Reactions of saccharides catalyzed by molybdate ions. XVI.* Preparation and epimerization of D-*glycero*-L-gluco- and D-*glycero*-L-mannoheptose

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D-*glycero*-L-Glucoheptose and D-*glycero*-L-mannoheptose were obtained by oxidative decomposition of 1-deoxy-1-nitroalditols prepared by nitromethane synthesis with D-galactose. The aldoheptoses epimerize under catalytic action of molybdate ions giving an equilibrium mixture of D-*glycero*-L-glucoheptose and D-*glycero*-L-mannoheptose in a ratio 4 : 1. The epimerization reaction was applied for reciprocal preparation of both of the mentioned aldoheptoses.

Окислительным разложением 1-деокси-1-нитроальдитолов, приготовленных нитрометановым синтезом из D-галактозы, были получены D-*глицеро*-L-глюкогептоза и D-*глицеро*-L-маногептоза. Альдогептозы при каталитическом действии молибдатных ионов эпимеризуют с образованием равновесной смеси D-*глицеро*-L-глюкогептозы и D-*глицеро*-L-маногептозы в отношении 4 : 1. Реакция эпимеризации была применена для приготовления указанных альдогептоз их взаимной эпимеризацией.

In previous papers we have shown that aldoses epimerize in mild acid aqueous solutions under catalytic action of molybdate ions forming an equilibrium mixture of epimeric aldoses in which the aldose having in the preferred conformation less factors of conformation instability predominates [1]. In homomorphous series of aldoses (xylose, chinovose, glucose or lyxose, rhamnose, mannose), the equilibrium ratio of epimeric aldoses is affected by substituents at C-5. For this reason we have concentrated on the preparation and epimerization of a further epimeric pair of aldoses.

Complexing of molybdate ions with aldoses in aqueous solutions brings about changes in the specific rotation of their original anomeric-tautomeric equilibria. Specific rotations of the molybdate complexes of aldoses show extreme values at pH 6 ± 0.2 (Fig. 1). In the homomorphous series of aldoses with L-lyxopyranose and L-xylopyranose as the basic members, the values of specific rotation of molybdate complexes are shifted to the values of specific rotation of their β- or α-anomers (Table 1). The changes in specific rotation are substantially influenced by the substituent at C-5 which, depending on its mass and character, increases the conformation stability of aldose and thus suppresses its ability to form the

* For Part XV see Ref. [3].

molybdate complex. The aldoses in the homomorphous series of lyxopyranose are particularly suitable for the formation of rather stabile molybdate complexes which, in contrast to the molybdate complexes of aldoses having *trans* arrangement of the hydroxyl groups at atoms C-2 and C-3, are electrophoretically mobile [2].

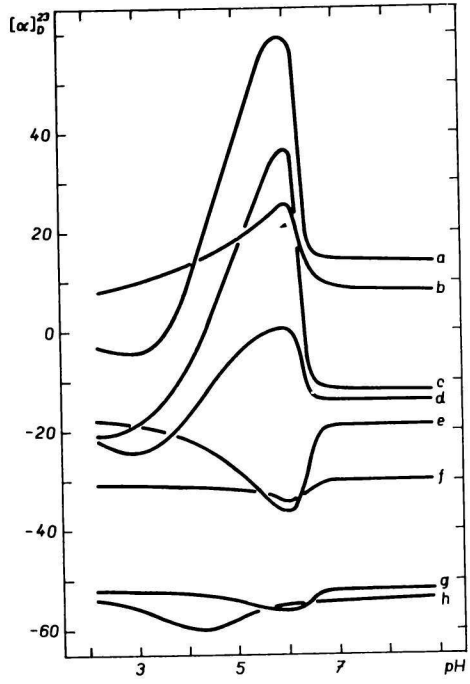


Fig. 1. Specific rotations of aldoses of the homomorphous series i solutions of molybdate as a functio of pH.
a) L-Lyxose ; *b*) L-rhamnose ; *c*) L-mannose ; *d*) D-*glycero*-L-mannoheptose ; *e*) L-xylose ; *f*) L-chinovo- ; *g*) L-glucose ; *h*) D-*glycero*-L-glucoheptose.

