EXPERIMENTAL[4]

3',4-(3,5-Dicarbethoxy-2,6-dimethyl-1,4-dihydro)bipyridine. A mixture of 50 g. (0.47 mole) of pyridine-3-carboxaldehyde, 130 g. (1.0 mole) of ethyl acetoacetate, and 22 g. (0.63 mole) of ammonium hydroxide (d. = 0.88) were heated at 80° for 4 hr. Ten milliliters of concd. ammonium hydroxide was added and the heating continued for 4 more hr. The crystals which separated on cooling were collected and recrystallized from ethanol to give 121.8 g., 80%, of the product as white needles, m.p. 192–194°.

Anal. Calcd. for $C_{13}H_{22}N_2O_4$: N, 8.48. Found: N, 8.56.

3',4-(3,5-Dicarbethoxy-2,6-dimethyl)bipyridine. The dihydrobipyridine, 99 g., was warmed with a solution of 108 ml. of water, 18 ml. of concd. sulfuric acid, and 24 ml. of concd. nitric acid. On cooling and neutralization with ammonium hydroxide, the precipitated solid was collected and recrystallized from ethanol to give 87 g., 97%, of the product as pale yellow needles, m.p. 86–87°. Its picrate melts at 132–135°.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: N, 8.53. Found: N, 8.65.

3',4-(3-Carbethoxy-5-carboxy-2,6-dimethyl)bipyridine. A solution of 10 g. of the dicarbethoxybipyridine and 1.71 g. of potassium hydroxide in 50 ml. of ethanol was refluxed for 1 hr. and evaporated to dryness. The residue was taken up in 200 ml. of water. The resulting solution was adjusted to *p*H 7 with dilute sulfuric acid and to this was added a solution of 6.2 g. of copper acetate in 100 ml. of water. The precipitated copper salt was suspended in water and treated with hydrogen sulfide. The filtered solution was evaporated to dryness and recrystallized from petroleum ether (b.p. 66–75°) to give 5.5 g., 60%, of the product as white crystals, m.p. 154–157°.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: N, 9.35; neut. equiv., 299. Found: N, 9.20; neut. equiv., 295.

3',4-(2,6-Dimethyl)bipyridine. A solution of 81.7 g. (0.25 mole) of the dicarbethoxybipyridine and 40 g. of potassium hydroxide in 350 ml. of ethanol was refluxed for 1 hr. and evaporated to dryness. The residue was ground with 164 g. of calcium oxide and heated in a flame under reduced pressure. The distillate was refractionated to give 4.0 g., b.p. 170–176°/15 mm. A second refractionation gave the product, b.p. 175–176°/15 mm., n_D^{25} 1.5998.

Anal. Calcd. for $C_{12}H_{12}N_2$: N, 15.21. Found: N, 15.37.

3',4-(2,6-Dimethyl)bipyridine and 3',4-(3-carbethoxy-2,6-dimethyl)bipyridine. The residue obtained on evaporation of the alcoholic potassium hydroxide saponification described above was taken up in water and filtered to remove unreacted ester. The solution was adjusted to *p*H 7.0 with sulfuric acid and an equivalent amount of copper acetate was added. The precipitated copper salts were collected, dried, and mixed with molecular copper.[5] The mixture was heated under reduced pressure over a flame and the distillate collected. Refractionation of the distillate gave 2.3 g.; 5% of the bipyridine, b.p. 174–176°/15 mm. and 3.4 g., 40%, of a fraction b.p. 146°/1 mm. which solidified on cooling. Recrystallization of this fraction from petroleum ether gave 3',4-(3-carbethoxy-2,6-dimethyl)bipyridine, m.p. 50–52°.

Anal. Calcd. for $C_{15}H_{16}N_2O_7$: N, 10.93. Found: N, 10.92.

3',4-(3-Carboxy-2,6-dimethyl)bipyridine. A solution obtained by refluxing the ester with alcoholic potassium hydroxide was evaporated to dryness. An aqueous solution of the residue was neutralized and treated with silver nitrate. The precipitated silver salt was collected, dissolved in water, and treated with hydrochloric acid to precipitate the silver. Evaporation of the filtrate gave a low yield of the product as white needles, m.p. 279° dec.

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: N, 12.25. Found: N, 12.25.

(4) Analyses by Micro Tech Laboratories.

