the product, m.p. 97–99°. Additional recrystallizations failed to remove the purple coloration.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde semicarbazone. The aldehyde, 0.0123 g. (0.005 mole), was dissolved in 30 ml. of ethanol and water added to just the turbidity point. Five milliliters of ethanol, 0.6 g. of semicarbazide hydrochloride, and 0.8 g. of finely powdered sodium acetate were added. After heating and cooling, the solution set to a solid mass. The crystals were collected and dried to give 1.23 g., 81.4%, of the product, m.p. 161–166°. Recrystallization from ethanol-water gave the analytical sample, m.p. 162–166°.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde dimethylhydrazone methiodide. Unsymmetrical dimethylhydrazine, 0.065 g., was added to a solution of 2.46 g. (0.01 mole) of the aldehyde in 50 ml. of ethanol. This mixture was heated to reflux for 1 hr. and allowed to stand at room temperature and then at 0°. The oil which separated was taken up in 75 ml. of ether, dried over magnesium sulfate. Addition of 2.5 g. of methyl iodide precipitated crystals which were collected and dried to yield 2.03 g., 47.2%, of the product, m.p. 167° dec. Recrystallization from water gave the analytical sample of the same melting point.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde anilide. A solution containing 50 ml. of ethanol, 2.46 g. (0.01 mole) of the aldehyde, and 1.1 g. of aniline was refluxed for 1.5 hr. Upon cooling to room temperature 25 ml. of water was slowly added and the mixture cooled to 0° to precipitate 1.96 g., 61%, of the product. Two recrystallizations from benzene–petroleum ether (b.p. 00–00°) gave the analytical sample melting at 62–65°.

4-[N,N-Bis(2-chloroethyl)amino]cinnamic acid. A mixture composed of 6.15 g. (0.025 mole) of the aldehyde, 45 ml. of pyridine, 1 ml. of piperidine, and 2.7 g. (0.026 mole) of malonic acid was heated to 95° for 3 hr. The dark solution was then poured into cold water. The oil which separated solidified upon further stirring to give the crude, orange product. Recrystallization from benzene–petroleum ether gave 2.80 g., 38.8%, of the pale tan product, m.p. 183–186°.

4-[N,N-Bis(2-iodoethyl)amino]benzaldehyde. Nine grams of sodium iodide was dissolved in 250 ml. of 2-butanone and to this was added 6.15 g. (0.025) of the aldehyde. This mixture was then heated to reflux for 6 hr. During this time the sodium chloride liberated by the reaction precipitated and and the solution became a bright yellow. After cooling to 5°, the sodium chloride was removed by filtration and the solution evaporated to dryness to give the crude product. Recrystallization from methanol-water gave 6.36 g., 59.2%, of the product. Two recrystallizations from benzene–petroleum ether gave the analytical sample melting at 105–107°. Care had to be taken during the recrystallizations not to heat the solvents too rapidly or decomposition of the unstable aldehyde resulted.

5-{4'-[N,N-Bis(2-iodoethyl)amino]benzylidine}barbituric acid. A solution containing 1.07 g. (0.0025 mole) of the aldehyde in 25 ml. of ethanol was added to 6 ml. of warm water containing 0.32 g. (0.0025 mole) of barbituric acid. This mixture was warmed at 75° for 2 min. and cooled. The precipitate was collected, washed with distilled water, and dried to give 1.18 g., 87.5%, of the crude product decomposing at 230°. This compound had little or no solubility in the common organic solvents and was washed with hot distilled water followed by hot methanol to give the analytical sample.

4-[N,N-Bis(2-iodoethyl)amino]benzaldehyde isonicotinoylhydrazone. A solution consisting of 2.14 g. (0.005 mole) of the aldehyde in 175 ml. of hot methanol was added to 20 ml. of hot methanol containing 0.75 g. of isonicotinoylhydrazine. The resulting mixture was heated and cooled. The crystals which separated were collected to give 2.08 g., 75.9%, of the yellow product decomposing at 205°. Recrystallization from toluene gave the analytical sample which also decomposed without melting.

Acknowledgment. The authors wish to acknowledge partial support of this research through grant C-2457 from the National Cancer Institute of the United States Public Health Service.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE 8, KY.

2,6-Dimethyl-4-(3'-pyridyl)pyridine-3,5-dicarboxylic Acid and Products Derived Therefrom

RICHARD H. WILEY AND J. S. RIDGWAY

Received May 9, 1960

The aldehyde–acetoacetic ester–ammonia synthesis, which has been successfully used with pyridine-2 and 4-aldehydes,[1] has now been extended to pyridine-3-carboxaldehyde. The condensation gives 80% of the 1,4-dihydro derivative which has been oxidized in 90% yield to diethyl 2,6-dimethyl-4-(3'-pyridyl)pyridine-3,5-dicarboxylate.[2] This ester is readily hydrolyzed by alcoholic potassium hydroxide to give the mono ester in 60% yield. Saponification of the second carbethoxy group is unusually difficult. Furthermore, the monocarbethoxy compound, obtained by decarboxylation of the ester-acid, gave only very low yields (*ca.* 1%) of the mono carboxylic acid under conditions which readily saponified the diester. Attempts to convert the diester directly to the mono acid gave the mono ester or, after decarboxylation, low (*ca.* 5%) yields of 2,6-dimethyl-4-(3'-pyridyl)pyridine.[3] Because the first of the two ester groups, both of which are in sterically comparable environments, is readily saponified, it does not appear that steric hindrance provides a logical explanation for the low yields encountered in saponification of the second carbethoxy group. Alternative conditions used for the ester hydrolysis were less effective. Thus, the use of diethylene glycol for the saponification gave similar results but the presence of the glycol complicates the isolation. Longer reaction times failed to improve the yield. The ester is recovered unchanged when its solution in concentrated sulfuric acid is poured into water. The over-all conversion of the ester to the dimethylbipyridyl is much less satisfactory than the corresponding reaction[1] with the 2- and 4-pyridyl isomers.

(1) R. F. Homer, *J. Chem. Soc.*, 1574 (1958).

(2) This nomenclature is currently used in Chemical Abstracts indexes. These acids have been named as derivatives of 2,6-dimethyl-dinicotinic acid and of 2,6-lutidine-3,5-dicarboxylic acid. They can also be named as bipyridines.

(3) This compound may be named 3',4-(2,6-dimethyl)-bipyridine.

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).

Acknowledgment: This research was supported in part by the Atomic Energy Commission under Contract No. AT-(40-1)-2162 between the University of Louisville and the Atomic Energy Commission. The authors acknowledge this support and are indebted to Dr. C. H. Jarboe, Jr., for helpful comments.

UNIVERSITY OF LOUISVILLE, LOUISVILLE, KY.

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

ROBERT G. TABORSKY

Received April 28, 1960

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.)