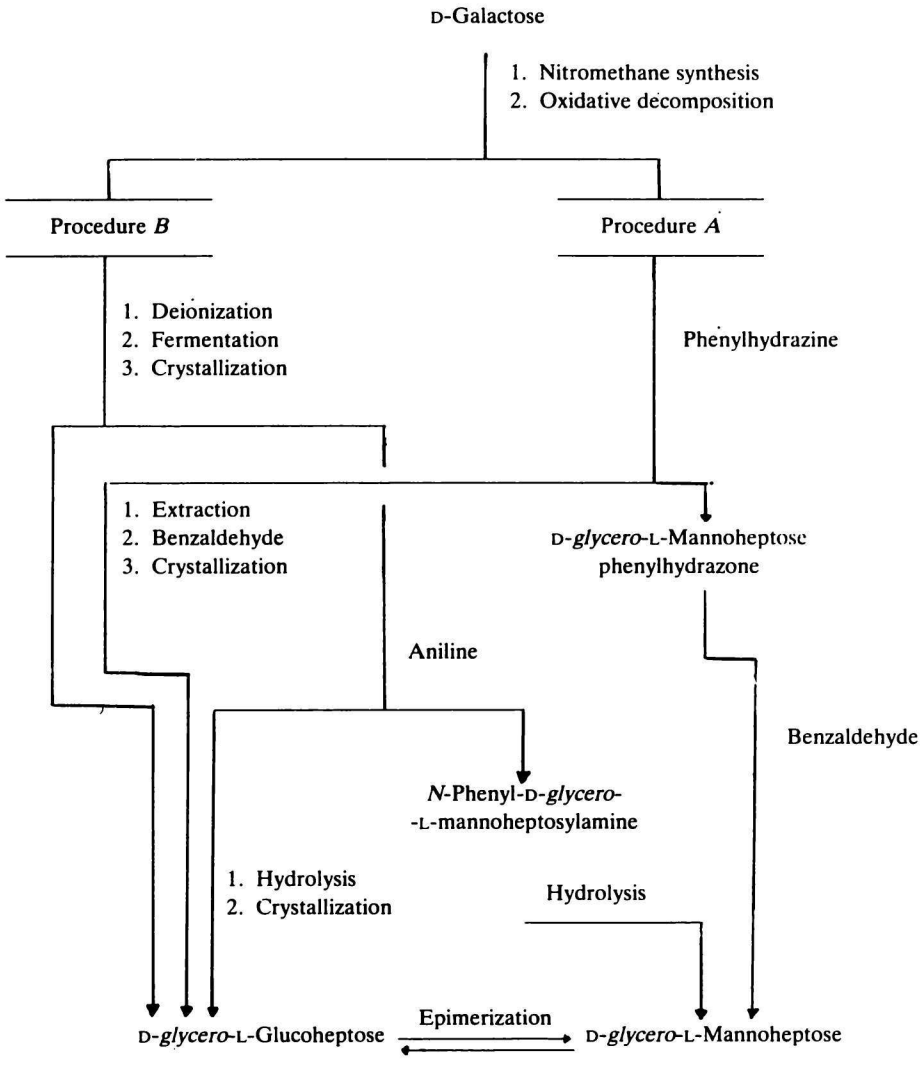
In the reaction catalyzed by molybdate ions, D-*glycero*-L-glucoheptose or D-*glycero*-L-mannoheptose epimerize under the formation of an equilibrium mixture of D-*glycero*-L-glucoheptose and D-*glycero*-L-mannoheptose in a ratio 4 : 1. The equilibrium ratio of aldoses resulting from the epimerization of aldohexoses (glucose—mannose 3 : 1), 6-deoxy-aldohexoses (chinovose—rhamnose 3 : 2), and aldopentoses (xylose—lyxose 10 : 9) increases with the mass of the C-5 substituent. The epimerization of aldose is an intramolecular process which involves the exchange of the hydrogen atoms at C-1 and C-2, and its efficiency is conditioned by the formation of the molybdate complex [3]. The possibility of an aldose to undergo such a rearrangement results in the formation of an equilibrium

Table 1

Extreme values of specific rotation of aldoses of the homomorphous series

Aldose	$[\alpha]_D^{23}$		$[\alpha]_D$ of anomer		Ref.
	in water (equil.)	in molybdate solution (pH 6)	α- (in water)	β- (in water)	
L-Lyxose	+14	+59		+73*	[5*a*]
L-Rhamnose	+ 8	+25		+38	[5*b*]
L-Mannose	−14.5	+36		+14	[5*c*]
D-*glycero*-L-Mannoheptose	−14	± 0		—	
L-Xylose	−19	−36	− 79		[6]
L-Chinovose	−30	−34	− 64		[7]
L-Glucose	−52	−56	−110		[8]
D-*glycero*-L-Glucoheptose	−53	−55 (−60 at pH 3.1)	—		

* Value of the optical antipode.



Scheme 1

mixture of epimeric aldoses, in which the aldose less suitable for the complexing with molybdate ions predominates.

The nitromethane synthesis with D-galactose described by *Sowden* and *Storbach* [4] gave 1-deoxy-1-nitroheptitols which after separation by fractional crystallization and decomposition by Nef reaction were converted to the corresponding aldoheptoses. In the present work, the sodium salts of nitroheptitols prepared from

D-galactose were decomposed by hydrogen peroxide under catalytic action of molybdate ions affording aldoheptoses (Scheme 1). This route is particularly convenient for the preparation of D-*glycero*-L-mannoheptose, because it can be isolated from the reaction mixture as its phenylhydrazone (only slightly soluble in water and alcohols). Unusually simple is the preparation of D-*glycero*-L-glucoheptose by molybdate catalyzed epimerization of D-*glycero*-L-mannoheptose since the product crystallizes directly from the reaction mixture at the equilibrium.

