[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

α-Oxygenated Pyridines. IV. The Synthesis of an Isomer of Pyridoxamine[1,2]

BY RAYMOND P. MARIELLA[3] AND ELIZABETH P. BELCHER[4]

RECEIVED FEBRUARY 23, 1952

3-Aminomethyl-4-hydroxymethyl-6-methyl-2-pyridol, an α-oxygenated isomer of pyridoxamine, was prepared but this showed no vitamin B_6 activity. Attempts to prepare a similar isomer of pyridoxin, either from this isomeric pyridoxamine or by reduction of related compounds, were unsuccessful.

As part of a program to synthesize α-oxygenated isomers of compounds possessing vitamin B_6 or anti-vitamin B_6 activity,[5] an isomer (IX) of pyridoxamine was prepared, but attempts to prepare a similar isomer (XI) of pyridoxin were unsuccessful.

The starting pyridone, 3-cyano-4-methoxymethyl-6-methyl-2(1)-pyridone (I) (Fig. 1), was prepared from methoxyacetylacetone[6-8] and cyanoacetamide.

The transformation of I to II was successfully accomplished by either phosphorus pentachloride alone[9] or preferentially using chlorobenzene as a solvent.[10]

The hydrogenation of II, using palladium chloride as a catalyst in alcoholic hydrogen chloride solution did not give the desired product (3-aminomethyl-4-methoxymethyl-6-methylpyridine dihydrochloride); diazotization and ether cleavage of this would have given 3-desoxypyridoxin. The identity of the isolated reduced product was shown to be III, and was further proved by conversion to IV.[11] Apparently, under the reducing conditions employed, hydrogenolysis occurred in both the α- and γ-positions, and hydrogenation resulted in the β-position.

The conversion of II to V was accomplished by use of anhydrous sodium methoxide. In one experiment, when wet methanol was inadvertently used, the amide VI was isolated.

The reduction of V in the presence of strong mineral acid yielded I exclusively, indicating preferential hydrolytic ether cleavage and formation of a cyanopyridone which resisted hydrogenation under these conditions.

Since the α-ether (V) was stable in acetic acid, the reduction proceeded smoothly in this solvent

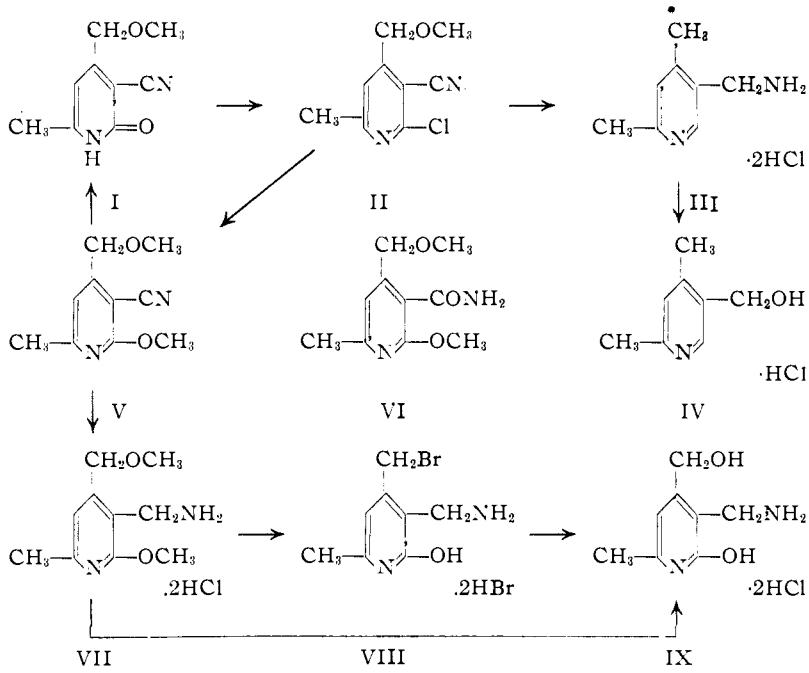

Fig. 1.

to yield VII. The conversion of VII to IX was accomplished either by heating with dilute mineral acid in a sealed tube or by conversion of VII first to VIII and then to IX.

