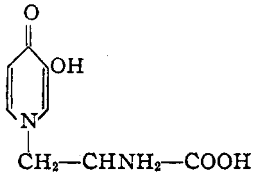
[Contribution from the Department of Research in Pure Chemistry, Mellon Institute]

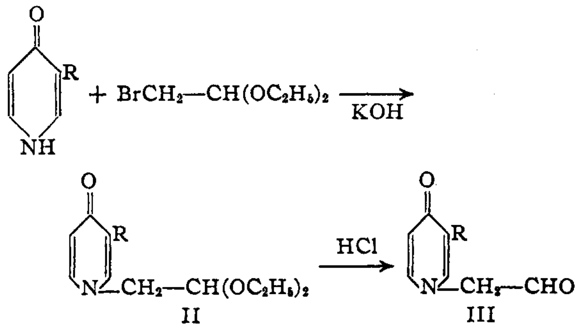
On the Structure of Leucaenine (Leucaenol) from *Leucaena Glauca* Bentham. IV

By A. F. Bickel[1]

In a number of investigations on the structure of leucaenine[2-6] it has been shown that this amino acid must be represented as β-[N-(3-hydroxypyridone-4)]-α-aminopropionic acid (I).


I

The object of the present investigation was to prepare [N-(3-methoxypyridone-4)]-acetaldehyde (IIIa), a compound which might serve as an intermediate in the synthesis of leucaenine by means of the Strecker reaction. IIIa might be prepared in the following manner.



(a) R = OCH_3 (b) R = H

The starting material for this synthesis, 3-methoxypyridone-4, is not easily available. Hence, in order to become acquainted with the reaction conditions, a similar synthesis, that of (N-pyridone-4)-acetaldehyde (IIIb) was first investigated. IIb was obtained in good yield by the reaction of pyridone-4, bromo-acetal and potassium hydroxide in alcoholic solution. The crude acetal was hydrolyzed to IIIb by boiling with dilute hydrochloric acid. The preparation of [N-(3-methoxypyridone-4)]-acetaldehyde (IIIa) was performed in the same manner. Although this aldehyde was not isolated in the pure state, its semicarbazone was prepared. Preliminary Strecker reactions carried out by the method of Cocker and Lapworth[7] have thus far been unsuccessful.

Experimental

All melting points given are corrected.

4-Hydroxypyridine was prepared according to the method of Königs and Greiner.[8]

(N-Pyridone-4)-acetaldehyde Diethyl Acetal.—A solution of 4.75 g. (0.05 mole) of 4-hydroxypyridine in 10 cc. of ethanol was mixed with 3.3 g. (0.05 mole) of 85% potassium hydroxide in 50 cc. of ethanol and 11.0 g. (0.055 mole) of bromoacetal was added. The resulting solution was heated in a sealed tube at 128–130° for seven hours, filtered from the separated potassium bromide (5.7 g. or 97% of the theoretical quantity), and evaporated *in vacuo*. The sirupy residue was dissolved in 30 cc. of water and rendered neutral with a few drops of concentrated hydrochloric acid.

The acetal was isolated as follows: The neutral aqueous solution was evaporated *in vacuo*. An alcoholic extract of the residue was filtered from a small amount of potassium chloride and concentrated *in vacuo*. On standing exposed to air, the resulting sirup yielded beautiful, colorless crystals of the acetal monohydrate, which were recrystallized from water, m. p., 87–89°. *Anal.*[9] Calcd. for $C_{11}H_{17}O_3N{\cdot}H_2O$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.44; H, 8.06; N, 6.18.

On drying over phosphorus pentoxide in a vacuum desiccator, the crystals lose water and revert to a sirup. The picrate was prepared by adding a small excess of picric acid dissolved in ethanol to a solution of the acetal in ethanol. Recrystallization was performed from the same solvent; m. p., 137–139°. *Anal.* Calcd. for $C_{11}H_{17}O_3N{\cdot}C_6H_3O_7N_3$: N, 12.72. Found: N, 12.49, 12.77.

