tionating column equipped with a total-condensation variable take-off stillhead. The ethyl alcohol formed in the alcoholysis was fractionated from the mixture at frequent intervals. About 1.5 cc. of material boiling below 150° was separated during the course of the reaction. The excess β-diethylaminoethanol was removed from the reaction mixture by distillation on the steam-bath under reduced pressure, and the residue was dissolved in a small amount of ice-water. The solution was extracted three times with ether and the extracts washed three times with ice-water and dried. On passing hydrogen chloride into the ether solution the product separated as a dark tar which was recrystallized from *n*-butyl alcohol; m. p. 208°, (dec.); yield, 1.3 g. (17%).

Anal. Calcd. for $C_{18}H_{38}O_4N_3SCl_3$: C, 43.3; H, 7.7; N, 8.4; S, 6.4; Cl, 21.3. Found: C, 43.9; H, 7.8; N, 8.5; S, 6.2; Cl, 20.3.

γ-Diethylaminopropyl Ester of Thiamorpholine-3,5-dicarboxylic Acid (Trihydrochloride).—This substance was prepared in the same general fashion as just described for the β-diethylaminoethyl ester; m. p. 215° (dec.).

Anal. Calcd. for $C_{20}H_{42}O_4N_3SCl_3$: N, 7.97. Found: N, 7.98, 7.71.

Thiamorpholine - 3,5 - di - (β - diethylaminoethyl) - carboxamide.—A mixture of 1 g. of the diethyl ester of thiamorpholine-3,5-dicarboxylic acid and 1.5 g. of β-diethylaminoethylamine was heated to 160–170° for twelve hours in an open test-tube supported in a Wood's metal bath. Excess amine was removed from the reaction mixture by distillation on the steam-bath under reduced pressure. The residue was dissolved in 50 cc. of dry ether and the product precipitated as the hydrochloride by adding an ethereal solution of hydrogen chloride. The material so obtained was a tan-colored, very hygroscopic, crystalline solid. It was purified by dissolving in hot absolute alcohol, adding ether to the point of turbidity, and allowing to cool. After four such recrystallizations a pure white, practically non-hygroscopic product was obtained which decomposed in the neighborhood of 245°, depending on the rate of heating; yield, 1.1 g. (55%).

Anal. Calcd. for $C_{18}H_{40}O_2N_5SCl$: C, 43.5; H, 8.1. Found: C, 43.0; H, 8.3.

We gratefully acknowledge a grant from Sharp and Dohme which made possible a part of this work.

Summary

Some new derivatives of thiamorpholine-3,5-dicarboxylic acid have been prepared, several of them having interesting pharmacological potentialities.

NEW HAVEN, CONN. RECEIVED APRIL 24, 1940

[CONTRIBUTION FROM THE HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Structure of Trimethyl Glucurone

BY RICHARD E. REEVES[1]

Pryde and Williams[2] have prepared from glucurone a crystalline trimethyl derivative which they regard to be 1,2,4-trimethylglucurone (I). Although no evidence substantiating this structure has been presented, Marrack and Carpenter[3] also refer to the trimethylglucurone as having this structure. Such a substance on hydrolysis and oxidation might be expected to yield 2,4-dimethylsaccharic acid, which is wanted as a reference compound in this Laboratory.

When the trimethylglucurone, m. p. 129–130°, was prepared, its properties were found to resemble those of a methylfuranoside more than the methylpyranoside called for by structural formula I. On acid hydrolysis reducing sugar was liberated at the rapid rate characteristic of methylfuranosides.[4] Pryde and Williams have noted the rapid fall in rotation when trimethylglucurone is dissolved in methanol containing hydrogen chloride. It is now shown that this fall in rotation is accompanied by the formation of an isomeric trimethylglucurone, m. p. 90–91°, having a low rotation. This suggests the rapid mutarotation which Levene and Meyer[5] have observed for α- and β-methylfuranosides under similar conditions.

The high melting trimethylglucurone was hydrolyzed and oxidized to a dimethylsaccharic acid which was characterized as the crystalline diamide. When the crude dimethylsaccharic acid was esterified with cold ethereal diazomethane, no crystalline dimethylsaccharic acid esters or lactone esters were obtained; instead there was produced an unsaturated dimethyl lactone methyl ester (II) known to have its methyl groups on positions 2 and 5.[6] This

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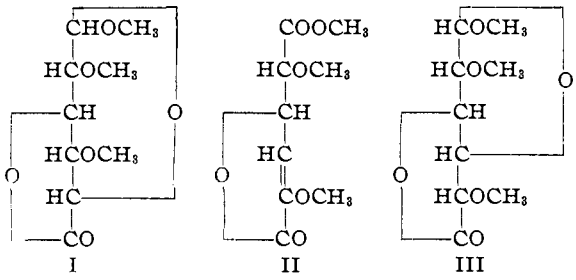
finding, together with the above-mentioned properties, make it appear that the furanoside structure III, 2,5-dimethyl-α-methylglycoside of glucurone, is probably the correct structure for the trimethylglucurone of Pryde and Williams. The low melting isomer and the diamide are regarded as 2,5-dimethyl-β-methylglycoside of glucurone and 2,5-dimethylsaccharic acid diamide, respectively.



