[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

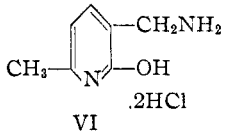
α-Oxygenated Pyridines. II. The Synthesis of 3-Hydroxymethyl-6-methyl-2-pyridol, an Isomer of 4-Deshydroxymethylpyridoxin[1]

BY RAYMOND P. MARIELLA[2] AND ANTON J. HAVLIK

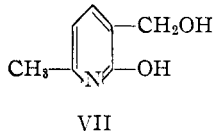
An α-oxygenated isomer of 4-deshydroxymethylpyridoxin, 3-hydroxymethyl-6-methyl-2-pyridol and related compounds have been synthesized. This analog exhibited some weak B_6 activity.

In continuing our studies on α-oxygenated pyridines,[3] we have synthesized an α-oxygenated isomer (VII) of 4-deshydroxymethylpyridoxin,[4] a weak inhibitor of pyridoxin.[5]

The reduction of 3-cyano-6-methyl-2(1)-pyridone (I) with a mixed palladium–platinum catalyst gave VI. It was not possible to convert VI into VII since the treatment of VI with nitrous acid in dilute hydrochloric acid solution produced a red amorphous solid. Similar observations on other β-aminomethyl-α-oxygenated pyridines have been made before.[3a,6]



VI



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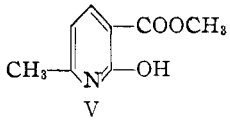
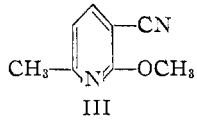
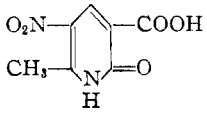


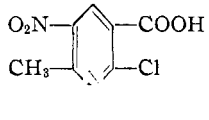
V



III



IX



XI

Hydrolysis of I gave 3-carboxy-6-methyl-2(1)-pyridone (IV). In view of the success[3a,7] of the conversion of heterocyclic esters to alcohols with lithium aluminum hydride, IV was converted into V by using diazomethane, but the reduction of V to VII was not successful. It was later found that it was possible to reduce IV directly to VII.

The reaction of 2-chloro-3-cyano-6-methylpyridine (II) with sodium methoxide gave III. 3-Cyano-6-methyl-5-nitro-2(1)-pyridone (VIII) was readily converted into the corresponding nicotinic acid (IX). The chlorination of VIII gave 2-chloro-3-cyano-6-methyl-5-nitropyridine (X), which was also converted into the corresponding nicotinic acid (XI).

5-Amino-2-chloro-3-cyano-6-methylpyridine (XII) exhibited a marked contrast in reactivity of the α-halogen as compared to the α-halogen in X. Treatment of X with various bases produces an instant deep purple color and only a black amorphous substance can be isolated from the solution. Similar treatment of XII with base left the starting compound unreacted. These results are consistent with the nature of the group in the position para to the halogen. The *p*-amino group (XII) decreases the reactivity of the halogen, whereas the *p*-nitro group increases the halogen reactivity. It may be that in basic solution a negative ion attacks the ring in X forming structures which are quinoid in nature and that these colored forms are not stable and polymerize.

Compounds IV, V, VI, VII, IX and XI did not exhibit any nicotinic acid activity and no anti-B_6 activity. Compounds IV and IX showed very weak B_6 activity, and compound VII was also B_6 active, about 1/1000 that of B_6, when tested against *Neurospora sitophila*.[8]

Acknowledgment.—We wish to acknowledge a special grant from the Graduate School of Northwestern University in support of this work.

Experimental[9]

3-Aminomethyl-6-methyl-2-pyridol Dihydrochloride (VI).—To a solution of 2.0 g. of I[4] in 200 ml. of methanol were added 2 g. of Norit, a solution of 200 mg. of palladium chloride in 5 ml. of concentrated hydrochloric acid, 10 mg. of platinum oxide and 5 ml. of a 15% solution of hydrogen chloride in absolute ethanol. The suspension was shaken with hydrogen at 70 pounds pressure and the absorption was complete in one hour. The suspension was then filtered and the filtrate taken to dryness. The residue was taken up in 5 ml. of concentrated hydrochloric acid, filtered hot, and absolute alcohol was added to the filtrate, causing the precipitation of white crystals, 1.5 g. (50% yield). Two recrystallizations from hydrochloric acid–ethanol gave white needles, m.p. 236–237°.

