this mixture was heated under gentle reflux for 72 hr. The mixture was then poured into 300 ml. of water and acidified with dilute hydrochloric acid solution. The solid which formed was separated by filtration and washed with three 50-ml. portions of water. The product was then crystallized from carbon tetrachloride until successive crystallization showed no increase in the melting point.

Alternate preparation of the bissulfone esters by the oxidation of the corresponding bissulfide ester. To 0.004 mole of the chromatographed bissulfide ester in a 50-ml. Erlenmeyer flask was added 10 ml. of glacial acetic acid and the flask was chilled in an ice bath. To the flask was added 0.09 mole of 30% hydrogen peroxide and the mixture was allowed to stand in the melting ice bath for 72 hr. The resulting solid was then crystallized from dioxane until successive crystallizations showed no increase in the melting point.

DEPARTMENT OF CHEMISTRY
DREXEL INSTITUTE OF TECHNOLOGY
PHILADELPHIA 4, PA.

4,5-Dihalo and 3-Amino Analogs of Pyridoxine. New Route to 4-Deoxypyridoxine[1,2]

G. E. MCCASLAND, L. KENNETH GOTTWALD AND, ARTHUR FURST

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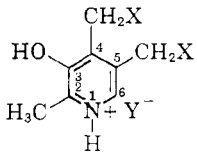
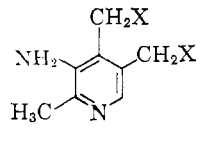
The anti-tumor action of nitrogen mustards has in part been attributed to their alkylating properties. Since pyridoxine (I) is involved in many physiological processes, it was of interest to synthesize an alkylating agent having a pyridoxine-like structure. An example would be the dibromomethyl hydrobromide (II), which because of its benzyl halide type structure would be expected to show good alkylating activity at least in neutral or basic solution. This compound had previously been prepared from the 3- or 4-alkyl ethers of pyridoxine by Harris and Folkers[3a] and Kuhn and Wendt.[3b] It presumably was also prepared from pyridoxine itself by Kreisky,[3c] but the first explicit description of the latter procedure is that now given.

The next compound investigated was the diiodide hydriodide (III). This product could not be obtained by treating the dibromide hydrobromide with sodium iodide in dry acetone. The dibromide free base was considered preferable for the sodium iodide reaction, but attempts to prepare the free base, even under the mildest conditions, led to a high-melting red-brown solid, which appears to be a polymeric quaternary salt[4] (V). It was then found that the diiodide hydriodide can be obtained by merely heating pyridoxine hydrochloride with concentrated hydriodic acid for a brief period; on cooling, pure III separates almost at once in the form of yellow crystals.

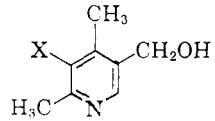
The corresponding dichloride hydrochloride[5] (IV) had previously been prepared,[6] by a sealed tube reaction of a pyridoxine alkyl ether with concentrated hydrochloric acid. We now find that IV is more conveniently prepared by reaction of pyridoxine itself with thionyl chloride.



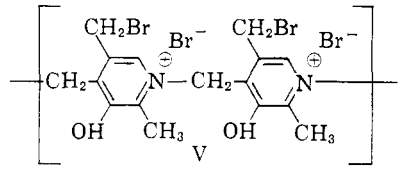


(I), X = OH, Y = Cl
(II), X = Y = Br
(III), X = Y = I
(IV), X = Y = Cl

(VI), X = OH (·HCl)
(VII), X = Br (·HBr)
(VIII), X = OAc (*N*-Ac)
(IX), X = OH (*N*-Ac)



(X), X = OH (·HCl)
(XI), X = NH_2 (·HI)



V

Some derivatives of 3-amino-3-deoxypyridoxine[7,8] (VI) were next examined. The 3-amino hydrochloride reacted with hydrobromic acid in much the same way as pyridoxine hydrochloride (see above),

(1) Paper VI on pyridoxine analogs. For preceding (unnumbered) papers, see G. E. McCasland, E. Blanz, Jr., and A. Furst, *J. Org. Chem.*, **24**, 1000 (1959) and references there cited. Taken in part from the M.S. thesis of L. Kenneth Gottwald, Graduate School, the University of San Francisco, 1961.