The diazotization of either VII or IX, when tried under a variety of conditions was unsuccessful. Similar results on analogous compounds have been reported.[12,13]

Since this route to an α-oxygenated isomer (XI) of pyridoxin failed, another approach was tried.

The lactone (X) is easily prepared from the starting pyridone (I).[6,7] This lactone grouping is very stable. The reduction of either X or XII to XI under a variety of conditions and using different catalysts was uniformly unsuccessful. It was hoped that if the ester of the acid (XII) could be formed, the reduction of such a compound would yield XI.

Alcohol and mineral acid converted XII back to the lactone (X). The treatment of XII with diazo-

(1) Presented in part before the Organic Section of the American Chemical Society, Chicago Meeting, September, 1950.

(2) Taken in part from the Ph.D. thesis of E. P. Belcher.

(3) Department of Chemistry, Loyola University, Chicago, Illinois.

(4) Eli Lilly and Company Fellow, 1949–1951.

(5) For the preceding paper see R. P. Mariella and E. P. Belcher, THIS JOURNAL, **74**, 1916 (1952).

(6) W. F. Bruce and H. W. Coover, Jr., *ibid.*, **66**, 2092 (1944).

(7) W. Wenner and J. T. Plati, *J. Org. Chem.*, **11**, 751 (1946).

(8) It was found that the conversion of chloroacetic acid to methyl chloroacetate and then to methyl methoxyacetate gave an over-all better yield than the conversion of chloroacetic acid to methoxyacetic acid and then to methyl methoxyacetate. This is in contrast to the results in preparing ethyl ethoxyacetate ("Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 260). The methyl methoxyacetate was readily condensed with acetone to yield methoxyacetylacetone.

(9) S. A. Harris, E. T. Stiller and K. Folkers, THIS JOURNAL, **61**, 1242 (1939).

(10) A. Ichiba and S. Emoto, *J. Sci. Papers Inst. Phys. Chem. Res. (Tokyo)*, **39**, 131 (1941).

(11) R. P. Mariella and J. L. Leech, THIS JOURNAL, **71**, 331 (1949).

(12) R. P. Mariella and E. P. Belcher, *ibid.*, **73**, 2616 (1951).

(13) R. P. Mariella and A. Havlik, *ibid.*, **74**, 1915 (1952).

methane yielded high-melting (265°) (XV) and low-melting (165°) (XIV) isomers; both had the same analysis. The structure XV was assigned to the higher melting isomer because of its insolubility in ether. XIV and XV were invariably formed in about a 4:1 ratio.

An attempt was made to reduce lactone formation tendency by forming an ester in the 4-position and XIII was formed from XII. Treatment of XIII with diazomethane, however, yielded only XIV and XV.

The reductions of XIV, XV and XIII using $LiAlH_4$ were not successful.

Compounds V, VI, VII, IX, X, XII, XIV and XV were found to have no B_6 or anti-B_6 activity, when tested against *Neurospora sitophila*.[14]

Acknowledgment.—We are indebted to the Graduate School of Northwestern University for a Grant in support of some of this work.

