in vacuo to give a white, crystalline residue, which was suspended in boiling ethanol (100 ml.) and water added dropwise to the first appearance of turbidity. Acetone (100 ml.) was added and the solution allowed to stand for 72 hr. in a refrigerator. The fine, white needles that crystallized were collected, washed with acetone, and dried; yield, 3.6 g. (80%), m.p. 267–269° dec.

Anal. Calcd. for $C_8H_{16}N_2O_2 \cdot 2H_2O$: C, 47.51; H, 6.98; N, 13.86. Found: C, 47.33; H, 6.80; N, 13.74.

The **hydrochloride** salt of the amino acid was formed in ethanolic hydrogen chloride and was recrystallized as described for the free acid, m.p. 282–283° dec.

Anal. Calcd. for $C_8H_{16}N_2O_2 \cdot HCl \cdot 0.5H_2O$: C, 45.18; H, 5.77; N, 13.23; Cl, 16.74. Found: C, 45.08; H, 5.94; N, 13.01; Cl, 16.85.

Ethyl 5-Amino-4,6-dimethylnicotinate (IXb).—A solution of 5-amino-4,6-dimethylnicotinic acid hydrochloride (5 g.) and ethanol saturated with hydrogen chloride (50 ml.) was refluxed for 4 hr. and then allowed to stand overnight. The solvent was removed *in vacuo* before the residue was treated with a sodium bicarbonate solution. The copious, white precipitate thus produced was collected on a filter, washed with water, and dried at 80° before being recrystallized from methanol (25 ml.) and water (50 ml.). Fine, white crystals deposited upon standing; yield, 2.4 g. (59%), m.p. 122–124°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.26; N, 14.43. Found: C, 61.65; H, 7.06; N, 14.41.

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Vitamin B_6 Analogs. III. Some 5-Aminomethyl and 5-Thiomethyl Derivatives of Pyridoxine and 4-Desoxypyridoxine[1]

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A number of analogs of pyridoxine and 4-desoxypyridoxine in which the hydroxyl of the 5-hydroxymethyl group is replaced by substituted amino and thio groups have been prepared and evaluated for B_6-antagonism and anticancer activity.

5-Bromomethyl-2,4-dimethyl-3-pyridinol (I) hydrobromide, obtained from 4-desoxypyridoxine (DOP)[2] by the procedure of Sakuragi and Kummerow,[3] was treated with 2-mercaptoethanol in ethanol containing a stoichiometric amount of sodium hydroxide. The resultant 5-[(2-hydroxyethylthio)methyl]-2,4-dimethyl-3-pyridinol (IIa), when treated with thionyl chloride in pyridine, gave no identifiable product. Chlorination in excess thionyl chloride, however, gave moderate yields of 5-[(2-chloroethylthio)methyl]-2,4-dimethyl-3-pyridinol (IIIa) hydrochloride.

2-Mercapto-1-propanol, conveniently prepared by the lithium aluminum hydride reduction of thiolactic acid, and *p*-chlorobenzenethiol reacted in similar fashion to yield 5-[(1-hydroxy-2-propylthio)methyl]-2,4-dimethyl-3-pyridinol (IIb) and 5-[(4-chlorophenylthio)-methyl]-2,4-dimethyl-3-pyridinol (IIc). Chlorination of IIb gave only poor yields of 5-[(1-chloro-2-propylthio)methyl]-2,4-dimethyl-3-pyridinol (IIIb) hydrochloride.

Using the general procedure of Kolesnikov and Mikhailovskaya,[4] 5-bromomethyl-2,4-dimethyl-3-pyridinol (I) hydrobromide was treated with a stoichiometric amount of hexamethylenimine in benzene to yield 5-(hexahydro-1*H*-azepin-1-ylmethyl)-2,4-dimethyl-3-pyridinol (IId).

When ethylenimine was used in place of hexamethylenimine under similar conditions, a product was obtained which is thought to be 5-(1-aziridinylmethyl)-2,4-dimethyl-3-pyridinol (IIe). Some decomposition took place upon removal of the solvent, however, and a test for presence of the aziridinyl ring[5] was negative.