(2) This work was aided by Grant CY-2798 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. Gifts of pyridoxine from Drs. Karl Folkers, Merck, Sharp & Dohme Co., and Walter Gakenheimer, The Stuart Co., are gratefully acknowledged.

(3) (a) S. Harris and K. Folkers, *J. Am. Chem. Soc.*, **61**, 1247 (1939); (b) R. Kuhn and G. Wendt, *Ber.*, **72**, 311 (1939); (c) Selma Kreisky, *Monats.*, **89**, 685 (1958).

(4) Compare the polymerization of 4-bromopyridine, H. S. Mosher, p. 516 in R. C. Elderfield (editor), *Heterocyclic Compounds*, Wiley, New York, Vol. I, 1950.

(5) It was hoped that this dihalo hydrohalide series could be completed by preparing a difluoride hydrofluoride. However, all attempts to prepare the fluorine analog were unsuccessful, and there is reason to believe that such a product if prepared, would be unstable.

(6) S. Harris and K. Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).

(7) (a) R. K. Blackwood, *et al.*, *J. Am. Chem. Soc.*, **80**, 6244 (1958); (b) R. G. Jones and E. Kornfeld, *J. Am. Chem. Soc.*, **73**, 107 (1951).

(8) The *mono*hydrochloride of 2-methyl-3-amino-4,5-di(hydroxymethyl)pyridine was obtained by Blackwood, *et al.* (*loc. cit.*) under conditions (excess hydrogen chloride) which one might think would give a dihydrochloride. They reported a m.p. of 197–199° and a correct analysis for the monohydrochloride. Jones and Kornfeld (*loc. cit.*) reported the free base (m.p. 141.5–152°, correct analysis) and a dihydrochloride (m.p. 176–177°), but gave no analysis or preparation details for the latter.

to give the expected dibromide hydrobromide[9] (VII).

Surprising results were obtained, however, when preparation of the 3-amino diiodide hydriodide was attempted. The 3-amino hydrochloride (unlike pyridoxine hydrochloride) liberated considerable free iodine on reaction with hot hydriodic acid; and the product on analysis was found to have the formula $C_8H_{12}N_2O \cdot HI$, indicating that *one*, but not both, of the two hydroxymethyl groups had been reduced down to methyl.

Since the side-chain at position 4 in pyridoxine commonly is more reactive to nucleophilic[10a] or reducing[11] reagents than that at 5, the new product was assigned the structure 2,4-dimethyl-3-amino-5-hydroxymethylpyridine (XI). This assignment was confirmed by treating the product with nitrous acid and obtaining the well-known[12,13,10b] and commercially available vitamin inhibitor, 4-deoxypyridoxine (X), sometimes ambiguously referred to as "deoxypyridoxine."[13a]

In the course of this work, the previously unreported triacetyl (VIII) and *N*-acetyl (IX) derivatives of the aminediol (VI) were prepared and characterized.

Biological tests of most of the above compounds are in progress and will be reported elsewhere.

EXPERIMENTAL

All melting points have been corrected and were measured on a micro hot-stage (*Monoscop* or *Nalge-Axelrod*). Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. Infrared spectra were determined with an Infracord Recording Infrared Spectrometer, using potassium bromide pellets.

2-Methyl-3-hydroxy-4,5-di(chloromethyl)pyridine hydrochloride. (A) To 2.06 g. of finely powdered, dry pyridoxine hydrochloride was added 15.0 ml. of thionyl chloride, and the mixture boiled under reflux (anhydrous conditions) for 1 hr. The solid did not dissolve, but appeared to change. The mixture was allowed to cool, and kept at 0° to 25° for several days. The crystals were collected and washed with benzene, and then with 10 ml. of anhydrous acetone. The resulting nearly colorless powder (not weighed) melted over the range 140–190°. It was dissolved in a small amount of absolute ethanol at the boiling point, and hot benzene was added. On cooling, there separated 1.6 g. (dry weight) of colorless needles. This material was dissolved in 25 ml. of boiling absolute ethanol, and 25 ml. of hot benzene was added. On cooling, there again separated colorless needles. These were collected, washed with a little acetone, and dried, giving 0.9 g. (37%) of nearly pure product, m.p. 175–190° dec., reported[6] m.p. 200° dec.

