[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

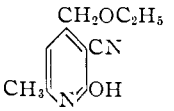
Chemistry of Vitamin B_6. XII. Synthesis of 2,5-Bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine, an Isomer of Pyridoxine

BY DOROTHEA HEYL, EILEEN LUZ AND STANTON A. HARRIS

RECEIVED APRIL 24, 1956

2-Methoxymethyl-4-methyl-5-cyano-6-hydroxypyridine, formed in addition to 2-methyl-4-methoxymethyl-5-cyano-6-hydroxymethylpyridine in the pyridoxine synthesis which begins with condensation of cyanoacetamide and methoxyacetylacetone, has been converted to 2,5-bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine, an isomer of pyridoxine. This compound was found to be inactive in a vitamin B_6 assay in rats.

The first step in the Harris–Folkers synthesis of pyridoxine[1,2] is the condensation of cyanoacetamide and ethoxyacetylacetone to form 2-methyl-4-ethoxymethyl-5-cyano-6-hydroxypyridine (3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (I)). Although this product is obtained in a yield of 85%,[2] the other isomer, 2-ethoxymethyl-4-methyl-5-cyano-6-hydroxypyridine (II) is also obtained. The



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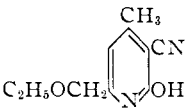
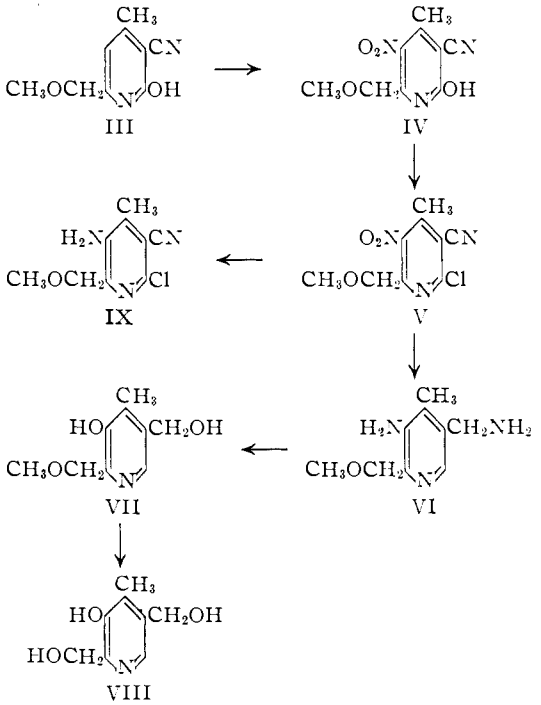


II

methoxy analog (III)[3] of this compound has been carried through a synthesis (compounds III to VIII) similar to the one which produces pyridoxine in order to test the biological activity of the pyridoxine isomer VIII. Experimental procedures were similar to ones already described.[1,4]



A similar synthesis leading to the same product is the subject of a patent.[5] The syntheses described here differ from the one in the patent in some of the experimental procedures and in that the intermediates are in the ethoxy series instead of the methoxy. The products of the two syntheses were identical in melting point.

Tests at the Merck Institute for Therapeutic Research by Dr. Gladys A. Emerson and Miss Dorothea Casey showed that in vitamin B_6 assays by the curative method in rats, 2,5-bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine was inactive.

Experimental[6]

2-Methoxymethyl-3-nitro-4-methyl-5-cyano-6-hydroxymethylpyridine (IV).—2-Methoxymethyl-4-methyl-5-cyano-6-hydroxymethylpyridine (III, 500 g.)[3] was nitrated as described by Harris and Folkers.[1] The crude nitro compound weighed 345 g. (55%), and was used directly in the next step. A pure sample, m.p. 191–192°, was obtained by recrystallization from absolute alcohol.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.44; H, 4.06; N, 18.83. Found: C, 48.51; H, 3.74; N, 18.89.

2-Methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine (V).—2-Methoxymethyl-3-nitro-4-methyl-5-cyano-6-hydroxymethylpyridine (345 g.) was chlorinated in the manner described by Harris and Folkers.[1] After removal of the chlorobenzene and volatile by-products by distillation the cooled residue crystallized. It was stirred thoroughly with 100 ml. of water and 20 ml. of ethyl alcohol, and was collected on a filter. The crystalline material was then extracted continuously with petroleum ether in a Soxhlet extractor for 25 hours, and the crystals obtained from the chilled extract collected; yield, 204 g. (55%) of 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine. A pure sample was obtained by two recrystallizations from alcohol–water; m.p. 78–79°.