Experimental

The ratio of epimeric aldoheptoses in the reaction mixtures at the equilibrium as well as the purity of isolated aldoheptoses were examined by chromatography on Whatman No. 1 paper in the solvent system *n*-butanol—ethanol—water (5 : 1 : 4, v/v) for 3 days followed by visualization with the hydrogen phthalate-aniline reagent and scanning of the colour spots with an ERI-10 densitometer (Zeiss, Jena). Melting points were determined on a Kofler stage and pH of solutions was measured with a Titrator equipment, type TTT2 (Radiometer, Copenhagen). Specific rotations were measured on a Perkin—Elmer type 141 polarimeter. The effect of pH on specific rotation of aldoses in the presence of molybdate was followed in aqueous solution containing 2% aldose (L-lyxose, L-rhamnose, L-mannose, D-*glycero*-L-mannoheptose, L-xylose, L-chinovose, L-glucose, D-*glycero*-L-glucoheptose) and 4% molybdenic acid (pH 2.2), ammonium molybdate (pH 5.7) or sodium molybdate (pH 8.9) or a mixture of these three basic solutions to give desired values of pH (Fig. 1).

Preparation of D-*glycero*-L-*glucoheptose and* D-*glycero*-L-*mannoheptose*

Nitromethane synthesis and oxidative decomposition

D-Galactose (100 g) was dissolved in dimethyl sulfoxide (250 ml), methanol (500 ml), nitromethane (200 ml) and, under occasional agitation, methanolic solution of sodium methanolate (25 g of sodium in 750 ml of methanol) were added. After 20 hrs sodium salts of nitroheptitols were separated from the reaction mixture by filtration and dissolved in 0.05 N-NaOH (1000 ml). To this solution, sodium molybdate (5 g) was added first and then 15% solution of hydrogen peroxide (200 ml) at a rate to keep the temperature of the reaction mixture below 30°C. After the mixture was left to stand for 24 hrs, 5% Pd/C (*ca.* 0.5 g) was added. Further standing for 24 hrs was followed by addition of acetic acid (25 ml), air bubbling for 4 hrs, filtration and isolation of aldoheptoses as described below (procedures *A* and *B*).

A. Isolation of aldoheptoses

D-*glycero*-L-Mannoheptose. To the solution obtained after oxidative decomposition of sodium salts of nitroheptitols, a solution of phenylhydrazine (60 ml) in ethanol (180 ml) was added and the reaction mixture was kept at room temperature for 20 hrs. D-*glycero*-L-Mannoheptose phenylhydrazone was filtered off (37 g, 21% yield based on the starting D-galactose), suspended in water (370 ml), and ethanol (35 ml), benzaldehyde (25 ml), and pyridine (10 ml) were added. After heating at 100°C for 3 hrs, the solution was filtered, extracted with ethyl acetate (3 × 100 ml), treated with charcoal and evaporated under reduced pressure to syrup. Resulting D-*glycero*-L-mannoheptose having $[\alpha]_D^{23}$ −15.5° (*c* 2, water) contained *ca.* 1% of D-*glycero*-L-glucoheptose. Chromatographically homogeneous D-*glycero*-L-mannoheptose was obtained after purification *via* *N*-phenyl-D-*glycero*-L-mannoheptosylamine. D-*glycero*-L-Mannoheptose (10 g) was dissolved in methanol (20 ml) and, after addition of aniline (5 ml), the mixture was crystallized in the dark at room temperature for 24 hrs to give

N-phenyl-D-*glycero*-L-mannoheptosylamine (9.5 g, *i.e.* 69.7%). Recrystallization from the mixture methanol—water (7:1) gave *N*-phenyl-D-*glycero*-L-mannoheptosylamine, m.p. 173—176°C, $[\alpha]_D^{23}$ +125° (5 min) → +115° (10 min) → +95° (30 min) → +86° (1 hr) → +85° (2 hrs), (*c* 0.2, methanol).

For $C_{13}H_{19}O_6N$ calculated: 54.73% C, 6.71% H, 4.91% N; found: 54.55% C, 6.75% H, 4.92% N.

Hydrolysis of *N*-phenyl-D-*glycero*-L-mannoheptosylamine by steam distillation followed by concentration of the solution afforded chromatographically homogeneous amorphous D-*glycero*-L--mannoheptose having softening point 57—61°C and $[\alpha]_D^{23}$ −14°±0.5° (*c* 2, water); Ref. [4] m.p. 83—85°C and $[\alpha]_D^{20}$ −13.7° (*c* 4, water).