(N-Pyridone-4)-acetaldehyde Hydrate.—The hydrolysis may be carried out after isolation of the acetal. It is simpler, however, to start with the aqueous solution of the original reaction mixture after neutralization with hydrochloric acid. This solution, treated with 8 cc. of 38% hydrochloric acid and 25 cc. of water, was refluxed for four hours. After evaporation *in vacuo*, a solution of the residue in 15 cc. of water was neutralized with sodium carbonate, a colorless crystalline precipitate of the aldehyde hydrate separating out. The product was collected, washed with small portions of ice-water until free from sodium chloride, and dried in the vacuum desiccator over phosphorus pentoxide. Yield was 4.3 g. (55% calculated on 4-hydroxypyridine). Recrystallization was performed from water. On heating, this compound turns brown above 110°, but does not melt.

Anal. Calcd. for $C_7H_7O_2N{\cdot}H_2O$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.98; H, 5.82; N, 8.97.

The picrate was prepared by adding an aqueous solution of picric acid to an aqueous solution of the aldehyde; recrystallization from water, m. p. 182.0–182.5° with decomposition.

Anal. Calcd. for $C_7H_7O_2N{\cdot}C_6H_3O_7N_3{\cdot}H_2O$: C, 40.63; H, 3.15; N, 14.58. Found: C, 40.90, 40.94; H, 3.20, 3.38; N, 14.42.

The semicarbazone was obtained by evaporating an aqueous solution of 155 mg. of aldehyde hydrate, 112 mg. of semicarbazide hydrochloride, and 53 mg. of sodium carbonate on the steam-bath until needles separated. On cooling, the crystals were filtered off and washed with ice-water. Recrystallization was performed from 50% ethanol; m. p. 208–208.5° with decomposition.

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.63; H, 5.38; N, 28.61.

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[1] Visiting Fellow, Netherland–America Foundation.

[2] Adams, Cristol, Anderson and Albert, This Journal, 67, 89 (1945).

[3] Bickel and Wibaut, *Rec. trav. chim.*, 65, 65 (1946).

[4] Wibaut and Kleipool, *ibid.*, 66, 24 (1947).

[5] Bickel, This Journal, 69, 1801, 1805 (1947); 70, 326 (1948).

[6] Adams, Jones and Johnson, *ibid.*, 69, 1810 (1947).

[7] Cocker and Lapworth, *J. Chem. Soc.*, 1391 (1931).

[8] Königs and Greiner, *Ber.*, 64, 1049 (1931).

[9] The microanalyses were carried out by Mr. G. L. Stragand of the University of Pittsburgh.

[N-(3-Methoxypyridone-4)]-acetaldehyde.—3-Methoxypyridone-4, bromoacetal and potassium hydroxide were caused to react in the manner described for pyridone-4. More than 90% of the theoretical quantity of potassium bromide was formed. No attempts were made to isolate the acetal; instead, its aqueous solution was refluxed with hydrochloric acid. On neutralizing with sodium carbonate, the liquid turned a dark brown but no aldehyde separated. By reaction of the crude material with semicarbazide, however, a semicarbazone was formed; its yield indicated that the over-all yield of aldehyde, calculated on 3-methoxypyridone-4, was about 40%. The semicarbazone was recrystallized from water and dried over phosphorus pentoxide in the vacuum desiccator; m. p. 188–188.5° with decomposition.

Anal. Calcd. for $C_9H_{12}O_3N_4 \cdot 2H_2O$: C, 41.53; H, 6.20; N, 21.53; H_2O, 13.84. Found: C, 41.86; H, 6.30; N, 21.41; H_2O, 13.76.

The anhydrous compound, which may be prepared by drying over phosphorus pentoxide at 100° (1 mm.), is very hygroscopic.

Summary

(N-Pyridone-4)-acetaldehyde and [N-(3-methoxypyridone-4)]-acetaldehyde have been synthesized.

