Reactions of saccharides catalyzed by molybdate ions XXXII.* Efficient preparation of D-mannose and methyl α-D-mannoside

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From a mixture of D-glucose and D-mannose obtained after molybdate catalyzed epimerization of D-glucose, D-mannose is isolated in the form of *N*-phenyl-D-mannosylamine or methyl α-D-mannopyranoside. Regenerated D-glucose is used in further epimerization cycles. In one such a cycle, D-mannose or methyl α-D-mannopyranoside is obtained in 20 % yield as referred to the starting D-glucose.

Из смеси D-глюкозы и D-маннозы, образующейся в результате эпимеризации D-глюкозы, катализируемой молибдатом, была выделена D-манноза в виде *N*-фенил-D-маннозиламина или метил α-D-маннопиранозида. Регенерированная D-глюкоза используется в дальнейших эпимеризационных циклах. В каждом таком цикле выход D-маннозы или метил α-D-маннопиранозида составляет 20 % в расчете на исходную D-глюкозу.

In a series of papers we have described a very efficient method for preparation of aldoses (aldotetroses through aldooctoses) by molybdate catalyzed epimerization of easily available aldoses. The epimerization itself is technically a very simple operation, however, when carried out on a preparative scale, there is usually a problem of easy and cheap separation of aldoses from the epimerization mixtures. The epimerization of glucose (D-glucose [1], D-[1-^{3}H]glucose [2], D-[U-^{14}C]glucose [3]) or mannose (D-mannose [1], D-[2-^{3}H]mannose [2], L-mannose [4]) always leads to an equilibrium mixture of glucose and mannose in the mass ratio 3 : 1. From such a mixture about 50 % of D-glucose is recovered by crystallization from alcohols [1, 4] and D-mannose is isolated as its phenylhydrazone [1] or *N*-phenylglycosylamine [5], or chromatographically [2, 3]. In this work we studied conditions of the isolation of D-mannose and regeneration of D-glucose from the equilibrium epimerization mixture *via* their *N*-phenylglycosylamines and methyl glycosides (Scheme 1).

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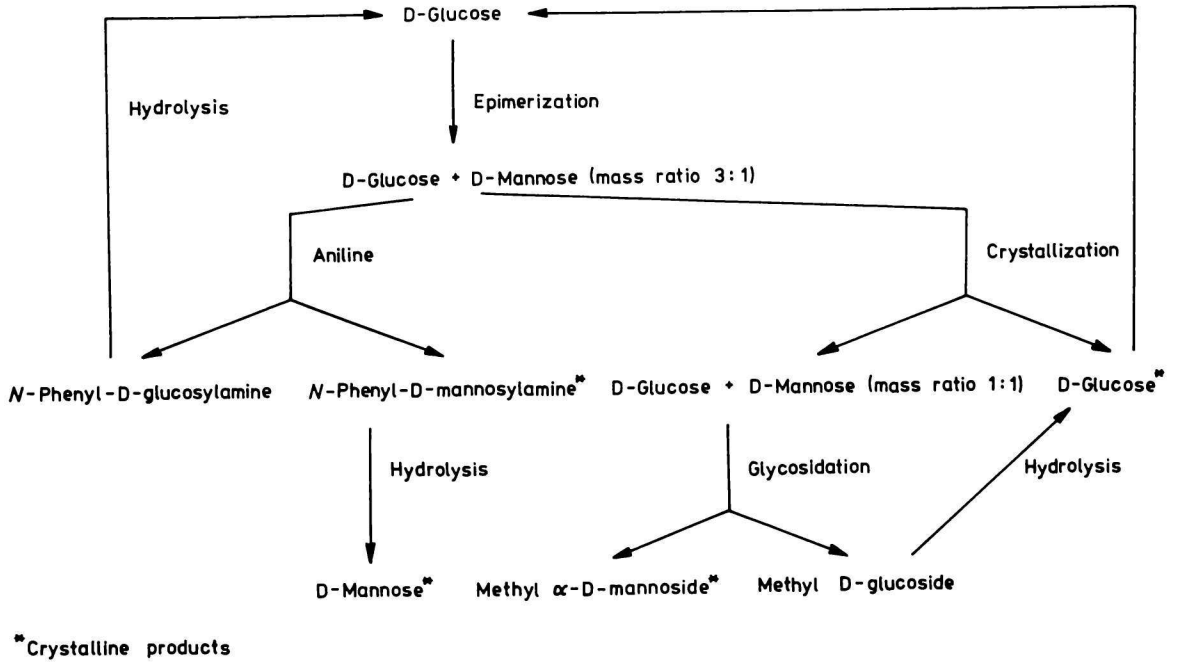
D-Glucose
Hydrolysis
Epimerization
D-Glucose + D-Mannose (mass ratio 3:1)
Aniline
Crystallization
N-Phenyl-D-glucosylamine
N-Phenyl-D-mannosylamine*
D-Glucose + D-Mannose (mass ratio 1:1)
D-Glucose*
Hydrolysis
Glycosidation
Hydrolysis
D-Mannose*
Methyl α-D-mannoside*
Methyl D-glucoside
*Crystalline products