(5) R. Q. Brewster and T. Groening, *Org. Syntheses*, **Coll. Vol. II**, 446 (1943).

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Preparation of 5-Hydroxy-4,6-dimethyl-3-Pyridinemethanol (4-Desoxypyridoxine) by the Use of Hydrazine

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4-Desoxypyridoxine has been prepared by treating hydrazine with pyridoxine or with its 4-methyl-ether in the form of their hydrochloride salts. 4-Desoxypyridoxine is the most active antagonist of pyridoxine known to this time. It has been found to be able to produce in a variety of animals general symptoms of acute pyridoxine deficiency.[1,2] It has also been found to exhibit antitumor activity[3] and to be an active synergist in this respect.[4]

An attempt was made to prepare the *N*-amino analogue of pyridoxamine (2-methyl-3-hydroxy-4-hydrazinomethyl-5-hydroxymethylpyridine) (I) by allowing hydrazine and 2-methyl-3-hydroxy-4-methoxymethyl-5-hydroxymethyl-pyridine (II) to react. The rationale for this attempt was based on the fact that ammonia and the above ether react to give pyridoxamine.[5] However, upon carrying out a number of reactions between hydrazine and the pyridoxine ether, under a variety of conditions, none of the desired 4-hydrazino compound could be isolated. Instead, when carrying out the reaction with excess hydrazine at reflux temperatures for eighteen hours, 4-desoxypyridoxine (III) was the sole product obtained in a 94% yield as illustrated in Fig. 1.

This appears to be the first reported instance of an alcohol in the form of its ether derivative being cleaved and reduced to a hydrocarbon by hydrazine. Such a reaction, however, has been performed by catalytic hydrogenation and in fact this constitutes an earlier method for preparing 4-desoxypyridoxine.[6] Pyridoxine itself has also been reduced by catalytic hydrogenation to 4-desoxypyridoxine.[6]

(1) W. H. Ott, *Proc. Soc. Exper. Biol. and Med.*, **61**, 125 (1946).

(2) C. W. Mushett, *Federation Proc.*, **6**, 397 (1947).

(3) S. Garatt, S. Garattini, and A. Vegeto, *Giorn. ital. chem. terap.*, **2**, No. 1–2, 41 (1955).

(4) R. W. Brockman, J. R. Thomson, F. M. Schebel, Jr., and H. E. Skipper, *Cancer Research*, **16**, 788 (1956).

(5) D. Heyl, S. A. Harris, and K. Folkers, U. S. Pat. **2,497,730** (1950).

(6) S. A. Harris, *J. Am. Chem., Soc.*, **62** 3203 (1940.)

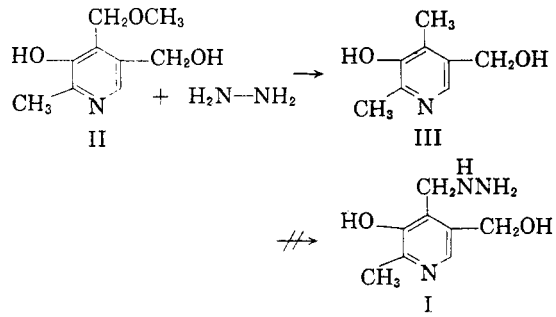

Figure 1

Yields have not been reported for these reductions. In the present work it was found, likewise, that hydrazine could reduce pyridoxine itself to the 4-desoxy derivative in a 98% yield under the conditions found optimum for the 4-methoxy ether transformation. It is interesting to note the lack of participation of the 5-hydroxymethyl group in these reductions. This fact indicates that probably this reaction will not serve as a general synthetic procedure with alcohols or ethers. Earlier methods for preparing 4-desoxypyridoxine other than the catalytic hydrogenation procedure referred to above are based on one of the widely used methods for preparing pyridoxine itself (6–9 steps), however, starting with suitable linear precursors to give a methyl group in the "4" position rather than a hydroxymethyl group.[7–9]

A series of experiments were carried out with the reaction under discussion upon 2-methyl-3-hydroxy-4-methoxymethyl-5-hydroxypyridine hydrochloride in order to investigate the effects of time, temperature, solvents, and amounts of reactants upon the course of the reaction. It was found that excess hydrazine, hydrazine reflux temperatures, and approximately eighteen hours of reaction time are required in order that a complete conversion to 4-desoxypyridoxine is affected. Forty-seven percent aqueous hydrazine at reflux for eighteen hours was equally effective in bringing about the conversion, but with 50% anhydrous hydrazine in methanol, no 4-desoxypyridoxine could be isolated after eighteen hours of reflux. Likewise, only starting material was recovered when excess anhydrous hydrazine was used at room temperature for six days, although total conversion was obtained at reflux temperatures in eighteen hours.