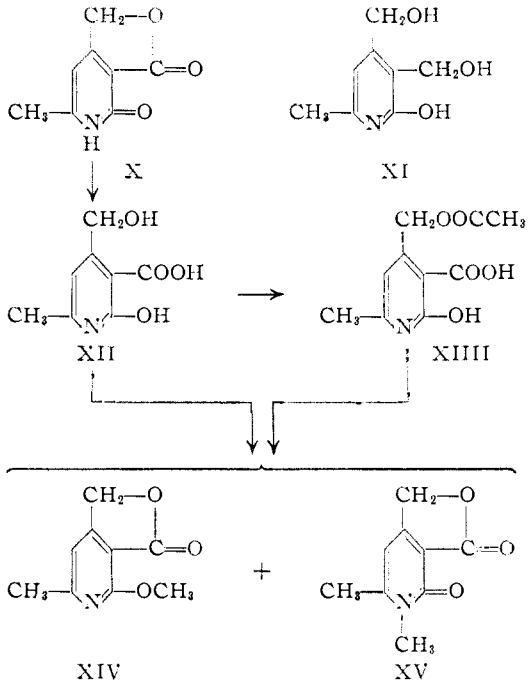

Fig. 2.

Experimental[15]

Methyl Methoxyacetate. Method A.—A solution of 374 g. of chloroacetic acid in 200 ml. of methanol containing 50 ml. of concentrated sulfuric acid was refluxed for six hours. The solution was neutralized with a saturated solution of sodium bicarbonate, filtered, and the aqueous layer extracted with ether. The dried ether extract was distilled. The methyl chloroacetate boiled at 126–130°, 304.8 g. (71% yield).

To a solution of 64 g. of sodium in 800 ml. of methanol was added, dropwise, with stirring, 260.7 g. of methyl chloroacetate. The mixture, heated under an infrared lamp to avoid bumping, was refluxed for 24 hours and then allowed to stand overnight. The solution was brought to a *p*H of 5–6 with concentrated hydrochloric acid, filtered, and distilled. The methyl methoxyacetate boiled at 126–131°, 241.6 g. (84%) (over-all yield 60%).

Method B.—Methoxyacetic acid was prepared according to the directions for making ethoxyacetic acid.[8] The product boiled at 110–112° at 25 mm. (21% yield). A stream of dry hydrogen chloride gas was passed through a solution of 92.5 g. of methoxyacetic acid in 112 g. of absolute methanol for five hours. The mixture was allowed to stand overnight and then neutralized with a saturated solution of sodium bicarbonate. The layers were separated and the aqueous layer extracted with ether. The dried ether solution of the ester was distilled to give 36.9 g. of methyl methoxyacetate, b.p. 126–130° (37%) (8% over-all yield).

3-Cyano-4-methoxymethyl-6-methyl-2(1)-pyridone (I).—This was prepared from methoxyacetylacetone[6] and cyanoacetamide, to give white crystals, m.p. 241° (92% yield).[7]

The mother liquor from the above reaction yielded fluffy cream-colored needles, m.p. 154° (7% yield) (3-cyano-6-methoxymethyl-4-methyl-2(1)-pyridone). Treatment with sulfuric acid[7] gave 6-hydroxymethyl-4-methyl-2-pyridol, m.p. 225°. A new picrate of this was prepared, m.p. 129°.

Anal. Calcd. for $C_{13}H_{12}N_4O_9$: N, 15.2. Found: N, 15.2.

2-Chloro-3-cyano-4-methoxymethyl-6-methylpyridine (II).—To a solution of 55 g. of I in 500 ml. of dry chlorobenzene was added 60 g. of phosphorus pentachloride. The mixture was heated gently until 200 ml. of distillate had been collected. The distillation was then continued under reduced pressure until no more material could be collected. The black, tarry residue was dissolved in benzene, the benzene solution washed with water several times, and the benzene then removed by distillation. The residual black product would not steam distil. Purification was achieved by vacuum distillation (95–105° at 1 mm.) and white shiny needles, m.p. 66–67° (68% yield) were obtained.

Anal. Calcd. for $C_9H_9ClN_2O$: N, 14.2. Found: N, 14.2.