Scheme 1

Aldoses of the homomorphous series of D-mannose can be separated from other aldoses and ketoses in the form of their well crystallizing *N*-phenylglycosylamines (lyxose [6], mannose [5, 7], mannoheptose [8]). 4-Nitrophenyl-*N*-glycosylamines proved to be useful for the isolation of D-glucose from a saccharose hydrolysate, D-mannose from a mannan hydrolysate [9] and L-arabinose from a mixture of arabinose and xylose originating in hemicellulose [10]. From *N*-phenylglycosylamines aldoses are liberated on hydrolysis with acetic acid [9, 10], formic acid [11] or by replacement of aniline with formaldehyde [7] or, more often, with benzaldehyde [12]. Another procedure for the liberation of aldoses is based on hydrolysis of *N*-phenylglycosylamines during a water vapour distillation [5, 6, 8]. Some methyl derivatives of aldohexoses are obtained from their *N*-phenylglycosylamines by hydrolysis catalyzed with an Amberlit IR 120 ion exchanger [13].

D-Glucose epimerization catalyzed by molybdate ions leads to an equilibrium mixture of epimeric aldoses containing 24—28 % of D-mannose. By the procedure suggested, from such a mixture 19—21 % of D-mannose is isolated as crystalline *N*-phenyl-D-mannosylamine from which D-mannose is liberated on hydrolysis in aqueous solution in the presence of strongly acidic ion exchangers (Amberlit IR 120, Dowex 50 W, Ostion KS, Wofatit KPS) (room temperature, 4—5 h). The liberated aniline remains bound to the ion exchanger so that the solution contains only D-mannose. This is a suitable procedure for liberation of ribose and lyxose from their N-phenylglycosylamines and liberation of arabinose from 4-nitrophenyl-*N*-arabinosylamine. During isolation of aldoses from the epimerization mixtures it is necessary to remove completely molybdate ions to prevent the reverse epimerization. The reverse epimerization can be efficiently prevented by oxalic acid or citric acid which form very stable complexes with molybdate ions [14]. The recovery of D-glucose from the mother liquor devoid of *N*-phenyl-D-mannosylamine is accomplished by means of a strongly acidic ion exchanger similarly as the liberation of D-mannose from its *N*-phenylglycosylamine. The regenerated D-glucose can be used in further epimerizations to D-mannose or can be fermented. The ion exchangers can be reused after recycling to the H^+ form with hydrochloric acid which liberates aniline as anilinium chloride.

A convenient reaction which can be coupled to the epimerization of D-glucose is the preparation of methyl α-D-mannopyranoside. From a pure D-mannose the glycoside is easily prepared by the Fischer method of glycosidation. A reflux of D-mannose in methanol at higher mass concentrations of mineral acids ($\varrho = 0.25$ % HCl) and elevated temperature gives methyl α-D-mannopyranoside as the main product [15]. Glycosidation under milder conditions (catalysis by a catex) leads to a mixture of methyl α-D-mannopyranoside and methyl α-D-mannofuranoside in the mass ratio 1 : 1 containing also small amounts of the corresponding β-anomers [16]. Interconversions of the isomeric forms of methyl D-mannoside occur already under very mild conditions ($\varrho = 0.01$ or 0.1 % HCl in methanol, 35 °C) and in all

cases they lead preferably to α-anomers [17]. The procedure of methyl α-D-mannopyranoside preparation described in the present paper explores conditions of the preferable formation of methyl α-D-mannopyranoside which is isolated from the reaction mixture by an exceptionally good crystallization from methanolic solution. After removal of a part of D-glucose by crystallization, the epimerization mixture usually contains 45—50 % of D-glucose and 50—55 % of D-mannose. After glycosidation ($\varrho = 1.35$ % H_2SO_4 in methanol, 65 °C, 8 h) the content of D-glucose and D-mannose in the mixture is reduced to 15 % and 5 %, respectively. From these results one may infer that glycosidation of D-mannose proceeds two times faster than that of D-glucose (Table 1). The yield of crystalline methyl α-D-mannoside referred to the starting D-mannose is about 80 %, regardless the glycosidation is carried out with pure D-mannose or with a D-glucose/D-mannose mixture in which D-glucose does not exceed the amount of D-mannose.