Experimental Part

High-Melting Trimethylglucurone.—Pryde and Williams[1] report a 25% yield of this substance following three methylations of glucurone with silver oxide and methyl iodide. By the present procedure a 50% yield was obtained after one methylation. To 5.11 g. of glucurone was added 15 cc. of acetone and 20 cc. of methyl iodide. The vigorously stirred mixture was cooled in an ice-bath during the addition of 3 g. of silver oxide. The temperature was gradually raised to 45° with the addition of 27 g. of silver oxide during nine hours. Fifteen cc. of methyl iodide and 10 cc. of acetone were added and the mixture was then refluxed at 45–48° for five hours. The product was extracted with chloroform and crystallized from acetone by the addition of ether, a second and third crop being obtained from the mother liquors. After recrystallization 2.71 g. of 2,5-dimethyl-α-methylglycoside of glucurone, m. p. 129–130°, was obtained; sp. rot. (D-line) (24°) 151° (*c*, 0.4 in $CHCl_3$).

Low-melting Trimethylglucurone.—Trimethylglucurone, m. p. 129–130°, (372.6 mg.) was dissolved at 23° in 15 cc. of methanol containing 3.6% dry hydrogen chloride. After seventy minutes the rotation (1-dm. tube) became constant at −0.03°. The solution was evaporated to dryness *in vacuo* and, when the residue was redissolved in methanol and again taken to dryness, crystals formed in the distillation flask. Recrystallization from methanol and ether gave 270 mg. of 2,5-dimethyl-β-methylglycoside of glucurone, m. p. 90–1°, sp. rot. (D-line) (21°) 2.0° (*c*, 1.0 in H_2O); (24°) −2.3° (*c*, 0.9 in $CHCl_3$).

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.53; H, 6.42; CH_3O, 42.6. Found: C, 49.24; H, 7.15; CH_3O, 42.85.

Kinetics of Hydrolysis.—Trimethylglucurone (94.6 mg.) m. p. 129–130° was refluxed in 50 cc. of 0.05 *N* hydrochloric acid and the reducing sugars were determined at intervals by the modified Hagedorn–Jensen procedure.[7] The results are given in cc. of 0.01 *N* thiosulfate required by 1 cc. of hydrolysate after refluxing for a stated length of time: 0 min., 0.11 cc.; 5 min., 1.76 cc.; 15 min., 3.91 cc.; 30 min., 4.65 cc.; 60 min., 4.49 cc. To minimize the effect of the gradual decomposition of reducing sugar a curve was drawn through the points and the velocity constant was calculated by the method of Guggenheim[8] for the first twenty minutes of the hydrolysis. The value was found to be $k = 1380 \times 10^{-5}$ min.$^{-1}$ for *N*/100 HCl at 100°, which is definitely within the range exhibited by most furanosides. When recalculated on the basis of natural logarithms the values found by Haworth and Hirst[4] for furanosides in 0.01 *N* acid at 100° range from 600×10^{-5} to $11{,}000 \times 10^{-5}$.

2,5-Dimethylsaccharic Acid Diamide.—Trimethylglucurone (100 mg.), m. p. 129–130°, was heated for four hours at 80–85° in 4 cc. of dilute nitric acid, sp. gr. 1.2. Nitric acid was removed by evaporating *in vacuo*, adding water and repeatedly evaporating to dryness *in vacuo*. The residue was then esterified by heating for three hours at 75° in a sealed tube with 4 cc. of methanol containing 2% dry hydrogen chloride. The hydrogen chloride was removed with silver carbonate. Attempts to obtain crystals from this ester both before and after vacuum distillation were unsuccessful. The sirup was dissolved in 2 cc. of methanol, cooled to 0°, and treated with ammonia gas. Crystals separated, and more were obtained by the addition of ether to the mother liquors; 43 mg. of crude material yielded 11 mg. of pure diamide, m. p. 169–170°, after three recrystallizations from ethanol.

Anal. Calcd. for $C_8H_{16}O_6N_2$: C, 40.68; H, 6.78; N, 11.88; CH_3O, 26.3. Found: C, 40.62; H, 6.77; N, 11.70; CH_3O, 26.46.

Unsaturated Saccharolactone Methyl Ester II.—Two hundred mg. of high-melting trimethylglucurone was hydrolyzed and oxidized with nitric acid as in the preparation of the diamide. The saccharic acid after removal of nitric acid and water was treated with 15 cc. of an 0.5 molar solution of diazomethane in ether, and allowed to stand at 0° for three days. The solution was filtered from a small flocculent precipitate, and concentrated to 3 cc. Forty mg. of crystals separated, which on recrystallization from acetone–ether melted at 85–86.5°. Mixed with the unsaturated lactone ester, m. p. 87–88°, prepared from saccharolactone methyl ester[9] the melting point was 86–87°.

Summary

Evidence is presented which indicates that the trimethylglucurone prepared by Pryde and Williams is the 2,5-dimethyl-α-methylglycoside of glucurone.

NEW YORK, N. Y. RECEIVED MARCH 29, 1940

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