In preparing 5-thiomethyl derivatives of pyridoxine (VI) it was first necessary to block the 4-hydroxymethyl group. After several attempts to duplicate Cohen and Hughes' procedure for the preparation of the cyclic ketal (IV)[6] failed, anhydrous hydrogen chloride was substituted for concentrated sulfuric acid and the time of reaction shortened. This modification[7] produced the desired cyclic ketal (IV) in much higher yield and eliminated the somewhat complex work-up that is necessary in the old procedure.

Isopropylidene pyridoxine (IV) hydrochloride was chlorinated in thionyl chloride to yield 5-chloromethyl-2,2,8-trimethyl-4*H*-*m*-dioxino-[4,5-*c*]pyridine (V) hydrochloride,[8,9] which was subsequently condensed with 2-mercaptoethanol in the manner already described to yield 5-[(2-hydroxyethylthio)methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine (VIa). Chlorination of VIa with thionyl chloride gave 5-[(2-chloroethylthio)-methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine (VIb) hydrochloride. Mild acid hydrolysis of the hydroxy compound (VIa) gave the expected derivative: 5-[(2-hydroxyethylthio)methyl]-3-hydroxy-2-methyl-4-pyridinemethanol (IXa) hydrochloride, but when the

(1) This work was supported by funds from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) R. G. Taborsky, *J. Org. Chem.*, **26**, 596 (1961).

(3) T. Sakuragi and F. A. Kummerow, *Arch. Biochem. Biophys.*, **71**, 303 (1957).

(4) G. S. Kolesnikov and N. N. Mikhailovskaya, *J. Gen. Chem. USSR*, **27**, 517 (1957).

(5) J. Epstein, R. W. Rosenthal, and R. J. Ess, *Anal. Chem.*, **27**, 1435 (1955).

(6) A. Cohen and E. C. Hughes, *J. Chem. Soc.*, 4384 (1952); J. Baddiley and A. P. Mathias, *ibid.*, 2583 (1952).

(7) A similar procedure using anhydrous hydrogen chloride was published after much of this work was completed: W. Korytnyk and W. Wiedeman, *ibid.*, 2531 (1962).

(8) L. A. Petrova and N. N. Beltsova, *Zh. Obshch. Khim.*, **32**, 274 (1961).

(9) V. Schmidt and G. Gieselmann, *Ann. Chem.*, **657**, 162 (1962).

chloro compound (VIb) was hydrolyzed under the same conditions, the chlorine atom was unexpectedly replaced by a hydroxyl group to yield also IXa. This degree of lability had not been experienced when working with similar compounds such as IIIa and IIIb. Further attempts were made to obtain 5-[(2-chloroethylthio)methyl]-3-hydroxy-2-methyl-4-pyridinemethanol (IXb) under different conditions; the pH of the system was varied from neutrality to highly concentrated acid; all attempts, however, produced only the hydroxy compound (IXa).

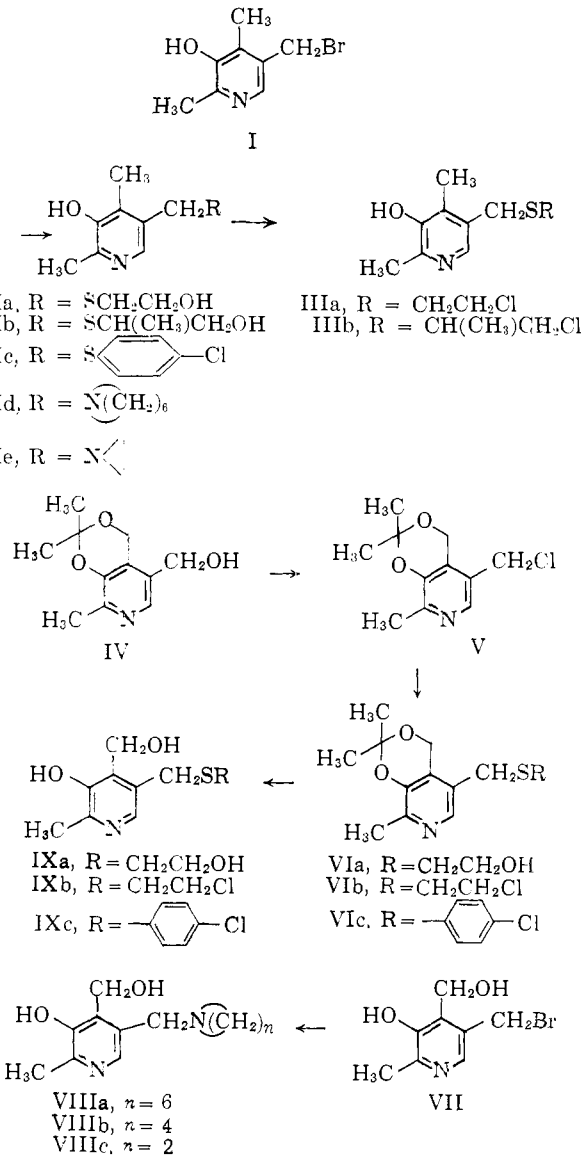
5-[(4-Chlorophenylthio)methyl-2,2,8-trimethyl-4*H*-*m*-dioxino-[4,5-*c*]pyridine (VIc) was prepared *via* the basic condensation of *p*-chlorobenzenethiol with 5-chloromethyl-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]-pyridine (V) hydrochloride; mild acid hydrolysis of VIc gave the pyridoxine analog (IXc) hydrochloride.