Both pyridoxine and its 4-methyl ether were allowed to react as their hydrochloride salts which were soluble in hydrazine; however, upon isolating either starting material or the 4-desoxypyridoxine that formed, these were obtained as the free bases together with hydrazine hydrochloride that had formed by interchange. It was possible to separate these two materials by taking advantage of the solubility of the free bases in ethanol and the relative insolubility of hydrazine hydrochloride in this solvent. 4-Desoxypyridoxine could then be much more readily isolated and purified by conversion to its hydrochloride than when attempts had been made to isolate and purify the free base. The hydrochloride was readily prepared by the addition of methanolic hydrogen chloride to an alcohol solution of the free base. Complete recovery of the 4-desoxypyridoxine hydrochloride was obtained by the addition of ether to the alcoholic solutions.

EXPERIMENTAL

Reagents. 2-Methyl-3-hydroxy-4-methoxymethyl-5-hydroxypyridine hydrochloride was obtained from Dr. Stanton Harris of Merck and Co., Rahway, N. J. Anhydrous hydrazine was prepared by treating 95% reagent grade hydrazine with 20% by weight of potassium hydroxide overnight. The resulting gel was filtered and the filtrate distilled at atmospheric pressure under anhydrous conditions. Authentic 4-desoxypyridoxine was obtained from the Nutritional Biochemicals Corporation, Cleveland, Ohio.

Preparation of 4-desoxypyridoxine (A). Ten grams (0.046 mole) of 2-methyl-3-hydroxy-4-methoxymethyl-5-hydroxymethylpyridine hydrochloride and 50 ml. of 95% hydrazine were refluxed for 18 hr. Most of the hydrazine was distilled off under vacuum with heating by steam. The residue was extracted with 60 ml. of boiling methanol which on filtering yielded the insoluble hydrazine monohydrochloride, m.p. 91–92° (lit.[10] m.p. 92.6°). The volume of the filtrate was reduced to 20 ml. and 15.0 ml. of 11.2% methanolic hydrogen chloride was added to give an immediate precipitate. The precipitate was isolated by vacuum filtration and 50.0 ml. of ether were added to the filtrate to give further precipitate which was filtered after 30 min. of standing. The total combined yield of materials was 8.1 g. (94%) melting at 266° dec. A portion was crystallized from ethanol to give a purer sample of 2-methyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride, m.p. 273° dec. (lit.,[6] m.p. 267–268°).

Anal. Calcd. for $C_8H_{12}ClNO_2$: C, 50.57; H, 6.38; Cl, 18.69; N, 7.39. Found: C, 50.71; H, 6.34; Cl, 18.13; N, 7.64.

Admixture with an authentic sample of 4-desoxypyridoxine hydrochloride, m.p. 275° dec., caused no depression of its melting point.

Preparation of 4-desoxypyridoxine (B). All conditions and isolation procedures for this experiment are identical with those of method A, except that, instead of the 4-methyl ether, 5.0 g. (0.024 mole) of pyridoxine hydrochloride and 25.0 ml. of 95% hydrazine were used. Four and five tenths grams (98% yield) of 4-desoxypyridoxine hydrochloride, m.p. 264° (dec.), were obtained. An analytical sample was prepared by crystallizing the product twice from ethanol, m.p. 274° dec.

Anal. Calcd. for $C_8H_{12}ClNO_2$: C, 50.57; H, 6.38; N, 7.39. Found: C, 50.66; H, 6.28; N, 7.53.

Admixture with an authentic sample of 4-desoxypyridoxine hydrochloride caused no depression of its melting point.

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(7) O. Zima and F. Jung, German Pat. **707,266** (1941); *Chem. Zentr.*, **1941**, II, 2353.

(8) H. M. Van Wagtendonk and J. P. Wilbaut, *Rec. trav. Chim.*, **61**, 788 (1942).

(9) H. W. Coover and N. J. Bowman, U. S. Pat. **2,481,573** (1949).

(10) N. A. Lange, *Handbook of Chemistry*, 8th Edition, Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 238.