Anal. Calcd. for $C_7H_{12}Cl_2N_2O$: C, 39.8; H, 5.7; N, 13.2. Found: C, 39.5; H, 5.8; N, 12.9.

Attempted Diazotization of VI.—To a hot solution of 2.8 g. of VI in 130 ml. of 3 *M* hydrochloric acid was added a solution of 4.4 g. of sodium nitrite in 10 ml. of water. The solution was kept at 90° until the evolution of nitrogen had ceased. The water was then removed under reduced pressure, and the orange-red residue extracted with four 20-ml. portions of boiling ethanol. The ethanol extracts were taken to dryness leaving a red tar-like residue, which could not be recrystallized nor sublimed.

3-Carbomethoxy-6-methyl-2-pyridol (V).—Diazomethane was generated from 31 g. of nitrosomethylurea, suspended in 200 ml. of ether, by the action of 50 ml. of 40% potassium hydroxide, and the diazomethane was distilled into a suspension of 3.0 g. of IV[10] in 300 ml. of methanol. After standing overnight, the suspension was filtered, and the filtrate taken to dryness. The residue was recrystallized from absolute ethanol giving granular crystals, m.p. 184–185°. This reaction was run several times, with an average yield of 78%. The compound gave a positive ferric chloride test.

(1) Taken in part from the M.S. Thesis of Anton J. Havlik. Graduate School Fellow 1950–1951.

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(3) For previous papers in this series see (a) R. P. Mariella and E. P. Belcher, THIS JOURNAL, **73**, 2616 (1951), and (b) R. P. Mariella and A. J. Havlik, *ibid.*, **73**, 1864 (1951).

(4) L. A. Perez-Medina, R. P. Mariella and S. M. McElvain, *ibid.*, **69**, 2574 (1947).

(5) R. P. Mariella and J. L. Leech, *ibid.*, **71**, 331 (1949).

(6) R. P. Mariella and E. P. Belcher, unpublished results.

(7) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951).

(8) Bioassays by the biochemical group at the Eli Lilly laboratories, Indianapolis, Indiana.

(9) Analyses by Misses Sorensen, Brauer and Hobbs.

(10) A. Dornow, *Ber.*, **73**, 153 (1940).

Anal. Calcd. for $C_8H_9NO_3$: N, 8.4. Found: N, 8.7.

When V was treated with lithium aluminum hydride using either ethyl ether or butyl ether as solvents it was not possible to isolate any VII.

3-Hydroxymethyl-6-methyl-2-pyridol (VII).—Since the reaction of lithium aluminum hydride in ethyl ether with IV was not successful, it was decided to use butyl ether. To a solution of 7.1 g. of IV in 500 ml. of dry butyl ether was added 4.5 g. of lithium aluminum hydride. Upon addition of the solid, a visible evolution of hydrogen occurred. The mixture was then refluxed for 16 hours, and then poured onto 500 g. of ice. Solid sodium bicarbonate was then added until a *p*H of 8 was attained. The mixture was then filtered, and the resulting two clear layers were separated. The water layer was extracted with various solvents, ethyl acetate, chloroform and benzene, using acidic and basic conditions, but all that was recovered was 3.1 g. of unreacted acid. The water layer was then brought to a *p*H of 8, and taken to complete dryness. The dry residue was extracted with three 100-ml. portions of ethyl acetate at room temperature. The combined extracts were evaporated, leaving 1.1 g. of a white solid, m.p. 150°. This was recrystallized several times from absolute ethanol, giving large crystals, m.p. 164–165°. These crystals gave a deep ferric chloride test.

Anal. Calcd. for $C_7H_9NO_2$: N, 10.1. Found: N, 10.2.

3-Cyano-6-methyl-2-methoxypyridine (III).—To a solution of 1 g. of sodium in 100 ml. of absolute methanol was added 1.4 g. of II,[5] and the mixture was refluxed for three hours. The cooled solution was then acidified with hydrochloric acid, and the precipitated sodium chloride filtered off. The filtrate was taken to dryness, and the residue was vacuum distilled at 184° and 5 mm. to yield white crystals, m.p. 81.5°, 0.8 g. (59%).

Anal. Calcd. for $C_8H_8N_2O$: N, 18.9. Found: N, 19.2.

3-Carboxy-6-methyl-5-nitro-2(1)-pyridone (IX).—A solution of 3 g. of VIII in 30 ml. of concentrated hydrochloric acid was refluxed for 24 hours. The cooled solution was brought to a *p*H of 8, and filtered. The filtrate was acidified, and the pink solid which formed was filtered, 2 g. (60%). Recrystallization from water gave a flesh-colored powder, m.p. 268°.

