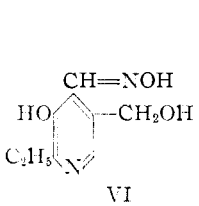
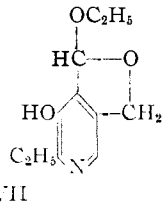
verted to the monoethyl acetal VII. These reactions are analogous to those previously described for the corresponding pyridoxal derivatives.[2,3]



VI



VII

Experimental[4]

The reactions carried out for the preparations of 2-isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine and 2-*n*-amyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine were similar to reactions previously described.[1,5] Only the physical properties of the intermediates and products are listed here.

2-Isobutyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIA) was prepared from 1-methoxy-7-methyl-2,4-heptanedione (IA) (b.p. 113° (24 mm.), $n^{29}D$ 1.4596). After one recrystallization from ethyl alcohol, the product melted at 204–205°.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.68; H, 7.25; N, 12.71.

2-Isobutyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIIA) was purified by two recrystallizations from ethyl alcohol, accompanied by decolorization with Darco; m.p. 167–168°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.62; H, 5.50; N, 15.83.

2-Isobutyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (IVA) was recrystallized three times from petroleum ether (b.p. 30–60°). It melted at 42–43°.

Anal. Calcd. for $C_{12}H_{14}N_3O_3Cl$: C, 50.80; H, 4.96; N, 14.82. Found: C, 50.82; H, 5.12; N, 15.08.

2-Isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride (VA) was recrystallized from hot water, with decolorization with Darco; m.p. 213–214°.

Anal. Calcd. for $C_{11}H_{18}NO_3Cl$: C, 53.33; H, 7.32; N, 5.66. Found: C, 53.35; H, 7.25; N, 5.90.

1-Methoxy-2,4-nonanedione (IB).—Condensation of methyl methoxyacetate with methyl *n*-amyl ketone yielded 1-methoxy-2,4-nonanedione; b.p. 138° (28 mm.), $n^{25}D$ 1.4602.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.50; H, 9.72.

2-*n*-Amyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIB) was recrystallized twice from absolute alcohol; m.p. 131–132°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.74; H, 7.64; N, 12.05.

2-*n*-Amyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIIB) was recrystallized twice from alcohol and once from dilute alcohol. It melted at 161–162°.

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 56.25; H, 5.79; N, 15.24.

2-*n*-Amyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (IVB) was recrystallized twice from petroleum ether (b.p. 30–60°); m.p. 42–43°.

Anal. Calcd. for $C_{13}H_{16}N_3O_3Cl$: C, 52.44; H, 5.42; N, 14.11. Found: C, 52.16; H, 5.00; N, 14.20.

2-*n*-Amyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride (VB) was recrystallized from alcohol containing a trace of hydrogen chloride. The product melted at 186–187°.

Anal. Calcd. for $C_{12}H_{20}NO_3Cl$: C, 55.05; H, 7.70; N, 5.35. Found: C, 54.93; H, 7.82; N, 5.47.

Oxime of 2-Ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine (VI).—2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride[1] (10.7 g.) was oxidized with manganese dioxide and sulfuric acid in a manner exactly analogous to the preparation of pyridoxal oxime.[2] The yield of the oxime of 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine was 4.8 g. (50%). After one recrystallization from water–alcohol and one from alcohol, the oxime melted at 225–226°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.22; H, 6.00; N, 14.12.

Monoethyl Acetal of 2-Ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine Hydrochloride (VII).—Conversion of 3.4 g. of the oxime of 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine (VI) to the corresponding monoethyl acetal was carried out in the manner previously described for the conversion of pyridoxal oxime.[3] The yield of the monoethyl acetal of 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine hydrochloride was 1.66 g. (39%); m.p. 137.5–138.5°. After one recrystallization from alcohol–ether containing a little hydrogen chloride and another recrystallization from alcohol containing a little hydrogen chloride, the material melted at 132–133°.

Anal. Calcd. for $C_{11}H_{16}NO_3Cl$: C, 53.77; H, 6.56; N, 5.70. Found: C, 54.00; H, 6.29; N, 5.63.

RESEARCH LABORATORIES
MERCK AND CO., INC.
RAHWAY, NEW JERSEY

(2) D. Heyl, *ibid.*, **70**, 3434 (1948).

(3) S. A. Harris, D. Heyl and K. Folkers, *ibid.*, **66**, 2088 (1944).

