

Reactions of Saccharides Catalyzed by Molybdate Ions. III.*

Preparation of L-Glucose by Epimerization of L-Mannose or L-Mannose Phenylhydrazone

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Received March 22, 1971

Epimerization of L-mannose in water solution under the catalytic action of molybdenic acid gives the equilibrium mixture of the epimeric aldoses L-glucose and L-mannose in the ratio 75 : 25. The same ratio of the aldoses is obtained during liberation of L-mannose from L-mannose phenylhydrazone with benzaldehyde in a mixture of water and ethanol in the presence of molybdenic acid. L-Glucose is isolated from the equilibrium mixture by crystallization.

Until now L-glucose was prepared from L-arabinose by cyanohydrine [1, 2] and nitromethane [3] synthesis. *Fischer* [1] obtained L-glucose in very low yields in the reaction of L-arabinose with hydrocyanic acid in aqueous solution, followed by hydrolysis of the aldonic acid nitriles, their separation and reduction by sodium amalgam. In the other procedure [2] the aldonic acid nitriles, as the products of the cyanohydrine reaction of L-arabinose in pyridine, were catalytically reduced, and succeeding separation of the epimeric aldose phenylhydrazones gave L-glucose and L-mannose phenylhydrazone in 28 and 56% yield, respectively. In the case of the cyanohydrine reaction of L-glucose [1, 2] the rule of *Maltby* is valid so that the epimer predominantly formed possesses *trans* arrangement of the hydroxyl groups at C-2 and C-4 [3, 4]. This consequently enables preparation of larger quantities of L-mannose than L-glucose.

The nitromethane synthesis with L-arabinose [5] gives a mixture of the epimeric 1-deoxy-1-nitro-hexitols which are separated by fractional crystallization to give at first 1-deoxy-1-nitro-L-mannitol (18.5%) and then 1-deoxy-1-nitro-L-glucitol (18.8%). Decomposition of these products affords L-glucose and L-mannose. In a simpler procedure, L-mannose can be isolated in the form of its phenylhydrazone in 22.6% yield directly by decomposition of sodium salts of the mixture of epimeric nitrohexitols. The preparation of L-mannose by nitromethane synthesis is essentially simpler than that of L-glucose due to the easier crystallization of 1-deoxy-1-nitro-L-mannitol and the insolubility of L-mannose phenylhydrazone.

During epimerization of D-glucose or D-mannose in water solution of molybdenic acid an equilibrium of the epimers is formed with the ratio D-glucose : D-mannose 75 : 25 [6]. Analogous epimerization of L-mannose into L-glucose is convenient for the preparation of the latter compound. Similarly as in the catalyzed epimerization of L-mannose in aqueous media, the equilibrium of the epimeric aldoses is also established during liberation of L-mannose from its phenylhydrazone with benzaldehyde in the presence of molybdenic

* For Part II. see Ref. [6].

acid in a mixture of water and ethanol. L-Glucose is isolated by crystallization in 40% yield. Repeated epimerization gives further crops of L-glucose. A twofold epimerization of L-mannose gives L-glucose in 66% yield while a threefold epimerization starting from L-mannose phenylhydrazone gives 63% yield. It is obvious that any ratio of the aldoses obtained in other procedures can be accommodated to the constant equilibrium ratio by the described epimerization and L-glucose can be obtained by crystallization.

Experimental

Specific rotations were measured on a Bendix—Ericsson type 143 A automatic polarimeter and melting points were determined on a Kofler microstage apparatus. Water solutions were deionized on an Amberlite 402 (OH⁻) column (55 × 1.8 cm). Starting compounds L-mannose and L-mannose phenylhydrazone were prepared as previously described [5].

Preparation of L-glucose

Epimerization of L-mannose

A mixture of L-mannose (4.0 g) and molybdenic acid (10–15 mg) in water (20 ml) was heated for 3 hours at 90°C. The reaction mixture was evaporated under a reduced pressure and the resulting syrupy residue was dissolved in methanol (50 ml), treated with charcoal and evaporated again. The dry residue was dissolved in methanol (2 ml) and ethanol (12 ml) was added under heating and the solution was allowed to stand for 24 hours at room temperature and after that for another 24 hours at 5°C. Crystalline L-glucose (1.7 g, 42% yield) was filtered off, the filtrate was evaporated to a syrup which was dissolved in water (15 ml) and, after addition of molybdenic acid (9–10 mg), processed as given above. The final syrupy residue was dissolved in a mixture of methanol—ethanol (1:6; 7 ml) and crystallized for 4 days to give further crop of L-glucose (0.95 g, 24%).

Epimerization of L-mannose phenylhydrazone

A mixture of L-mannose phenylhydrazone (100 g), water (750 ml), ethanol (130 ml), benzaldehyde (80 ml), benzoic acid (8 g), and molybdenic acid (1 g) was kept for 3 hours at 95°C. The reaction mixture was then filtered, the solid residue was washed with water (2 × 50 ml) and the filtrate was extracted at first with chloroform (1 × 200 ml) and then with ethyl acetate (3 × 150 ml). The aqueous layer was evaporated *in vacuo*, the residue was dissolved in methanol (30 ml) and, after addition of ethanol (180 ml) under heating, crystallized for 3 days at room temperature to give L-glucose (22 g). The mother liquor concentrated to a half volume gave on crystallization (4 days) further yield of L-glucose (4 g). The filtrate from the second crystallization was evaporated to the syrupy water (200 ml) and molybdenic acid (0.1 g) was added and the solution was heated for 3 hours at 90°C. The solution was then filtered and the filtrate was extracted with ethyl acetate (2 × 50 ml). The aqueous layer was evaporated, the residue was dissolved in methanol, purified on charcoal, evaporated again, and crystallized from the methanol—ethanol mixture (100 ml) to give L-glucose (11 g). Repeating the procedure described in the second epimerization afforded further crop of L-glucose (5 g). Thus the overall yield of L-glucose is 42 g, 63%.

Recrystallization of L-glucose

A diluted solution of L-glucose (50 g) in water was at first deionized on an ion-exchanger column, then evaporated to dryness. The residue was dissolved in a mixture of water (25 ml), methanol (100 ml), and ethanol (150 ml), filtered under heating and left to stand for 24 hours at room temperature to give crystals of α ,L-glucose (27 g), m.p. 141–143°C, $[\alpha]_D^{24} -107.2^\circ$ (3 min) $\rightarrow -106.3^\circ$ (4 min) $\rightarrow -105.0^\circ$ (5 min) $\rightarrow -99.6^\circ$ (10 min) $\rightarrow -80.3^\circ$ (30 min) $\rightarrow -65.7^\circ$ (1 hour) $\rightarrow -57.9^\circ$ (2 hours) and $-51.4 \pm 0.2^\circ$ (24 hours) (c 4.0, water).

Ref. [1] m.p. 141–143°C, $[\alpha]_D^{20} -95.5^\circ$ (7 min) $\rightarrow -51.4^\circ$ (12 hours) (water); Ref. [2] m.p. 144–147°C, $[\alpha]_D^{20} -51.4^\circ$ (c 4, water + traces of NH_3) and $[\alpha]_D^{20} -52.0^\circ$ for a recrystallized product; Ref. [5] m.p. 146–147°C, $[\alpha]_D^{22} -52.6^\circ$ (c 2.6, water).

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Translated by P. Biely