The 5-aminomethyl derivatives of pyridoxine (VIII) were obtained by treating the appropriate imine with 5-bromomethyl-3-hydroxy-2-methyl-4-pyridinemethanol (VII) hydrobromide, obtained by preferential hydrolysis[8] of 4,5-bis(bromomethyl)-2-methyl-3-pyridinol hydrobromide.[10] In this manner, 5-(hexahydro-1*H*-azepin-1-ylmethyl)-3-hydroxy-2-methyl-4-pyridinemethanol (VIIIa) and 3-hydroxy-2-methyl-5-(1-pyrrolidinylmethyl)-4-pyridinemethanol (VIIIb) hydrobromide were obtained by using hexamethylenimine and pyrrolidine.

Condensing ethylenimine with VII produced a yellow oil thought to be 5-(1-aziridinylmethyl)-3-hydroxy-2-methyl-4-pyridinemethanol (VIIIc) which, like its 4-desoxypyridoxine analog (IIe), underwent partial decomposition during work-up to yield a product showing a negative aziridine test.

Biological Results.—The target compounds IIa–d, IIIa and b, IXa and c were all evaluated in the three-tumor screen of CCNSC in the usual manner.[11] No significant activity was observed with any of these compounds.

These compounds were also evaluated by a standard procedure[12] for their ability to either antagonize or replace the B_6 vitamins in cultures of *Saccharomyces carlsbergensis*. Compounds IIa, IIc, IIIa, and IXa, all derivatives of "5-thio-4-desoxypyridoxine" or "5-thiopyridoxine," exhibited some anti-B_6 activity. The most potent of the group was 5-[(2-chloroethylthio)methyl]-2,4-dimethyl-3-pyridinol (IIIa) hydrochloride, which showed about 70% of the activity of 4-desoxypyridoxine (DOP) in this test system. Since IIIa failed to inhibit S180 in mice on a complete diet, but showed the same order of anti-B_6 activity as DOP in the bacterial system, it was evaluated, along with the latter compound, for its effectiveness against S180 in mice maintained on a B_6-deficient diet.[13] No tumor inhibition by IIIa under these conditions was observed although DOP in the same test showed its usual effectiveness.[13]



Experimental

All melting points were determined in an open capillary and are corrected.

5-[(2-Hydroxyethylthio)methyl]-2,4-dimethyl-3-pyridinol (IIa).—Sodium hydroxide (3.52 g. of 97% reagent; 0.084 mole) in ethanol (100 ml.) and 2-mercaptoethanol (3.40 g., 0.042 mole) were mixed and heated to gentle reflux. To this refluxing solution was added dropwise, over the period of 1 hr., a solution of 5-bromomethyl-2,4-dimethyl-3-pyridinol hydrobromide (12.93 g., 0.042 mole) in ethanol (100 ml.). Heating was continued for 10 min. after completion of addition before allowing the system to cool to room temperature with stirring. The reaction mixture was refrigerated at 0° overnight; the sodium bromide was collected on a filter and the filtrate evaporated *in vacuo*. The residual oil solidified upon cooling and was recrystallized from benzene containing just enough ethanol to effect solution at the boiling point. A small amount of sodium bromide was filtered before the hot solution was allowed to cool; yield, 4.1 g. (46%), m.p. 140–142° dec.