Table 1

Glycosidation of the epimerization mixture of D-glucose and D-mannose obtained after removal of a part of D-glucose by crystallization
Glycosidation conditions: $\varrho = 1.35$ % H_2SO_4 in methanol, 65 °C

$\frac{t}{h}$	$\frac{w\text{(D-Mannose)}}{\%}$	$\frac{k}{h^{-1}}$	$\frac{w\text{(D-Glucose)}}{\%}$	$\frac{k'}{h^{-1}}$	k/k'
0	100 (52)*		100 (48)*		
0.5	61 (32)		88 (42)		
1	47 (24)	0.51	78 (37)	0.24	2.2
1.5	39 (20)	0.37	72 (35)	0.16	2.3
2	32 (17)	0.39	66 (32)	0.17	2.3
3	23 (12)	0.33	57 (27)	0.15	2.3
4.5	15 (8)	0.28	45 (22)	0.16	1.8
6	10 (5)	0.27	36 (17)	0.15	1.8
8	6 (3)		30 (14)		

* Actual content of D-glucose and D-mannose in the glycosidation mixture (66 % of D-glucose were removed from the original epimerization mixture by crystallization).

Experimental

Epimerization of D-*glucose*

A mixture of D-glucose (300 g), water (900 cm³), ammonium molybdate (1.5 g), and acetic acid (6 cm³) was heated at 95—100 °C for 4 h and then concentrated *in vacuo* to a sirup from which D-mannose was isolated *via* *N*-phenyl-D-mannosylamine (see the "Isolation of D-mannose") or as methyl α-D-mannopyranoside.

Isolation of D-*mannose*

A hot sirupy residue obtained after concentration of the epimerization mixture of D-glucose was poured to a warm ethanolic solution of aniline (900 cm^3 of 96 % ethanol and 120 cm^3 of aniline) and left to stand at room temperature for 8—20 h. The separated white crystals of *N*-phenyl-D-mannosylamine (80—90 g) were filtered off and the mother liquor was used for regeneration of D-glucose (see the "Regeneration of D-glucose — Procedure *A*").

Liberation of D-mannose from *N*-phenyl-D-mannosylamine was done either by a water vapour distillation technique (Procedure *A*) or by hydrolysis catalyzed by a strongly acidic ion exchanger in the H^+ form (Procedure *B*).

Procedure A

An aqueous solution of *N*-phenyl-D-mannosylamine (300 g) was subjected to water vapour distillation (terminated after collection of 2—2.5 dm^3 of distillate), the hydrolysate was filtered and, after addition of a strongly acidic ion exchanger in the H^+ form (50 cm^3, Wofatit KPS), stirred at room temperature for 4 h. The ion exchanger was filtered off and the filtrate mixed with oxalic acid (1—2 g) and evaporated under reduced pressure to a residue which was crystallized from 96 % ethanol (200 cm^3).

Procedure B

A mixture of *N*-phenyl-D-mannosylamine (200 g), water (1000 cm^3), and a strongly acidic ion exchanger in the H^+ form (500 cm^3, Ostion KS 0210) was stirred at room temperature for 5 h. After removal of the ion exchanger, the filtrate was supplied with oxalic acid and further processed as in the procedure *A*.

D-Mannose, recrystallized from methanol, showed m.p. = 129—130 °C and $[\alpha]_D^{23} = (+26.5° \pm 0.5°)$ (5 min) $\rightarrow (+13.5° \pm 0.5°)$ (24 h) ($\varrho = 1$ %, water) and $[\alpha]_D^{23} = (-32° \pm 1°)$ ($\varrho = 1$ %, 4 % aqueous solution of ammonium molybdate). Ref. [18] gives for α-D-mannopyranose m.p. = 133 °C and $[\alpha]_D = +29.3° \rightarrow +14.2°$ (water); and for β-D-mannopyranose m.p. = 132 °C and $[\alpha]_D = -17.0° \rightarrow +14.2°$ (water).

Methyl α-D-*mannopyranoside*

Methyl α-D-mannopyranoside was obtained by glycosidation of the epimerization mixture of D-glucose and D-mannose (Procedure *A*) or by glycosidation of pure D-mannose (Procedure *B*).

Procedure A

The sirupy residue obtained after D-glucose epimerization (see the "Epimerization of D-glucose") was dissolved in methanol (200 cm^3), warmed up and, under heating, diluted with ethanol (200 cm^3) and left to stand at room temperature for 20 h. Crystalline D-glucose

(140—170 g) was filtered off and the mother liquor evaporated to dryness. The residue was dissolved in methanol (1000 cm^3) and, after addition of dimethyl sulfate (10 cm^3), heated at 65 °C for 8 h. After 20 h standing at room temperature the first crop of crystalline methyl α-D-mannoside (30—32 g), $[\alpha]_D^{23} = (+77° \pm 1°)$ (*c* 1, water), was isolated. Concentration of the mother liquor to one third of the volume followed by crystallization gave the second portion of the product (12—14 g), $[\alpha]_D^{23} = (+74° \pm 1°)$ ($\varrho = 1$ %, water).

