[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Open Chain Derivatives of *d*-Mannose

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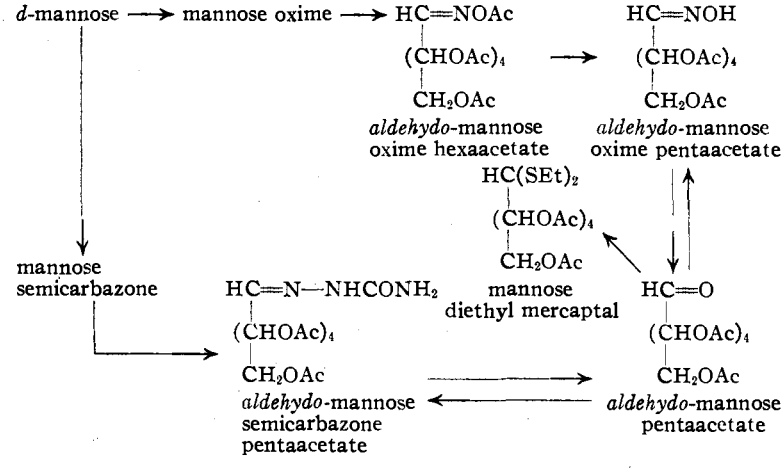
Application of the controlled hydrolysis, with mercuric chloride and cadmium carbonate, to acetylated sugar mercaptals[1] having the *cis*-configuration on carbon atoms two and three, such as mannose, rhamnose and α-glucoheptose, has led to impure sirupy products instead of the desired crystalline *aldehydo*-sugar acetates. The new synthesis of *aldehydo*-sugar acetates reported from this Laboratory[2] offered a different method of approach which has now been applied to *d*-mannose. The desired *aldehydo*-mannose pentaacetate was not obtained in crystalline form but a sirupy product was secured which was less impure than that produced by de-mercaptalation. This sirup was characterized by a number of crystalline derivatives, of an open chain structure, which are of interest and which can be produced by direct acetylation methods.

Deulofeu and co-workers[3] have shown that the low temperature acetylation of mannose oxime gives the open chain or *aldehydo*-mannose oxime hexaacetate in good yield. The assignment of an open chain structure to this compound was based upon its transformation to the acetylated nitrile on heating, a reaction characteristic of the open chain aldose oxime hexaacetates.[4] In the work herein reported, the O-acetyl of the oxime group has been selectively hydrolyzed and the resulting crystalline oxime pentaacetate has been deoximated with nitrous acid to produce the *aldehydo*-mannose pentaacetate as a sirup. This sirup was characterized by two crystalline derivatives, mannose diethyl mercaptal pentaacetate and *aldehydo*-mannose semicarbazone pentaacetate. The formation of these two carbonyl derivatives without loss of acetyl groups indicated that the sirup was essentially the *aldehydo*-pentaacetate. Mild acetylation of mannose semicarbazone formed the same crystalline semicarbazone pentaacetate as was obtained by the reaction between the deoximated product and semicarbazide. Removal of the semicarbazide group from this substance with nitrous acid yielded a sirupy pentaacetate which could be oximated to produce a crystalline *aldehydo*-mannose oxime pentaacetate identical with that obtained from the selective hydrolysis of the oxime hexaacetate of Deulofeu and co-workers. The relationships between these compounds are shown in Fig. 1. It would appear from these results and from those of Deulofeu and co-workers, that *d*-mannose shows a pronounced tendency to react in its open chain form.

Fig. 1

Interrelationships in the *aldehydo*-mannose series



Experimental

Preparation of *Aldehydo*-*d*-mannose Oxime Hexaacetate.—This substance was prepared by the low temperature acetylation of mannose oxime as described by Deulofeu and co-workers,[3] except that mechanical stirring was employed and the reaction was satisfactorily completed in twelve hours at 2° instead of in eight days at 0°; m. p. 91–92°; $(\alpha)^{25}D$ −8.5° (*c*, 4; $CHCl_3$). Deulofeu and co-workers record the constants: m. p. 94°; $(\alpha)^{20}D$ −8.3° ($CHCl_3$).