Anal. Calcd. for $C_7H_6N_2O_5$: N, 14.1. Found: N, 14.4.

3-Carboxy-2-chloro-6-methyl-5-nitropyridine (XI).—A solution of 3 g. of X[4] in 30 ml. of concentrated hydrochloric acid was refluxed for 24 hours. The resulting solution was cooled, and filtered, 2.2 g. (66%). The crude crystals were dissolved in a solution of sodium hydroxide and filtered, and the filtrate acidified to a *p*H of 4–5, and the pure acid precipitated. Recrystallization of these crystals from water gave a fine powder, m.p. 261–262°.

Anal. Calcd. for $C_7H_5ClN_2O_4$: N, 12.9. Found: N, 12.9.

Reaction of X and XII.—When 1 g. of XII[4] was refluxed in a solution of 0.5 g. of sodium in 50 ml. of methanol for two hours and the solution worked up as described in the formation of III, only unreacted XII could be isolated, m.p. 227°.

An attempt was made to prepare a Grignard reagent with XII, using magnesium in absolute ether, but no Grignard reagent could be obtained.

When X[4] was added to sodium methoxide in methanol, or sodium cyanide in water, the solution turned dark purple immediately. The workup of the solutions yielded a dark amorphous solid, which could not be crystallized from such solvents as ethanol, water, methanol, petroleum ether, and dioxane, and which could not be sublimed. It is interesting to note that VIII could be mixed with bases without any color formation.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

α-Oxygenated Pyridines. III. The Reaction of N-Bromosuccinimide with Some Pyridine Derivatives[1]

BY RAYMOND P. MARIELLA[2] AND ELIZABETH P. BELCHER

The bromination of 4,6-dimethyl-2-pyridol, of 4,6-dimethyl-2-aminopyridine and of 2-acetamino-4,6-dimethylpyridine with N-bromosuccinimide has been investigated. The reaction even in the presence of benzoyl peroxide and ultraviolet light is predominantly nuclear. When a high concentration of benzoyl peroxide is used only 4,6-dimethyl-2-pyridol underwent both nuclear and side-chain bromination.

In conjunction with our work on compounds structurally related to pyridoxin,[3] we have investigated the reaction of various pyridine derivatives, 4,6-dimethyl-2-pyridol, 4,6-dimethyl-2-aminopyridine and 2-acetamino-4,6-dimethylpyridine with N-bromosuccinimide. It was expected that by carrying out this reaction in the presence of benzoyl peroxide and ultraviolet light bis-bromomethylpyridines might be prepared which on further reaction would lead to bis-hydroxymethylpyridols. These pyridols somewhat similar in structure to pyridoxin might be expected to have some vitamin or antivitamin activity.

There have been many reports in the recent literature on the reaction of N-bromosuccinimide with aromatic compounds. These include the benzenoid compounds and picolines discussed in the review by Djerassi,[4] the methylfurans studied by Buu-Hoï,[5] and the methylthiophenes studied by both Campaigne[6] and Dittmer.[7] In all cases it was shown that, in the absence of peroxides, the reaction occurs with the aromatic nucleus; in the presence of small percentages of peroxides the reaction is predominantly with the aliphatic side-chain. This latter reaction is particularly favored if the reaction is carried out in a quartz vessel under ultraviolet light.[4,6] The orientation of the reaction with aromatic compounds substituted with groups other than alkyl has not been widely studied. There is some work on substituted 4-pyrones[8] which showed that even in the absence of peroxides 2,6-dimethyl-4-pyrone will react with N-bromosuccinimide to form 2-bromomethyl-6-meth-

(1) Taken in part from the Ph.D. thesis of E. P. Belcher. Eli Lilly Fellow, 1949–1951.

(2) Department of Chemistry, Loyola University, Chicago 26, Illinois.

(3) (a) R. P. Mariella and J. L. Leech, THIS JOURNAL, **71**, 331 1949); (b) R. P. Mariella and E. P. Belcher, *ibid.*, **73**, 2616 (1951).

(4) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(5) Ng. Ph. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(6) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

(7) K. Dittmer, R. P. Martin, W. Herz and S. J. Cristol, *ibid.*, **71**, 1201 (1949).

(8) J. LeCocq, *Ann. Chim.*, **3**, 62 (1948).