This compound could also be prepared in somewhat lower yields (50–60%) by carrying out the reaction in the absence of a solvent.[2]

The Reduction of II.—To a solution of 4 g. of II in 125 ml. of absolute ethanol were added 15 ml. of 20% alcoholic hydrogen chloride, 1 g. of palladium chloride dissolved in 2 ml. of hot concentrated hydrochloric acid, and 2 g. of Norit. The suspension was shaken under forty-five pounds pressure of hydrogen. More catalyst (1 g. of palladium chloride in 2 ml. of hot concentrated hydrochloric acid) was added whenever the hydrogen absorption ceased. Usually, five additional portions of catalyst were necessary. The suspension was filtered, and the catalyst and support washed three times with absolute ethanol. The combined filtrate and washings were evaporated to dryness in a stream of air, leaving an oily residue. Addition of a few drops of concentrated hydrochloric acid followed by a few ml. of absolute ethanol and scratching caused the formation of fluffy white crystals. These were dissolved in water, filtered to remove any unreacted starting material and the filtrate again evaporated to dryness. The oily residue, crystallized as before from concentrated hydrochloric acid and absolute ethanol, gave 3.7 g. of pure product (66% yield, corrected), which melted at 218–220°.

The melting point of a mixture of these crystals with those of 5-aminomethyl-2,4-dimethylpyridine dihydrochloride (prepared by the reduction of 2-chloro-3-cyano-4,6-dimethylpyridine)[11] was not depressed,

The dipicrate melted at 193–195°. *Anal.* Calcd. for $C_{20}H_{18}N_8O_{14}$: N, 18.8. Found: N, 18.9.

The monochloroplatinate was prepared, m.p. 250–253° (dec.). *Anal.* Calcd. for $C_8H_{14}Cl_6NPt$: Pt, 35.7. Found: Pt, 35.4.

Since mixed melting points at high temperatures may not be too critical, III was converted into IV by use of nitrous acid.[11] The monohydrochloride, so formed, melted at 218–219°, and did not depress an authentic sample.

Anal. Calcd. for $C_8H_{12}ClNO$: C, 55.36; H, 6.97; Cl, 20.4; N, 8.1. Found: C, 55.88; H, 6.87; Cl, 19.8; N, 8.0.

The free base of IV was prepared by neutralizing an aqueous solution of the amine hydrochloride with sodium bicarbonate solution. The ether extract of this solution was dried, distilled to dryness, and the residue vacuum sublimed to give colorless crystals, m.p. 38.5–39.5°.

Anal. Calcd. for $C_8H_{11}NO$: N, 10.2. Found: N, 10.2.

The nitrate salt of IV was prepared by cooling an aqueous solution of IV and nitric acid. Filtration, followed by vacuum distillation of the filtrate, gave white crystals, m.p. 162–163°.

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.02; H, 6.04; N, 14.0. Found: C, 48.02; H, 5.92; N, 14.2.

(14) We are indebted to the biological research group of Eli Lilly and Company for these tests.

(15) Analyses by Misses Hobbs, Hines, Sorensen and Brauer.

The acetate of IV was prepared. A solution of 0.35 g. of IV in 20 ml. of acetic anhydride was refluxed for one hour and then distilled to dryness under reduced pressure. Vacuum sublimation of the residue gave white crystals, m.p. 125–127°, which gave an immediate precipitate with aqueous silver nitrate.

Anal. Calcd. for $C_{10}H_{14}ClNO_2$: C, 55.68; H, 6.54; N, 6.50. Found: C, 55.72; H, 6.56; N, 6.7.

3-Cyano-2-methoxy-4-methoxymethyl-6-methylpyridine (V).—To a solution of 0.7 g. of freshly cut sodium in 75 ml. of absolute methanol was added 5 g. of II. The solution which turned greenish-blue immediately, was refluxed for 24 hours in anhydrous atmosphere. The cooled solution was acidified with hydrochloric acid, filtered, distilled to dryness, and the residue extracted with ether. The dried ether extract was evaporated to dryness leaving yellow crystals (essentially quantitative). Purified by vacuum sublimation, the colorless crystals melted at 56–58°.

Anal. Calcd. for $C_{10}H_{11}N_2O$: N, 14.6. Found: N, 14.6.