Aldehydo-*d*-mannose Oxime Pentaacetate.—*Aldehydo*-*d*-mannose oxime hexaacetate (7.5 g.) and 6.5 g. of oxalic acid dihydrate were dissolved in 80 cc. of warm methanol and the solution refluxed for thirty minutes. The solvent

(1) M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929).

(2) M. L. Wolfrom, L. W. Georges and S. Soltzberg, *ibid.*, **56**, 1794 (1934).

(3) V. Deulofeu, P. Cattaneo and G. Mendivelzua, *J. Chem. Soc.*, 147 (1934).

(4) M. L. Wolfrom and A. Thompson, THIS JOURNAL, **53**, 625 (1931).

was removed under reduced pressure and the crystalline residue was washed with several 50-cc. portions of cold water to remove the oxalic acid; yield 4.9 g.; m. p. 119–122°; $(\alpha)_D$ +14° ($CHCl_3$). Pure material was obtained by digestion with ether followed by recrystallization from the minimum amount of hot ethanol by the addition of water; m. p. 122–123°; $(\alpha)^{29}_D$ +15° (*c*, 4; $CHCl_3$).

Anal. Calcd. for $C_6H_8O_6N(COCH_3)_5$: N, 3.45; acetyl, 12.35 cc. of 0.1 *N* NaOH per 100 mg. Found: N, 3.53; acetyl (Freudenberg[5] method), 12.3 cc.

Further acetylation of this substance under mild conditions produced *aldehydo-d*-mannose oxime hexaacetate. The pentaacetate (4.4 g.) was dissolved at 0° in a previously cooled solution of acetic anhydride (13 cc.) and pyridine (26 cc.) and maintained at 0° for one hour. The product was obtained in crystalline form by pouring into 300 cc. of ice and water; yield 3.8 g.; m. p. 89–90°. Pure material was obtained by recrystallization from a small amount of hot ethanol by the addition of water; yield 2.5 g.; m. p. 91–92°; $(\alpha)^{29}_D$ −8.4° (*c*, 4; $CHCl_3$).

De-oximation of *Aldehydo-d*-mannose Oxime Pentaacetate.—*Aldehydo-d*-mannose oxime pentaacetate (1.6 g.) was de-oximated with nitrous acid as described by Wolfrom, Georges and Soltzberg[2] for the corresponding glucose compound. The sirup (1.2 g.) obtained after chloroform removal resisted crystallization and was purified by precipitation from acetone solution by the addition of petroleum ether. The product reduced Fehling's solution and gave a Schiff free aldehyde test.

Anal. Calcd. for $C_6H_7O_6(COCH_3)_5$: acetyl, 12.8 cc. of 0.1 *N* NaOH per 100 mg. Found: acetyl, 12.24 cc.

That the sirup was moderately pure *aldehydo-d*-mannose pentaacetate was proved by the preparation of two crystalline derivatives. Treatment of the sirup with ethyl mercaptan and zinc chloride according to the procedure of Wolfrom and Thompson[6] yielded crystalline mannose diethyl mercaptal pentaacetate; m. p. 51–52° (unchanged on admixture with the product obtained on acetylation of mannose diethyl mercaptal);[7] $(\alpha)^{25}_D$ +32° (*c*, 4; $CHCl_3$). Pirie records the constants: m. p. 51–52°; $(\alpha)^{17}_D$ +31° ($CHCl_3$).