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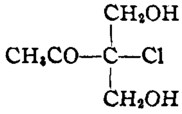
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY AND COMMERCIAL SOLVENTS CORPORATION]

The Condensation of Chloroacetone with Formaldehyde

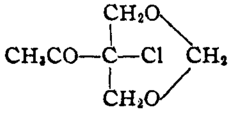
BY CHARLES D. HURD, WARREN D. MCPHEE[1] AND GLEN H. MOREY

While the condensation of formaldehyde with lower ketones has been studied extensively, the reaction of this aldehyde with chloroacetone has not previously been investigated. From the reaction of one mole of chloroacetone with 2.1 moles of formaldehyde, there are obtained three substances: A, a crystalline solid melting at 61–62°; B, a colorless oil distilling at 93.5° (10 mm.); C, a colorless oil distilling at 73–74.5° (10 mm.). From the evidence presented herein, it has been concluded that these substances are respectively 2-chloro-2-acetyl-1,3-propanediol, 2-chloro-2-acetyl-1,3-propanediol formal and 4-hydroxy-3,3-dichloro-2-butanone.



$CH_3CO-C(CH_2OH)_2-Cl$

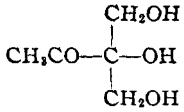
A



B

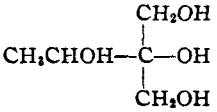
$CH_3COCCl_2CH_2OH$

C



$CH_3CO-C(CH_2OH)_2-OH$

D



$CH_3CHOH-C(CH_2OH)_2-OH$

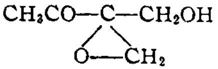
E

In determining the structure of substance A, it is apparent from the empirical formula that two hydroxymethyl groups have been introduced. It is necessary only to ascertain which α-carbon atom carries them. This was done by oxidation of A to acetic acid and by reaction with sodium hypoiodite with the formation of iodoform. ω-Chloroacetophenone is known to give a negative iodoform reaction,[2] and chloroacetone was found to give similar results. In view of these facts, A was assigned the structure shown.

Compound B differs from A only by the presence of one more carbon atom. It seemed logical that B should be the cyclic formal derived from A by reaction with a third mole of formaldehyde. Compound A was converted into B by means of dry formaldehyde in ether in the presence of a trace of acid, thus proving the structure of B. The compound so synthesized was shown to be identical with B.

The high chlorine content of C indicated that it was derived from dichloroacetone, which is generally present in small amounts in chloroacetone. Structure C, analogous to structure A, was selected because this compound gives a positive iodoform test. The formula was confirmed by synthesis of C from α,α-dichloroacetone and formaldehyde.

2-Chloro-2-acetyl-1,3-propanediol, A, was readily converted to its diacetate with ketene and to its dibenzoate with benzoyl chloride. Upon treatment with aqueous or alcoholic alkali, there is obtained a triol believed to be acetylglycerol, D. There is no evidence on the question whether this comes by direct saponification or by way of dehydrohalogenation to an ethylene oxide intermediate,



By the reaction of three moles of formaldehyde per mole of chloroacetone in the presence of one mole of sodium hydroxide, there is obtained substance D. The latter was identical with the triol obtained by alkaline hydrolysis of A. Substance D was reduced by sodium in alcohol to a tetrol, 2-hydroxymethyl-1,2,3-butanetriol, E.

Experimental

Reaction of Chloroacetone and Formaldehyde.—Chloroacetone (containing a little α,α-dichloroacetone) and formalin (40% solution) were mixed in a molar ratio of 1:2.1. The mixture was agitated at 25° for thirty minutes, during which time 2 *N* sodium hydroxide solution was added dropwise till 0.27 mole of the base was added. There was some heat of reaction during this addition, and the two-layer system gradually became homogeneous. The

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[1] Holder of Commercial Solvents Corporation Fellowship, 1938–1940.

[2] Fuson and Tullock, THIS JOURNAL, **56**, 1638 (1934).