This material (0.9 g.) was recrystallized from 10 ml. of ethanol, without benzene, giving 0.7 g. of colorless rosettes of fine needles, m.p. unchanged.

Anal. Calcd. for $C_8H_{10}Cl_3NO$: C, 39.61; H, 4.16; Cl, 43.86; N, 5.78. Found: C, 39.27; H, 4.21; Cl, 43.97; N, 5.84.

The compound is very soluble in water; the solution has a *p*H of about 4, and gives a positive test for chloride with silver nitrate.

(B) Pyridoxine hydrochloride (6.2 g.) was allowed to react with thionyl chloride (43.5 ml.) as above, but was kept at 25° only for 12 hr. The crude product was simply washed with acetone, giving 7.1 g. (90%) of material melting at 185–195° dec.

(C) Attempts to prepare the dichloride hydrochloride by use of phosphorus pentachloride in carbon tetrachloride, or by use of concentrated aqueous hydrochloric acid (with or without zinc chloride), failed to yield any pure product.

2-Methyl-3-hydroxy-4,5-di(bromomethyl)pyridine hydrobromide. A solution of 21.4 g. of pyridoxine hydrochloride in 200 ml. of 8.8*M* hydrobromic acid was boiled under reflux for 15 min. On cooling the solution, crystals deposited, which were collected, and washed with two 30-ml. portions of water and then with two 15-ml. portions of acetone, giving 24.2 g. of nearly colorless crystals, m.p. 224–228° dec. (reported[3a] m.p. 223–224°).

Attempted preparation of free base. A 1.88-g. portion of the hydrobromide was stirred with a solution of 0.463 g. (1.1 moles) of sodium bicarbonate in 20 ml. of water. The mixture turned pink, then red. The solid did not dissolve appreciably, but its crystal form appeared to change. There was a mild effervescence. After 100 min. stirring, the mixture was filtered, and the residue washed with four 5-ml. portions of water, and dried. This gave 0.6 g. of a brown-red powder, m.p. above 325°. The *p*H of the filtrate was about 2, probably indicating displacement of one or both bromomethyl bromine atoms. The product was insoluble even at the boiling point in ethanol, water, or 6*M* hydrochloric acid.

2-Methyl-3-hydroxy-4,5-di(iodomethyl)pyridine hydroiodide. A solution of 2.06 g. of pyridoxine hydrochloride in 67.2 g. (39.5 ml.) of 7.6*M* hydriodic acid was heated just to its boiling point, then immediately cooled to 25°, and refrigerated at 0–5° overnight. The crystals which separated were collected, washed freely with water, and then with acetone, and dried. There was obtained 1.3 g. (25%) of light yellow crystals, which decomposed gradually when heated over the range 120–160°.

A sample was analyzed without further purification.

Anal. Calcd. for $C_8H_{10}I_3NO$: C, 18.59; H, 1.95; I, 73.66; N, 2.71; Found: C, 19.07; H, 2.11; I, 73.05; N, 2.64.

On ignition, a sample of the material turned black, melted, and emitted purple vapor.

In a later run on 7.9 g. of starting material, the volume of hydriodic acid was decreased to 6.3 ml./g., but this did not improve the percentage yield.

An attempted preparation of the diiodide hydriodide by reaction of the dibromide hydrobromide with sodium iodide in acetone failed to give the desired product.

2-Methyl-3-amino-4,5-di(bromomethyl)pyridine hydrobromide. A mixture of 2.05 g. of the aminodiol monohydrochloride[7,8] (m.p. 195–197°) and 17 ml. of 8.8*M* aqueous hydrobromic acid was boiled under reflux for 15 min. On cooling the resulting clear solution, light tan crystals separated. These were collected by filtration, washed with three 15-ml. portions of water, and then with two 10-ml. portions of acetone, and dried. There was obtained 1.26 g. (34%) of pure product, m.p. 220° dec.

A sample was recrystallized for analysis from 8.8*M* hydrobromic acid (8 ml./g.), giving colorless crystals, m.p. 226° dec.