***Aldehydo-d*-mannose Semicarbazone Pentaacetate.**—An amount of 2.4 g. of the sirupy *aldehydo-d*-mannose pentaacetate, obtained by the de-oximation procedure, was dissolved in 35 cc. of hot water, the solution cooled rapidly to room temperature and treated with a solid mixture of semicarbazide hydrochloride (0.95 g.) and potassium acetate (1.5 g.). The semicarbazone separated in crystalline form; yield 1.3 g., m. p. 173–175° (dec.); $(\alpha)^{23}_D$ +9.4° (*c*, 2.5; $CHCl_3$). Pure material was obtained on recrystallization from hot water; m. p. 177–178° (dec.); $(\alpha)^{25}_D$ +9.2° (*c*, 2.5; $CHCl_3$).

Anal. Calcd. for $C_7H_{10}O_6N_3(COCH_3)_5$: N, 9.40; acetyl, 11.2 cc. of 0.1 *N* NaOH per 100 mg. Found: N, 9.12; acetyl, 11.3 cc.

Aldehydo-d-mannose semicarbazone pentaacetate was also obtained in good yield by the direct acetylation of mannose semicarbazone.[8] An amount of 6 g. of mannose semicarbazone was added to a solution of pyridine (36 cc.) and acetic anhydride (18 cc.) and the mixture shaken mechanically at room temperature for four hours. The semicarbazone dissolved and the solution was kept at ice box temperature for twelve hours and was then poured into 800 cc. of ice and water. The crystalline product that separated was removed by filtration and washed with cold water; yield 5 g.; m. p. 176–179° (dec.); $(\alpha)^{23}_D$ +8.9° (*c*, 2; $CHCl_3$). Pure material was obtained on one recrystallization from hot water; m. p. 178–180° (dec.) (m. p. unchanged on admixture with product from the de-oximation); $(\alpha)^{21}_D$ +9.3° (*c*, 2.5; $CHCl_3$).

Splitting of *Aldehydo-d*-mannose Semicarbazone Pentaacetate with Nitrous Acid.—*Aldehydo-d*-mannose semicarbazone pentaacetate (3.2 g.) obtained from the acetylation of mannose semicarbazone was dissolved in 40 cc. of hot ethanol and a warm solution of 10 g. of sodium nitrite in 200 cc. of hot water added. The solution was then placed in a water-bath maintained at 70° and treated with hydrochloric acid and additional sodium nitrite as described by Wolfrom, Georges and Soltzberg[2] for the de-oximation of *aldehydo*-glucose oxime pentaacetate. The sirup so obtained was dissolved in 30 cc. of hot water, cooled to room temperature and treated with a solid mixture of hydroxylamine hydrochloride (0.6 g.) and potassium acetate (1.2 g.). Crystals formed after several hours; m. p. 118–120°. These were recrystallized from hot ethanol by the addition of water; m. p. 121–123° (m. p. unchanged on admixture with the previously described preparations of *aldehydo*-mannose oxime pentaacetate); $(\alpha)^{21}_D$ +13 ± 1° (*c*, 2.3; $CHCl_3$). The isolation of this product from the oximated sirup indicated that the sirup was essentially *aldehydo-d*-mannose pentaacetate.

Summary

1. *Aldehydo-d*-mannose semicarbazone pentaacetate and *aldehydo-d*-mannose oxime pentaacetate have been synthesized in crystalline condition. Proof is furnished for the structure of these compounds.

2. Mild acetylation of *d*-mannose semicarbazone produces *aldehydo-d*-mannose semicarbazone pentaacetate in good yield.

3. Nitrous acid treatment of either *aldehydo-d*-mannose semicarbazone pentaacetate or *aldehydo-d*-mannose oxime pentaacetate produces *aldehydo-d*-mannose pentaacetate as a sirup characterized by several crystalline derivatives.

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(6) M. L. Wolfrom and A. Thompson, THIS JOURNAL, **56**, 882 (1934).

(7) N. W. Pirie, *Biochem. J.*, **30**, 374 (1936).

(8) Maquenne and Goodwin, *Bull. soc. chim.*, [3] **31**, 1075 (1904).