Anal. Calcd. for $C_9H_8N_3O_3Cl$: C, 44.74; H, 3.37; N, 17.39. Found: C, 45.09; H, 3.31; N, 17.29.

2-Methoxymethyl-3-amino-4-methyl-5-cyano-6-chloropyridine (IX).—A solution of 4 g. of a 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine in alcohol was hydrogenated with Adams platinum catalyst as described by Harris and Folkers.[1] The yield of 2-methoxymethyl-3-amino-4-methyl-5-cyano-6-chloropyridine was 2.2 g. (63%). After recrystallization from alcohol the material melted at 138–139°.

Anal. Calcd. for $C_9H_{10}N_3OCl$: C, 51.07; H, 4.76; N, 19.85. Found: C, 51.03; H, 4.82; N, 19.63.

2-Methoxymethyl-3-amino-4-methyl-5-aminomethylpyridine Dihydrochloride (VI).—A solution of 3 g. of 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine in 125 ml. of methyl alcohol containing hydrochloric acid was hydrogenated with palladium–charcoal as catalyst until six moles of hydrogen had been absorbed. After removal of the catalyst, the solution was concentrated to dryness and the residue crystallized from methyl alcohol–ether containing a little hydrogen chloride; yield, 1.86 g. (59%) of 2-methoxymethyl-3-amino-4-methyl-5-aminomethylpyridine dihydrochloride. Several recrystallizations from methyl alcohol containing a trace of hydrogen chloride and one

(1) S. A. Harris and K. Folkers, THIS JOURNAL, **61**, 1245 (1939).
(2) S. A. Harris, E. T. Stiller and K. Folkers, *ibid.*, **61**, 1242 (1939).
(3) W. Wenner and J. P. Plati, *J. Org. Chem.*, **11**, 756 (1946).
(4) S. A. Harris and K. Folkers, THIS JOURNAL, **61**, 3307 (1939).
(5) F. Hoffmann-LaRoche & Co. A.-G., Swiss Patent 224,314, *C.A.*, **43**, 1811g (1949).

(6) We are indebted to Mr. Richard Boos and his associates for the microanalyses.

from methyl alcohol alone yielded a product of m.p. 207–208°.

Anal. Calcd. for $C_9H_{17}N_3OCl_2$: C, 42.49; H, 6.74; N, 16.53. Found: C, 42.72; H, 6.95; N, 16.51.

2-Methoxymethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (VII).—A solution of 2.2 g. of sodium nitrite in 25 ml. of water was added with stirring during 5 minutes to a solution of 3.42 g. of 2-methoxymethyl-3-amino-4-methyl-5-aminomethylpyridine dihydrochloride. The temperature of the reaction mixture rose to 50°, and after an additional half-hour of stirring, the mixture was heated at 60–70° for 15 minutes. It was then concentrated to dryness under reduced pressure, and dried thoroughly. The residue was dissolved in absolute alcohol, and the salt removed by filtering. Addition of acetone precipitated 2-methoxymethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride in a yield of 1.37 g. (46%). One recrystallization followed by sublimation gave a product which melted at 177.5–178.5°.

Anal. Calcd. for $C_9H_{14}NO_3Cl$: C, 49.21; H, 6.42; N, 6.38. Found: C, 49.50; H, 6.22; N, 6.62.

2,5-Bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine Hydrochloride (VIII).—2-Methoxymethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride (3.7 g.) was hydrolyzed by means of 2.5 *N* hydrochloric acid in a sealed tube at 155° as described by Harris and Folkers.[4] Crystallization of the product from alcohol resulted in 1.5 g. (43%) of 2,5-bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine hydrochloride. After two recrystallizations from alcohol the product melted at 184–185°.

Anal. Calcd. for $C_8H_{12}NO_3Cl$: C, 46.72; H, 5.84; N, 6.81. Found: C, 46.63; H, 5.76; N, 6.95.