Anal. Calcd. for $C_8H_{11}Br_3N_2$: C, 25.63; H, 2.96; Br, 63.94; N, 7.47. Found: C, 25.67; H, 2.95; Br, 64.11; N, 7.57.

(9) In the previous preparation of this compound a different starting material was used. See *Chem. Abs.*, **40**, 906 (1946); **41**, 1395 (1947).

(10) (a) S. Harris *et al.*, *J. Am. Chem. Soc.*, **66**, 2088 (1944); (b) S. Harris, *J. Am. Chem. Soc.*, **62**, 3203 (1940).

(11) D. Heyl, *et al.*, *J. Am. Chem. Soc.*, **75**, 653 (1953).

(12) T. Moller, *et al.*, *Naturwiss.*, **27**, 228 (1939).

(13) H. Van Wagtendonk and J. Wibaut, *Rec. trav.*, **61**, 728 (1942).

(13a) NOTE ADDED IN PROOF: It has very recently been reported that 4-deoxypyridoxine can be prepared in excellent yield by prolonged boiling of a mixture of pyridoxine hydrochloride and excess 95% hydrazine. See R. Taborsky, *J. Org. Chem.*, **26**, 596 (1961).

2,4-Dimethyl-3-amino-5-hydroxymethylpyridine hydriodide. A 1.0-g. portion of the aminodiol in 6.5 ml. of 7.6*M* hydriodic acid was heated just to boiling, then quickly cooled, and stored at 0–5° overnight. The dark oil which had separated was stirred with a little absolute ethanol, giving a mass of almost black, gummy crystals, weight 0.59 g. A sample of this material was crystallized from absolute ethanol for analysis, giving light yellow crystals, m.p. 190–196°. The analysis indicated that instead of producing the expected diiodide hydriodide, the reaction had given a product in which one of the hydroxymethyl groups was reduced down to methyl, with liberation of free iodine in the reaction mixture.

Anal. Calcd. for $C_8H_{11}N_2I_3$: C, 18.63; H, 2.15; N, 5.43; I, 73.79. Calcd. for $C_8H_{13}N_2OI$: C, 34.29; H, 4.98; N, 9.95; I, 45.30. Found: C, 34.27; H, 4.92; N, 10.06; I, 44.90.

From the original hydriodic acid filtrate on evaporation a second crop, 0.21 g. of crude product, m.p. 165–175°, was obtained, but has not been further purified.

Preparation of 4-deoxypyridoxine hydrochloride (New method). The 3-amine (50 mg.) was dissolved in 1.0 ml. of water, and silver chloride (43 mg.) was added. The mixture was heated with stirring for 5 min., during which time the white silver chloride was partly converted to yellow silver iodide. The mixture was filtered, and the residue washed with 1.0 ml. of water. The combined aqueous filtrate was acidified with 0.2 ml. of 12*M* hydrochloric acid. To this solution at 25° was added 23 mg. of sodium nitrite (dissolved in 1.0 ml. of water). Nitrogen bubbles appeared immediately. The solution was heated to near-boiling until effervescence ceased (10–15 min.).

The solution was vacuum-distilled to dryness, and 0.5 ml. of 12*M* hydrochloric acid was added to the residue. The distillation to dryness was repeated. The residue was then extracted with 2.0 ml. of absolute ethanol, cooled and filtered. To the filtrate was added ether, with stirring, until crystals began to separate. The crystals were collected and dried, giving about 10 mg. of material melting at 255° dec. The reported[13] m.p. for 4-deoxypyridoxine hydrochloride is 257°; for 5-deoxypyridoxine hydrochloride[11] it is 143°.

The infrared spectrum of 4-deoxypyridoxine hydrochloride so prepared was found to be identical with that of an authentic sample.

2-Methyl-3-acetamido-4,5-di(acetoxymethyl)pyridine. A mixture of 1.0 g. of the aminodiol monohydrochloride,[7,8] 0.80 g. of fused sodium acetate, and 20 ml. of acetic anhydride was boiled under reflux for 20 min., and the solvent then removed by vacuum-distillation. The residue was extracted with 15 ml. of chloroform, and the extract treated with decolorizing carbon. The chloroform was removed by vacuum-distillation. The residual brown oil was stirred with 2.0 ml. of ether, giving a solid product. This was collected, again washed with a little ether, and dried, giving 0.40 g. (28%) of colorless product, m.p. 131–133°.