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

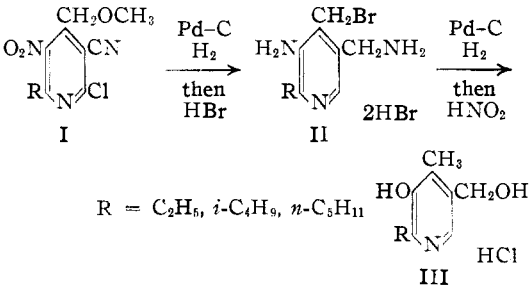
(5) S. A. Harris and K. Folkers, THIS JOURNAL, **61**, 1245, 3307 (1939).

Chemistry of Vitamin B_6. XI. Homologs of 4-Desoxypyridoxine

BY DOROTHEA HEYL, EILEEN LUZ, STANTON A. HARRIS AND KARL FOLKERS

RECEIVED APRIL 22, 1953

4-Desoxypyridoxine was shown to be a potent vitamin B_6 inhibitor.[1] Because of the biological interest in this compound, the preparation of homologs for further biological study was undertaken. Three homologs, represented by structure III, in which the methyl group in position 2 of 4-desoxypyridoxine has been replaced by ethyl, isobutyl and *n*-amyl groups, have now been prepared by synthesis through the intermediates I and II.



I II

R = C_2H_5, *i*-C_4H_9, *n*-C_5H_{11}

III

2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride and 2-isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride have also been prepared by the direct hydrogenolysis of the 2-ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride[2] and 2-isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride.[3] Hydrogenolysis of pyridoxine hydrochloride to form 4-desoxypyridoxine hydrochloride was described previously.[4]

(1) W. H. Ott, *Proc. Soc. Exp. Biol. Med.*, **61**, 125 (1946); W. W. Cravens and E. E. Snell, *ibid.*, **71**, 73 (1949).

(2) S. A. Harris and A. N. Wilson, THIS JOURNAL, **63**, 2526 (1941).

(3) D. Heyl, E. Luz, S. A. Harris and K. Folkers, *ibid.*, **75**, 4079 (1953).

(4) S. A. Harris, *ibid.*, **62**, 3293 (1940).

Experimental[5]

2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III).—2-Ethyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I, 25.6 g.) was shaken with palladium-Darco and hydrogen in a solution containing hydrochloric acid under 2–3 atmospheres of pressure until 6 moles of hydrogen had been absorbed. The reduction was finished in 21 hours. After removal of the catalyst, the solution was concentrated under reduced pressure to a thick oil. This oil was heated with 400 ml. of 40–42% hydrobromic acid, and about 250 ml. distilled at atmospheric pressure. The black color was removed with Darco. The solution, after further concentration under reduced pressure, was diluted with alcohol, which caused crystallization of 27.1 g. of crude 2-ethyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide (II); m.p. 217–220° dec. Concentration of the filtrate left an oil which was again subjected to the hydrobromic acid treatment. Another 3.8 g. of product brought the yield to 76%.

A solution of 18.0 g. of this material in 600 ml. of water was shaken with 3 g. of 5% palladium chloride on Darco catalyst under 2–3 atmospheres of hydrogen. There was almost no hydrogen uptake for about an hour; then one mole was rapidly absorbed. The catalyst was removed by filtering, and the solution, combined with the reduction product of another 12 g. of bromomethyl compound II, was concentrated under reduced pressure to about 100 ml., and then shaken with 48 g. of silver chloride for several hours. The solid material was removed by filtering. The resulting solution containing 2-ethyl-3-amino-4-methyl-5-aminomethylpyridine dihydrochloride was diluted to 450 ml. and heated to 85°. A solution of 11.2 g. of sodium nitrite in 150 ml. of water, and 15 ml. of 12 *N* hydrochloric acid were added simultaneously over a period of 20 minutes. After an additional 10 minutes of stirring at 85°, the solution contained no nitrous acid, and was decolorized with Darco and concentrated to dryness under reduced pressure.

The residue, dissolved in a minimum amount of warm water, was treated with an excess of sodium bicarbonate and extracted continuously with chloroform for two days. After removal of the chloroform under reduced pressure, the residue was dissolved in alcohol and treated with an excess of alcoholic hydrogen chloride. 2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride (III) was obtained in a yield of 5.2 g. (35%, based on 30 g. of crude 2-ethyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide); after two recrystallizations from alcohol the m.p. was 174–176°.

Anal. Calcd. for $C_9H_{14}NO_2Cl$: C, 53.07; H, 6.93; N, 6.88. Found: C, 52.81; H, 6.64; N, 7.13.

2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III) **by Hydrogenolysis of 2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine Hydrochloride.**—A mixture of 1.0 g. of 2-ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride,[2] 1 ml. of 6 *N* hydrochloric acid, 1 g. of 5% palladium on Darco catalyst and 125 ml. of water was shaken under 2–3 atmospheres of hydrogen for one hour. Approximately one mole of hydrogen was absorbed. After removal of the catalyst, the solution was concentrated to 3 ml., treated with an excess of sodium bicarbonate, and extracted continuously with chloroform for 17 hours. 2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride (0.19 g., 21%) was isolated as described in the preceding experiment; the m.p., 178–179°, was not lowered when this material was mixed with a sample prepared by the method described above.