Procedure B

A mixture of D-mannose (100 g), methanol (1000 cm^3), and dimethyl sulfate (10 cm^3) was heated at 65 °C for 8 h and then kept at room temperature for 20 h. Crystalline methyl α-D-mannoside (89 g) was filtered off and the filtrate was supplied with a new portion of D-mannose (100 g) and the volume adjusted with methanol to 1000—1100 cm^3. This new reaction mixture was refluxed for 8 h and further processed as above to give further methyl α-D-mannoside (87 g). The next glycosidation cycle was started after addition of further D-mannose (100 g) to give a third crop of methyl α-D-mannoside (85 g). Finally, the filtrate was neutralized with powdery calcium carbonate or barium carbonate, evaporated and crystallized to give the fourth portion of methyl α-D-mannoside.

Recrystallization of methyl α-D-mannoside

Methyl α-D-mannoside (100 g) was dissolved under heating in 5 % aqueous solution of acetic acid (150 cm^3). The hot solution was filtered to a hot methanol (450 cm^3) and then left to crystallize at room temperature for 5—20 h to give methyl α-D-mannopyranoside, m.p. = 186—188 °C and $[\alpha]_D^{23} = (+78° \pm 0.5°)$ (ϱ = 2 %, water); Ref. [16] m.p. = 190—192 °C, $[\alpha]_D^{20} = +78°$ ($\varrho = 2$ %, water).

Regeneration of D-*glucose*

Regeneration of D-glucose from the epimerization mixture was done by procedure *A* after removal of D-mannose *via* *N*-phenyl-D-mannosylamine or by procedure *B* after removal of D-mannose as methyl α-D-mannoside.

Procedure A

The mother liquor obtained after the removal of crystalline *N*-phenyl-D-mannosylamine (see the "Isolation of D-mannose") was concentrated to a half volume, diluted with water (1000 cm^3), mixed with a strongly acidic cation exchanger in the H^+ form (Ostion KS 0210, 1000 cm^3) and the mixture was stirred at room temperature for 5 h. The ion exchanger was filtered off, washed with water and the filtrate was concentrated to a 15—25 % D-glucose sirup (determined refractometrically), acidified with acetic acid (pH 3—5) and, after addition of molybdic acid (1 g), subjected to further epimerization cycle and subsequent isolation of D-mannose.

Procedure B

The methyl α-D-mannoside mother liquor (see the "Methyl α-D-mannopyranoside — Procedure *A*") was diluted with water (500 cm^3) and ammonium molybdate (1 g) was added. After removal of methanol by distillation (90 °C, 2 h), the mixture was heated at 95—100 °C for 3 h, then cooled, neutralized with powdery calcium carbonate or barium carbonate, filtered, the filtrate concentrated and used for further cycle of D-mannose isolation.

Methylglycosidation of D-*glucose/*D-*mannose mixture*

The epimerization of D-glucose (300 g) (see the "Epimerization of D-glucose") gave an equilibrium mixture of D-glucose and D-mannose in the mass ratio 73:27 from which 145 g of D-glucose was removed by crystallization (see the "Methyl α-D-mannopyranoside — Procedure *A*"). The mother liquor containing D-glucose and D-mannose in the mass ratio 48:52 was evaporated to dryness, dissolved in methanol (1000 cm^3), warmed up to 65 °C and mixed with dimethyl sulfate (10 cm^3). From the reaction mixture kept at 65 °C aliquots were taken at time intervals and analyzed for the content of D-glucose and D-mannose (Table 1).

Determination of D-*glucose and* D-*mannose*

2 cm^3 aliquots taken were mixed with 2 cm^3 of 10 % aqueous solution of D-galactose (internal standard), and 5×10^{-3} cm^3 of this mixture were chromatographed on Whatman No. 1 paper in ethyl acetate—pyridine—water (volume ratio 8:2:1, 23 °C, 25 h). The dry chromatogram was detected with the anilinium hydrogen phthalate reagent (1 cm^3 of aniline and 1.5 g of phthalic acid in 100 cm^3 of acetone). The spots of D-galactose, D-glucose, and D-mannose developed during heating (105 °C, 5 min) were separately eluted with 5 cm^3 of water (5 h, room temperature) and the absorbance of the solutions was measured at 410 nm in 1 cm cuvettes. The ratio of absorbances corresponds to the mass ratio of aldoses. The rate constants of the glycosidation of D-mannose (k) and D-glucose (k') were calculated using the rate equation of the first-order reaction (Table 1).

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