Anal. Calcd. for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.0. Found: C, 56.42; H, 7.20; N, 6.30; S, 14.9.

The hydrochloride formed in methanolic hydrogen chloride: m.p. 180–182°.

Anal. Calcd. for $C_{10}H_{15}NO_2S \cdot HCl$: C, 48.08; H, 6.46; Cl, 14.2. Found: C, 47.75; H, 6.53; Cl, 14.5.

5-[(2-Chloroethylthio)methyl]-2,4-dimethyl-3-pyridinol (IIIa) Hydrochloride.—Thionyl chloride (35 ml.) was added to 5-[(2-hydroxyethylthio)methyl]-2,4-dimethyl-3-pyridinol (6.0 g., 0.028 mole). After the initial exothermic reaction had subsided, the solution was gently refluxed for 5 min. under anhydrous conditions. The excess thionyl chloride was removed *in vacuo* and

(10) G. E. McCasland, L. K. Gottwald, and A. Furst, *J. Org. Chem.*, **26**, 3542 (1961).

(11) *Cancer Chemotherapy Rept.*, **1**, 42 (1959).

(12) E. E. Snell and J. C. Rabinowitz, *Anal. Chem.*, **19**, 277 (1947).

(13) H. E. Skipper, J. R. Thomson, and F. M. Schabel Jr., *Cancer Chemotherapy Rept.*, **29**, 63 (1963).

the residual dark oil taken up in ethanol, treated with charcoal, and filtered. The filtrate was evaporated to half volume, then allowed to stand at 0° for several hr. The initial, dark-colored crystalline precipitate was recrystallized from absolute ethanol to yield a nearly colorless product which was collected on a filter and dried for 3 hr. at 80°, yield 3.7 g. (57%), m.p. 150.5–152.5°.

Anal. Calcd. for $C_6H_{14}ClNOS \cdot HCl$: C, 44.78; H, 5.64; Cl, 26.4. Found: C, 44.73; H, 5.70; Cl, 26.3.

2-Mercapto-1-propanol,[14]—A solution of thiolactic acid (50 g.) in ether (250 ml.) was added dropwise to a stirred solution of lithium aluminum hydride (18 g.) in ether (500 ml.). Stirring was continued for 1 hr., then ethyl acetate in ether was added to the mixture to destroy any excess lithium aluminum hydride. Hydrochloric acid (500 ml., 10% solution) was added and the organic layer was separated. The aqueous layer was extracted with two 200-ml. portions of ether and these extracts were added to the original ether layer. After drying over sodium sulfate the solvent was removed *in vacuo* before the residue distilled to give 2-mercapto-1-propanol, yield 22 g. (52%), b.p. 57–59° (12 mm.) [lit. b.p. 60–62° (12 mm.)].

5-[(1-Hydroxy-2-propylthio)methyl]-2,4-dimethyl-3-pyridinol (IIb).—Sodium hydroxide (5.4 g. of 97% reagent, 0.130 mole) in absolute ethanol (100 ml.) and 2-mercapto-1-propanol (6.0 g., 0.065 mole) were mixed and heated to gentle reflux. To the refluxing solution was added dropwise, over the period of 1 hr., a solution of 5-bromomethyl-2,4-dimethyl-3-pyridinol hydrobromide (20.0 g., 0.065 mole) in absolute ethanol (100 ml.). After completion of addition heating was continued for 10 min. and the mixture was allowed to cool to room temperature with stirring. The sodium bromide was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was taken up in absolute ethanol (40 ml.) and the remaining sodium bromide filtered before the filtrate was again evaporated to dryness *in vacuo*. The residue was slurried vigorously with ethyl acetate until finely divided, then collected by filtration and dried at 80°, yield 14.5 g. (95%), m.p. 143–146°.

Anal. Calcd. for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16. Found: C, 58.18; H, 7.52; N, 5.93.