2,5-Bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine.—A solution of the hydrochloride in water was neutralized with sodium bicarbonate. The insoluble material was collected on a filter and washed sparingly with alcohol and then with ether. After drying at 25° (1 mm.) for 3 hours, the material melted at 96–98° and contained one mole of water.

Anal. Calcd. for $C_8H_{11}NO_3 \cdot H_2O$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.24; H, 6.82; N, 7.59.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Condensation of Carboxylic Acid Hydrazides with Carbon Disulfide

BY C. AINSWORTH

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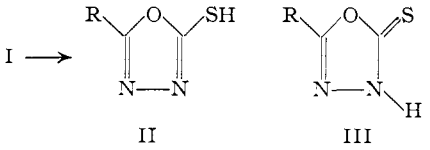
The reaction of carboxylic acid hydrazides, carbon disulfide and alcoholic alkali to form 2-substituted-Δ^2-1,3,4-oxadiazoline-5-thiones has been found to be general for aliphatic, aromatic and heterocyclic carboxylic acid hydrazides and dihydrazides. An interesting thermal isomerization of 2-(3-(5)-pyrazolyl)-Δ^2-1,3,4-oxadiazoline-5-thione (VIII) to 7-mercaptopyrazolo[1,5-d]*as*-triazin-4(5H)-one (X) was observed.

The reaction of a carboxylic acid hydrazide with carbon disulfide was first reported by Busch and Starke,[1] who obtained potassium 3-benzoyldithiocarbazate (I, R = phenyl, R_1 = H) from benzoic acid hydrazide, carbon disulfide and alcoholic potassium hydroxide. Hoggarth[2] observed that compounds of type I when heated lost hydrogen sulfide and formed 2-substituted-1,3,4-oxadiazole-5-thiols (II). This observation was verified recently

$$RCONHNHR_1 + CS_2 + KOH \longrightarrow RCONHNHR_1CS_2K + H_2O$$

I

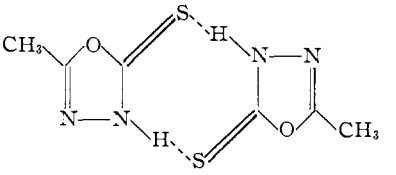


II III

by Young and Wood,[3] who also discussed the mechanism of the reaction.

A study of the reaction in this Laboratory was undertaken prior to Hoggarth's report and was prompted by our interest in azoles. The preparation of compounds of type I[4] has now been extended to heterocyclic (I, R = 4-pyridyl, R_1 = H) and N-substituted (I, R = methyl, R_1 = phenyl) acid hydrazides.

The ring-closed products, not reported previously, are contained in Table I. These compounds were prepared by heating a mixture of the appropriate carboxylic acid hydrazide, carbon disulfide and alcoholic alkali. Structure III, rather than II, was assigned to these products on the basis of the infrared findings.[5] The spectrum of 2-methyl-Δ^2-1,3,4-oxadiazoline-5-thione (III, R = CH_3) was used as a reference and is summarized in Table II. The assignment of the bands below 8 μ was assisted by a dilution study that indicated a monomer–dimer equilibrium. The structure of the dimer is presumed to be



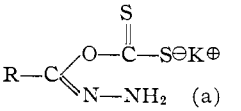
The absorbance of the monomer NH band at 2.90 μ was determined for two different total concentrations (0.136 and 0.513 *M*) and was used to calculate a value of 0.088 for the dissociation constant in chloroform at 27°.

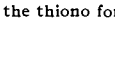
(1) M. Busch and M. Starke, *J. prakt. Chem.*, [2] **93**, 49 (1916).

(2) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(3) R. W. Young and K. H. Wood, THIS JOURNAL, **77**, 400 (1955).

(4) Young and Wood (ref. 3) considered the possibility of the initial reaction of carbon disulfide taking place at the oxygen atom of the carboxylic acid hydrazide giving rise to a structure such as (a). We find that the infrared spectra of potassium 3-benzoyldithiocarbazate and its methyl ester are very similar to each other, but show none of the characteristic absorption of potassium ethyl xanthate which has intense bands between 8.5 and 10.0 μ attributed to the grouping





(a)

(5) A more detailed study will be published by H. Boaz. Young and Wood (ref. 3) mentioned the possibility of this system existing in the thiono form, at least in the solid state.