When the above directions were followed and wet methanol inadvertently used, a product corresponding to the amide VI was found, m.p. 126–127°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.17; H, 6.67; N, 13.3. Found: C, 57.31; H, 6.45; N, 13.4.

V remained unchanged in contact with glacial acetic acid whereas alcoholic hydrogen chloride containing a slight amount of concentrated hydrochloric acid converted V readily to I. Attempted hydrogenation of V using hydrogenation conditions as indicated in the reduction of II gave only I.

3-Aminomethyl-2-methoxy-4-methoxymethyl-6-methylpyridine (VII).—To 125 ml. of glacial acetic acid were added 4.5 g. of V, 5.0 g. of palladium-on-charcoal (5%), 2.5 g. of sodium acetate and 0.15 g. of platinum oxide. The mixture was shaken at room temperature under fifty pounds pressure with hydrogen until the theoretical amount of hydrogen had been absorbed. It was not necessary at any time to add additional catalyst. The solution was filtered, the catalyst and support washed with acetic acid, and the combined filtrate and washings evaporated to a very small volume in a stream of air. This residue was added to a solution of 14 g. of picric acid in 100 ml. of absolute ethanol and allowed to stand overnight. **The monopicrate** was isolated by filtration (90% yield) and recrystallized from absolute ethanol, m.p. 183–184°.

Anal. Calcd. for $C_{16}H_{19}N_5O_9$: C, 45.15; H, 4.50; N, 16.46. Found: C, 44.98; H, 4.49; N, 16.23.

The picrate was added to 60 ml. of (1:1) hydrochloric acid and the mixture allowed to stand. The picric acid which had formed was filtered off and the filtrate evaporated to dryness in a stream of air. The oily residue was crystallized by dissolving it in a few drops of concentrated hydrochloric acid and then adding a few ml. of absolute ethanol. Cooling and scratching gave a voluminous precipitate of very pale pink platelets of the **dihydrochloride**, m.p. 270–272°.

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2O_2$: N, 10.4. Found: N, 10.5.

3-Aminomethyl-4-hydroxymethyl-6-methyl-2-pyridol (IX). Method (a) (sealed tube).—A solution of 0.5 g. of VII in 20 ml. of 2.5 *N* hydrochloric acid was heated in a sealed tube at 180° for four hours. The cooled tube was opened, and the dark solution digested with Norit and filtered. The filtrate, distilled to dryness at reduced pressure, left a white crystalline residue (60%) which was recrystallized from 80% ethanol. The hydrochloride was isolated as white needles, m.p. 265–267° (dec.). An aqueous solution did not cause a ferric chloride solution to deepen appreciably in color.

Method (b).—A solution of 0.4 g. of VII in 20 ml. of 48% hydrobromic acid was refluxed for ten minutes and then distilled to dryness. Since the residual dried crystals (VIII), m.p. 238–240°, darkened rapidly they were immediately converted into IX. A solution of these crystals in 75 ml. of water was refluxed 30 minutes. Freshly prepared silver chloride was added and the mixture allowed to stand one hour. After filtration, the filtrate was taken to dryness under reduced pressure. The residue, crystallized from 80% ethanol, melted at 268–270°, and did not depress the m.p. of a sample prepared by method (a). The over-all yield from VII by this method was 40%.

Anal. Calcd. for $C_8H_{14}Cl_2N_2O_2$: N, 11.6. Found: N, 11.3.

Reaction of Diazomethane with XII.—To a suspension of 3.4 g. of XII in 200 ml. of methanol was added an ether solution of approximately 4.2 g. of diazomethane. There was a considerable evolution of a colorless gas, and the yellow color of the solution disappeared, and the acid dissolved fairly rapidly. A precipitate appeared almost immediately after complete solution of the acid. The mixture was allowed to stand overnight and was then filtered. The precipitate (13%) was recrystallized from 75% methanol to give white needles, m.p. 267–268° (dec.). The compound is presumably the lactone of 3-carboxy-1,6-dimethyl-4-hydroxymethyl-2(1)-pyridone (XV).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.31; H, 5.02; N, 7.8. Found: C, 60.37; H, 5.06; N, 7.6.