5-[(1-Chloro-2-propylthio)]-2,4-dimethyl-3-pyridinol (IIIb) Hydrochloride.—5-[(1-Hydroxy-2-propylthio)methyl]-2,4-dimethyl-3-pyridinol (1.0 g.) was refluxed gently with excess thionyl chloride (15 ml.) for 5 min. under anhydrous conditions; the solution was evaporated to dryness *in vacuo;* the residue was washed with benzene before it was dissolved in absolute ethanol, treated with charcoal, filtered, and evaporated to dryness. The yellow oil slowly crystallized upon standing several days. The crystals were washed with a 1:1 mixture of ethanol–ether and dried at 80° for 1 hr. before being recrystallized from ethanol–ether, yield 0.6 g. (48%), m.p. 128.5–131.5°.

Anal. Calcd. for $C_{11}H_{16}ClNOS \cdot HCl$: C, 46.81; H, 6.08; N, 4.96. Found: C, 46.82; H, 5.93; N, 5.00.

5-[(4-Chlorophenylthio)methyl]-2,4-dimethyl-3-pyridinol (IIc).—Sodium hydroxide (2.8 g. of 97% reagent, 0.068 mole) in ethanol (50 ml.) and *p*-chlorobenzenethiol (4.85 g., 0.034 mole) were mixed and added dropwise, over the period of 1 hr., to a refluxing solution of 5-bromomethyl-2,4-dimethyl-3-pyridinol hydrobromide (10.0 g., 0.034 mole) in ethanol (70 ml.). After completion of addition refluxing was continued for 10 min. The system was cooled to room temperature with stirring and the sodium bromide removed by filtration. The filtrate was decolorized with charcoal, heated to boiling, and treated with water to the point of persistent cloudiness. Upon cooling, *off*-white platelets were deposited, yield 6.0 g. (63%), m.p. 164.5–167.5°.

Anal. Calcd. for $C_{14}H_{14}ClNOS$: C, 60.08; H, 5.09; N, 5.00. Found: C, 59.85; H, 4.98; N, 4.49.

The hydrochloride was prepared by dissolving the free base in warm alcoholic hydrogen chloride and adding absolute ether. Upon standing at 0° the hydrochloride salt crystallized as white granules, m.p. 199.5–202°.

Anal. Calcd. for $C_{14}H_{14}ClNOS \cdot HCl$: C, 53.17; H, 4.78; Cl, 22.4. Found: C, 52.92; H, 4.84; Cl, 22.4.

5-(Hexahydro-1*H*-azepin-1-ylmethyl)-2,4-dimethyl-3-pyridinol (IId).—5-Bromomethyl-2,4-dimethyl-3-pyridinol hydrobromide (10.0 g., 0.033 mole) was added with stirring to a solution of hexamethyleneimine (9.7 g., 0.098 mole) in benzene (100 ml.). After the initial exothermic reaction subsided, stirring was continued until the system spontaneously cooled to room temperature and for 1 hr. thereafter. The hexamethyleneimine hydrobromide was collected on a filter and washed thoroughly with benzene; these washings were added to the original filtrate. All benzene was removed *in vacuo* over a water bath to leave a yellow, oily residue that crystallized upon cooling. Attempts to recrystallize the product from benzene, cyclohexane, hexane, and various combinations thereof failed. The oil was suspended in vigorously stirred cyclohexane until solidification took place. The finely divided white solid was collected on a filter and dried *in vacuo* over phosphorus pentoxide, yield 7.5 g. (100%), m.p. 117–119.5°.

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 71.75; H, 9.47; N, 11.95. Found: C, 71.60; H, 9.43; N, 11.82.

Isopropylidene Pyridoxine Hydrochloride: 2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine-5-methanol (IV) Hydrochloride.—Pyridoxine hydrochloride (20.0 g.) was suspended in anhydrous acetone (400 ml.) with vigorous stirring while anhydrous hydrogen chloride was bubbled into the mixture. When the acetone became saturated, introduction of the gas was discontinued, the flask was stoppered, and the reaction mixture stirred for an additional 5.5 hr. At the end of this time the isopropylidene pyridoxine hydrochloride was collected on a filter, washed with acetone, and dried *in vacuo* over phosphorus pentoxide. A ferric chloride color test for β-hydroxypyridines was negative, and a mixture melting point with an authentic sample of pyridoxine hydrochloride showed depression. The product was recrystallized from ethanol–ether, yield 19.9 g. (80%), m.p. 216–217° dec.; m.m.p. with pyridoxine hydrochloride, 193.5–194.5° dec.