D-*glycero*-L-Glucoheptose. The filtrate obtained after separation of D-*glycero*-L-mannoheptose phenylhydrazone was extracted with ethyl acetate (150 ml). The aqueous phase was further extracted with *n*-butanol to isolate D-galactose and D-*glycero*-L-glucoheptose phenylhydrazones. The *n*-butanol solution was evaporated and the residue was crystallized from ethanol to separate D-galactose phenylhydrazone. In order to isolate D-*glycero*-L-glucoheptose, the mother liquor was treated with benzaldehyde as described in the procedure for isolation of D-*glycero*-L-mannoheptose.

B. Isolation of aldoheptoses

The solution obtained after oxidative decomposition of nitroheptitols was deionized on columns of ion-exchangers Wofatit KPS in the H^+ form (5 × 130 cm) and Wofatit SBW in the acetate form (3 × 130 cm). The water eluate (8 l) was evaporated to a syrup which was dissolved in tap water (3 l). D-Galactose was removed by 2 week fermentation with added baker's yeast (25 g). The solution was then filtered, treated with charcoal and evaporated to syrup which was crystallized from a mixture water—methanol (1:2) at room temperature to give the first crop of crystalline D-*glycero*-L-glucoheptose (14.1 g). The mother liquor was evaporated to syrup (53 g) which was dissolved in methanol (106 ml) and, after addition of aniline (26.5 ml), crystallized for 24 hrs. After separation of crystalline *N*-phenyl-D-*glycero*-L-mannoheptosylamine (16.5 g, *i.e.* 10.4% based on the starting D-galactose), the mother liquor was hydrolyzed by steam distillation, evaporated and crystallized to give a further crop of crystalline D-*glycero*-L-glucoheptose (5.2 g, *i.e.* the total yield of 16.5%).

Recrystallization of D-*glycero*-L-glucoheptose (A g) from a mixture of water (2A ml) and methanol (3A ml) gave a chromatographically homogeneous product (70% yield) having m.p. 196—198°C and $[\alpha]_D^{23}$ −20° (4 min) → −53.5° (equil.) (*c* 2, water); Ref. [4] m.p. 198—199°C and $[\alpha]_D^{20}$ −50.7° (equil.) (*c* 4.6, water).

Preparation of D-*glycero*-L-*glucoheptose by epimerization of* D-*glycero*-L-*mannoheptose*

A mixture of D-*glycero*-L-mannoheptose (10 g), water (50 ml), and molybdenic acid (0.1 g) was heated at 90°C for 5 hrs. The reaction mixture was evaporated to dryness, and water (20 ml) and methanol (30 ml, under heating) were added. The resulting solution was crystallized to give D-*glycero*-L-glucoheptose (5.5 g). The mother liquor was evaporated, dissolved in water (25 ml) and epimerized and further treated as described above to give additional crystalline D-*glycero*-L-glucoheptose (2.1 g).

Preparation of D-*glycero*-L-*glucoheptose from* D-*glycero*-L-*mannoheptose phenylhydrazone*

A mixture of D-*glycero*-L-mannoheptose phenylhydrazone (20 g), water (150 ml), ethanol (25 ml), benzaldehyde (15 ml), and molybdenic acid (0.5 g) was heated at 95°C for 6 hrs. The reaction mixture was then filtered, the filtrate extracted by ethyl acetate (3 × 50 ml), purified with activated charcoal and concentrated to syrup. The syrupy residue was dissolved in water (15 ml) and, after addition of

methanol (50 ml, under heating), crystallized to give D-*glycero*-L-glucoheptose (5.1 g). The mother liquor was concentrated and epimerized as described in the foregoing section. This treatment afforded a further portion of crystalline D-*glycero*-L-glucoheptose (2.5—3 g).

The traces of molybdate present in the crystalline D-*glycero*-L-glucoheptose arising from the epimerization procedures were removed in water solutions on an anion exchanger (in the acetate form).

Preparation of D-*glycero*-L-*mannoheptose by epimerization of* D-*glycero*-L-*glucoheptose*

After the epimerization of D-*glycero*-L-glucoheptose (10 g) had reached the equilibrium of epimeric aldoheptoses, a part of D-*glycero*-L-glucoheptose was regenerated in the manner described in the procedure for preparation of D-*glycero*-L-glucoheptose by epimerization of D-*glycero*-L-mannoheptose. The mother liquor was mixed with phenylhydrazine (2.5 ml) and left to stand at room temperature for 20 hrs. D-*glycero*-L-Mannoheptose phenylhydrazone formed (3.1 g, *i.e.* 22%, m.p. 175—180°C; Ref. [4] m.p. 191—192°C) was filtered off and D-*glycero*-L-mannoheptose was liberated as given in the procedure *A*.

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