A sample was recrystallized for analysis from benzene (12 ml./g.), giving colorless platelets, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.12; H, 6.16; N, 9.52. Found: C, 57.30; H, 6.12; N, 9.59.

The infrared spectrum showed N-H stretching absorption at 3300 cm.$^{-1}$, and ester and amide carbonyl absorption at 1740 and 1650 cm.$^{-1}$, respectively.

2-Methyl-3-acetamido-4,5-di(hydroxymethyl)pyridine. The water-soluble triacetyl derivative (0.42 g.) was dissolved in 12.0 ml. of 0.5*M* sodium hydroxide, and the solution kept at about 20° for 2 hr. The clear solution was adjusted to *p*H 6–7 by addition of acetic acid, and the solvent then removed by vacuum-distillation. The colorless solid residue was extracted with acetone for 24 hr., using a Soxhlet extractor. On cooling the extract in the refrigerator colorless crystals separated. These were collected and dried, giving 0.10 g. of product, m.p. 185–186°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.14; H, 6.71; N, 13.32. Found: C, 56.99; H, 6.88; N, 13.32.

The filtrate was evaporated, and the residue recrystallized from ethyl acetate-alcohol (5:1), giving an additional 0.050 g., m.p. 184–186°.

A coupling test[14] for free aromatic primary amino groups was negative. Comparison of the infrared spectrum with that of the triacetyl starting material disclosed that the ester carbonyl peak had disappeared and that an O-H stretching peak was now present at 3520 cm.$^{-1}$

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF SAN FRANCISCO
SAN FRANCISCO 17, CALIF.

(14) R. Shriner, R. Fuson, and D. Curtin, *The Systematic Identification of Organic Compounds*, Wiley, New York, 4th edition, 1956, p. 127.

A New Synthesis of D-Rhamnose (6-Deoxy-D-mannose)[1]

W. WERNER ZORBACH AND CESARIO O. TIO[2]

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D-Rhamnose (6-deoxy-D-mannose) (IV), the enantiomorph of the naturally occurring L-rhamnose (6-deoxy-L-mannose) has been synthesized by Haskins, Hann, and Hudson[3] *via* the following sequence: methyl α-D-mannopyranoside → methyl 2,3,4-tri-*O*-benzoyl-6-*O*-*p*-tolylsulfonyl-α-D-mannoside → methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-α-D-mannoside → methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-mannoside → methyl 6-deoxy-α-D-mannopyranoside → D-rhamnose (IV). Their synthesis was carried out, however, prior to the advent of metal hydrides as reducing agents in organic chemistry. The ability of lithium aluminum hydride to convert primary *O*-*p*-tolylsulfonyl esters to methyl groups provided the key step in the presently described synthesis in which D-mannose was converted to D-rhamnose (IV) in four steps.

Initially, we envisaged a synthesis starting with methyl α-D-mannopyranoside. Attempts to secure a crystalline methyl 6-*O*-arylsulfonyl-α-D-mannopyranoside failed and when methyl α-D-mannopyranoside was treated in pyridine with *p*-toluenesulfonyl, *p*-nitrobenzenesulfonyl, *p*-fluorobenzenesulfonyl, and β-naphthalenesulfonyl chlorides only sirups resulted.[4] We were, however, successful when D-mannose was first converted to D-mannose dimethyl dithioacetal (I)[5] which, when treated under the usual conditions with *p*-toluenesulfonyl chloride, gave crystalline 6-*O*-*p*-tolylsulfonyl-D-man-

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(2) This paper is taken from a dissertation submitted by C. O. Tio to the Graduate School of Georgetown University in partial fulfillment of the degree of Master of Science in Chemistry.

(3) W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **68**, 628 (1946).

(4) The authors are indebted to Mr. G. D. Valiaveedan for carrying out these exploratory sulfonations.

(5) H. Zinner, *Chem. Ber.*, **84**, 780 (1951).