Anal. Calcd. for $C_{9}H_{13}NO_3 \cdot HCl$: C, 53.77; H, 6.57; N, 5.70. Found: C, 54.06; H, 6.60; N, 5.74.

The free base was liberated by dissolving the salt in an aqueous solution of sodium bicarbonate, m.p. 110–112°.

5-[(2-Hydroxyethylthio)methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine (VIa).—Sodium hydroxide (2.03 g. of 97% reagent, 0.0492 mole) in ethanol (45 ml.) and 2-mercaptoethanol (1.92 g., 0.0246 mole) were mixed and heated to gentle reflux. To the refluxing solution was added dropwise, over the period of 1 hr., a solution of 5-chloromethyl-2,2,8-trimethyl-4*H*-*m*-dioxino-[4,5-*c*]pyridine hydrochloride (6.5 g., 0.0246 mole) in absolute ethanol (50 ml.). Refluxing was continued for 10 min. after completion of addition before allowing the mixture to cool to room temperature with stirring. The sodium chloride was removed by filtration, and the filtrate evaporated to dryness *in vacuo*. The oily residue was taken up in absolute ethanol, the remaining sodium chloride filtered, and the ethanolic solution evaporated almost to dryness, leaving pink crystals that were collected on a filter, washed with ether, and dried on the filter. The product gave a negative ferric chloride test, yield 5.0 g. (75%), m.p. 101–103.5°.

Anal. Calcd. for $C_{13}H_{19}NO_3S$: C, 57.96; H, 7.11; N, 5.20. Found: C, 58.21; H, 7.24; N, 5.29.

5-[(2-Chloroethylthio)methyl]-2,2,8-trimethyl-4-*m*-dioxino-[4,5-*c*]pyridine (VIb) Hydrochloride.—5-[(2-Hydroxyethylthio)-methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine (2.5 g.) was refluxed gently with excess thionyl chloride (10 ml.) for 20 min. under anhydrous conditions. At the end of this time, the excess thionyl chloride was removed *in vacuo*. The solid residue was slurried with anhydrous benzene (50 ml.) until finely divided, collected on a filter, and washed with benzene before recrystallizing from absolute ethanol. The product gave a negative ferric chloride test, yield 2.1 g. (70%), m.p. 179–182°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2S \cdot HCl$: C, 48.16; H, 5.91; N, 4.32; Cl, 21.9. Found: C, 47.64; H, 5.94; N, 4.22; Cl, 21.6.

5-[(4-Chlorophenylthio)methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino-[4,5-*c*]pyridine (VIc).—Sodium hydroxide (2.4 g. of 97% reagent, 0.0568 mole) in absolute ethanol (65 ml.) and *p*-chlorobenzenethiol (4.1 g., 0.0284 mole) were mixed and heated to gentle reflux. To the refluxing solution was added dropwise, over the period of 1 hr., a solution of 5-chloromethyl-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine hydrochloride (7.5 g., 0.0284 mole) in absolute ethanol (50 ml.). Refluxing was continued for 10 min. after completion of addition, and stirring was continued until the mixture had cooled to room temperature. The sodium chloride was removed by filtration and the filtrate decolorized with charcoal. After removal of the charcoal, the clear solution was heated to boiling and treated with water to the point of persistent cloudiness before being allowed to stand at 0° overnight. The product was collected on a filter, washed with water, and dried *in vacuo* over phosphorus pentoxide. The faintly yellow crystals

(14) W. Davies and W. E. Savige, *J. Chem. Soc.*, 317 (1950).

gave a negative ferric chloride test, yield 7.1 g. (75%), m.p. 91–94°.

Anal. Calcd. for $C_{17}H_{18}ClNO_2S$: C, 60.78; H, 5.40; N, 4.17; Cl, 10.6. Found: C, 60.67; H, 5.44; N, 3.90; Cl, 10.5.

