hot acetone. The solution was cooled, then chilled to −30° and a small precipitate of colored impurities filtered off. Evaporation of the filtrate left pure 2-methyl-3-hydroxy-4,5-dihydroxymethylpyridine (vitamin B_6 free base); m.p. 152–153°. The hydrochloride prepared from this melted at 205–206° (dec.), and the m.p. was unchanged when mixed with authentic vitamin B_6 hydrochloride.

Summary

3-Hydroxymethylpyridine, 2-methyl-4,5-dihydroxymethylpyridine, 2,6-dimethyl-3,4-dihydroxymethylpyridine and 2-methyl-3-amino-4,5-dihydroxymethylpyridine have been prepared by reduction of the corresponding carboxylic acid esters with lithium aluminum hydride.

Vitamin B_6 has been prepared by reduction of dimethyl 2-methyl-3-hydroxy-4,5-pyridinedicarboxylate and of dimethyl 2-methyl-3-acetoxy-4,5-pyridinedicarboxylate with lithium aluminum hydride. It has also been prepared from 2-methyl-3-amino-4,5-dihydroxymethylpyridine by treatment with nitrous acid.

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(12) The hydrochloride of this compound, prepared by a different method, has been described by Ichibo, Michi and Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **39**, 126 (1941); [*C. A.*, **41**, 6246 (1947)].

(13) Staudinger and Gaule, *Ber.*, **49**, 1897 (1916).