The ether methanol filtrate from above was distilled to dryness leaving a white crystalline residue, which was recrystallized from methanol to give white platelets, m.p. 163–164° (56%), presumably the lactone of 3-carboxy-4-hydroxymethyl-2-methoxy-6-methylpyridine (XIV).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.31; H, 5.02; N, 7.8. Found: C, 60.42; H, 4.72; N, 7.9.

Reaction of XII with Alcoholic Sulfuric Acid.—A solution of 1.5 g. of XII in 50 ml. of absolute ethanol containing 10 ml. of concentrated sulfuric acid was refluxed for three hours and then poured into 50 ml. of water. The only insoluble solids were white crystals, m.p. 330° (dec.), which did not depress the m.p. of an authentic sample of X.

Anal. Calcd. for $C_8H_7NO_3$: C, 57.81; H, 4.22; N, 8.4. Found: C, 58.25; H, 4.35; N, 8.5.

Treatment of XII with alcoholic hydrogen chloride gave only X.

4-Acetoxymethyl-3-carboxy-6-methyl-2-pyridol (XIII).—A solution of 1 g. of XII in 25 ml. of acetic anhydride was refluxed for three hours and then allowed to stand overnight. The solution was poured into water and the resulting mixture distilled to dryness. The residue was extracted with aqueous sodium bicarbonate leaving a residue (0.5 g.) which did not depress the m.p. of X. Acidification of the extract gave a precipitate which was recrystallized from 70% ethanol to give pale yellow needles, m.p. 226° (50% yield).

Anal. Calcd. for $C_{10}H_{11}NO_5$: N, 6.2. Found: N, 6.3.

The reaction of XIII with diazomethane gave a compound m.p. 256°, which did not depress the m.p. of XV, and a compound m.p. 157° which did not depress the m.p. of XIV.

Reduction Experiments. (a) With $LiAlH_4$.—In reduction experiments with X using $LiAlH_4$ the following solvents were used: ethyl ether, tetrahydrofuran with ethyl ether (1:1), dioxane with ethyl ether (1:2), *n*-butyl ether and *n*-butyl ether with dioxane (1:1). Variations in the time of refluxing (one to seven days), variations in the method of adding reagents, and variation in working up the product failed to yield any XI. The only product which could be isolated (besides unreacted X) was a light yellow oil, which was not basic and did not give a positive ferric chloride test.

(b) With Copper Chromite.—Experiments using copper chromite at 170° and 190 atmospheres of hydrogen for six hours failed to reduce X to XI.

(c) With Sodium Amalgam.—Pieces of a 1% sodium amalgam were dropped into a suspension of 2.5 g. of X in 150 ml. of glacial acetic acid. The reaction flask was loosely stoppered, shaken and allowed to stand two hours. The reaction mixture was filtered through celite and the pale yellow filtrate distilled to dryness. The residue was taken up in dilute hydrochloric acid and the unreacted lactone (1.3 g.) filtered off. The filtrate was made basic with sodium bicarbonate and extracted with ether. The dried ether extract was evaporated to dryness in a stream of air leaving an oily yellow residue. This was dissolved in absolute alcohol and precipitated by the addition of a few drops of water, m.p. 154°. It did not form a picrate, nor a hydrochloride. It gave a negative ferric chloride test and did *not* contain nitrogen. It did absorb bromine from a carbon tetrachloride solution. The aqueous residue after extraction with ether contained ammonia. The compound analyzed as $C_7H_{12}O$. This was not further investigated.

Anal. Calcd. for $C_7H_{12}O$: C, 74.93; H, 10.79. Found: C, 74.75; H, 10.44.

EVANSTON, ILLINOIS