5-(Hexahydro-1*H*-azepin-1-ylmethyl)-3-hydroxy-2-methyl-4-pyridinemethanol (VIIIa).—5-Bromomethyl-3-hydroxy-2-methyl-4-pyridinemethanol hydrobromide (5.0 g., 0.0160 mole) was added with stirring to a solution of hexamethylenimine (4.75 g., 0.0479 mole) in benzene (50 ml.). After the initial exothermic reaction had subsided, stirring was continued until the mixture had cooled to room temperature and for 2 hr. thereafter. The hexamethylenimine hydrobromide was removed by filtration and washed with benzene. The benzene washings were added to the original filtrate, and the clear yellow solution was evaporated to dryness *in vacuo*. The yellow, oily residue crystallized upon cooling at 0° for several hours. The crystals were slurried with cyclohexane until finely divided, collected on a filter, and dried over phosphorus pentoxide, yield 4.0 g. (100%), m.p. 128.5–130.5°.

Anal. Calcd. for $C_{14}H_{22}N_2O_2 \cdot 0.25H_2O$: C, 65.98; H, 8.90; N, 10.99. Found: C, 65.86; H, 8.86; N, 10.91.

An anhydrous sample of this material could not be obtained.

3-Hydroxy-2-methyl-5-(1-pyrrolidinylmethyl)-4-pyridinemethanol (VIIIb) Hydrobromide.—Finely ground 5-bromomethyl-3-hydroxy-2-methyl-4-pyridinemethanol hydrobromide (5.0 g., 0.016 mole) was added to a solution of pyrrolidine (3.45 g., 0.048 mole) in benzene (50 ml.) with vigorous stirring. Stirring was continued for 1 hr. before collecting the precipitate on a filter and washing it with benzene. The washings were combined with the filtrate and the clear benzene solution evaporated to dryness at room temperature. The residual oil crystallized upon standing at 0° overnight, was collected, washed with ether, and dried over phosphorus pentoxide, yield 2.6 g. (54%), m.p. 200–203° dec.

Anal. Calcd. for $C_{12}H_{18}N_2O_2 \cdot HBr$: C, 47.53; H, 6.32; N, 9.28. Found: C, 47.47; H, 6.9; N, 9.17.

5-[2-Hydroxyethylthio)methyl]-3-hydroxy-2-methyl-4-pyridinemethanol (IXa) Hydrochloride. A.—5-[(2-Hydroxyethylthio)methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine (1.0 g.) was dissolved in 5% hydrochloric acid and allowed to stand overnight at room temperature before evaporating to dryness *in vacuo*. The product, after 2 recrystallizations from ethanol–ether, gave a positive ferric chloride test, was collected on a filter, washed with ether, and dried over phosphorus pentoxide, yield 0.9 g. (90%), m.p. 146–148°.

Anal. Calcd. for $C_{10}H_{15}NO_3S \cdot HCl$: C, 45.18; H, 6.07; N, 5.27. Found: C, 45.05; H, 6.14; N, 5.09.

B.—5-[(2-Chloroethylthio)methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino-[4,5-*c*]pyridine hydrochloride (2.0 g.) was mixed with 5% hydrochloric acid, allowed to stand at room temperature overnight, then refluxed for 10 min. before removing the solvent *in vacuo*. The residue was recrystallized twice from absolute ethanol–ether to yield white crystals giving a positive ferric chloride test; yield, 0.9 g. (52%); m.p. 146–148°, mixture melting point with an authentic sample of 5-[(2-hydroxyethylthio)-methyl]-3-hydroxy-2-methyl-4-pyridinemethanol hydrochloride prepared as before, 146–148°.

Anal. Calcd. for $C_{10}H_{15}NO_3S \cdot HCl$: C, 45.18; H, 6.07; N, 5.27. Found: C, 45.14; H, 6.28; N, 5.23.

5-[(4-Chlorophenylthio)methyl]-3-hydroxy-2-methyl-4-pyridine Methanol (IXc) Hydrochloride.—5-[(4-Chlorophenylthio)-methyl]-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine (4.0 g.) was dissolved in warm 5% hydrochloric acid and allowed to stand at 0° for several hours. The product, which gave a positive ferric chloride test, was collected on a filter, washed, and dried over phosphorus pentoxide, yield 3.2 g. (81%), m.p. 153–155.5°.

Anal. Calcd. for $C_{14}H_{14}ClNO_2S \cdot HCl$: C, 50.60; H, 4.55; N, 4.22; Cl, 21.3. Found: C, 50.49; H, 4.85; N, 3.98; Cl, 21.3.

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