2-Isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III).—2-Isobutyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine[3] (I, 13.4 g.) was hydrogenated in the manner described for the ethyl homolog. The reduction required 5 hours. The gummy residue, after concentration of the filtrate, was treated with 200 ml. of 40–42% hydrobromic acid. After removal of one third of the solution by distillation at atmospheric pressure, the dark color was removed by treatment with Darco, and the resulting solution concentrated under reduced pressure to 25 ml. Crystalline 2-isobutyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide (II), m.p. 211–213° dec., was obtained in a yield of 6.73 g. The yield was increased to 14.3 g. (69%) after further concentration of the filtrate.

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

A mixture of 6.7 g. of this material, 1.5 g. of 10% palladium on Darco and 125 ml. of water was shaken with hydrogen under 2–3 atmospheres of pressure. One mole of hydrogen was consumed in several minutes. After removal of the catalyst, the solution was concentrated to dryness under reduced pressure. The white, crystalline residue was slurried with alcohol and collected on a filter. Two fractions, totaling 4.8 g., of 2-isobutyl-3-amino-4-methyl-5-aminomethylpyridine dihydrobromide were obtained. A solution of this material in 78 ml. of water was heated to 85° and treated simultaneously with 5.2 ml. of 6 *N* hydrochloric acid, and 1.95 g. of sodium nitrite dissolved in 26 ml. of water. The additions required 10 minutes and were followed by 10 minutes of stirring at 85°. After decolorization with Darco, the solution was concentrated to dryness under reduced pressure. The residue, dissolved in a small amount of water, was treated with an excess of sodium bicarbonate and extracted continuously with chloroform for 19 hours. The product, 2-isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride, was isolated and purified as described above for the ethyl homolog; yield 1.00 g. (28%, based on 6.7 g. of 2-isobutyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide); m.p. 163–165°.

Anal. Calcd. for $C_{11}H_{18}NO_2Cl$: C, 57.01; H, 7.83; N, 6.05. Found: C, 56.85; H, 7.79; N, 6.13.

2-Isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride by Hydrogenolysis of 2-Isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine Hydrochloride.—The hydrogenolysis was carried out on 3.0 g. of material exactly as described for the ethyl homolog, with the exception that the mixture was shaken with hydrogen for 2.5 hours. 2-Isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride, m.p. 160–162°, was obtained in a yield of 0.77 g. (27%) after isolation as described for the ethyl homolog.

2-*n*-Amyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III).—2-*n*-Amyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I, 29.8 g.) was hydrogenated and heated with hydrobromic acid as described for the ethyl homolog. 2-*n*-Amyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide (II), m.p. 215–218°, was obtained in a yield of 5.0 g. Concentration of the filtrate and further treatment with hydrobromic acid yielded another 11.4 g. raising the yield to 37%.

This material (5.0 g.) was subjected to hydrogenation and diazotization as described for the ethyl homolog, and the product was isolated in the same manner. 2-*n*-Amyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride was obtained in a yield of 1.46 g. (53%, based on 5.0 g. of 2-*n*-amyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide). After one recrystallization from alcohol, the material had a m.p. of 125.0–125.5°.

Anal. Calcd. for $C_{12}H_{20}NO_2Cl$: C, 58.64; H, 8.20; N, 5.70. Found: C, 58.72; H, 8.13; N, 5.95.

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, NEW JERSEY

Chloro-substituted Alkenyl Dithiocarbamates

BY MARION W. HARMAN AND JOHN J. D'AMICO

RECEIVED APRIL 13, 1953

Although a number of alkyl esters of substituted dithiocarbamic acids have been prepared, no reference to the preparation of chloro-substituted alkenyl dithiocarbamates has been found.[1–7] The purpose of this investigation was the synthesis of compounds of this type.

The compounds were prepared by treating either sodium dimethyldithiocarbamate, sodium diethyl-

(1) R. Conrad and F. Salomon, *J. prakt. Chem.*, **10**, 28 (1874).
(2) S. M. Delepine, *Bull. soc. chim. France*, **27**, 588 (1902).
(3) M. T. Bogert, THIS JOURNAL, **25**, 290 (1903).
(4) J. V. Braun, *Ber.*, **56**, 1573 (1923).
(5) W. H. Davies and W. A. Sexton, *Biochem. J.*, **40**, 381 (1946).
(6) P. Briesley, *Florists Exchange*, **109**, 13 (1947).
(7) M. W. Harman, U. S. Patent 2,413,917.