Reactions of saccharides catalyzed by molybdate ions. XVII.* Preparation of D-*glycero*-D-guloheptose and D-*glycero*-D-idoheptose

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Oxidative decomposition of epimeric nitroheptitols prepared by nitromethane synthesis with D-glucose gave D-*glycero*-D-guloheptose and D-*glycero*-D-idoheptose. In alkaline medium the main oxidative reaction is accompanied by a side elimination reaction leading to D-glucose.

Окислительным распадом эпимерных нитрогептитолов приготовленных нитрометановым синтезом из D-глюкозы была приготовлена D-*глицеро*-D-гулогептоза и D-*глицеро*-D-идогептоза. В щелочной среде рядом с основной реакцией окисления нитрогептитолов на альдогептозы протекает и побочная параллельная реакция выделения, которая ведет к D-глюкозе.

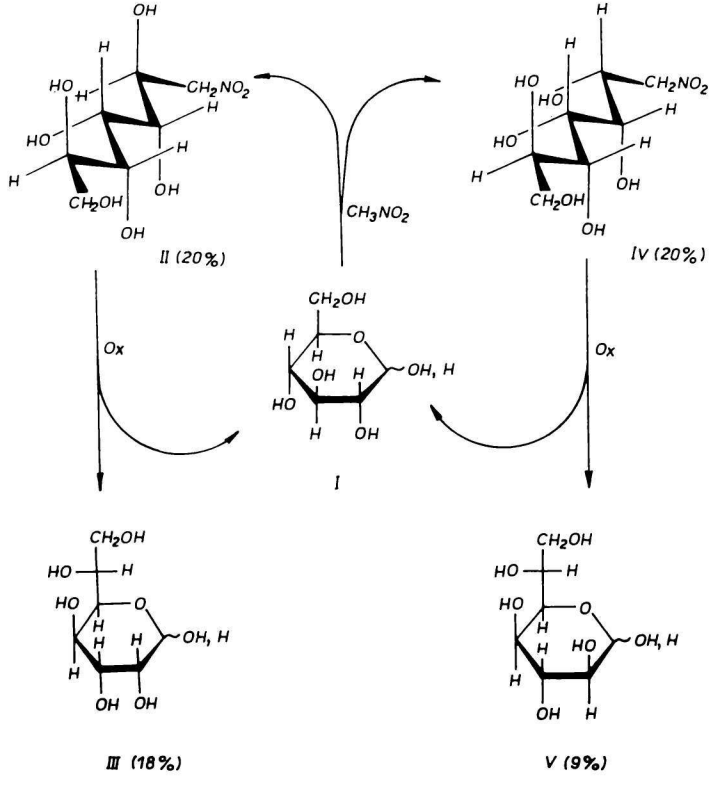
Nitromethane synthesis with 4,6-*O*-benzylidene-D-glucose gives 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol, which on the Nef reaction affords D-*glycero*-D-guloheptose isolated in the form of its benzylphenylhydrazone [1]. *Williams* and *Perry* [2] carried out nitromethane synthesis with D-glucose in methanolic solution of sodium methanolate and obtained a mixture of 1-deoxy-1-nitroheptitols (24% of D-*glycero*-D-gulo- and 19% of D-*glycero*-D-idoheptitol) which were separated by fractional crystallization. Subsequent Nef reaction afforded D-*glycero*-D-guloheptose and D-*glycero*-D-idoheptose (isolated in the form of dibenzyldithioacetal). Nitromethane synthesis with D-glucose in the presence of water and barium hydroxide leading to one epimer only, 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol, has also been described [3].

In our preceding works [4—7] the oxidative decomposition of sodium salts of nitroalditols with hydrogen peroxide under catalytic effect of molybdate ions was applied for preparation of the corresponding aldoses. Nitromethane synthesis followed by oxidative decomposition yielded 48% of L-mannose from L-arabinose, 62% of L-galactose and 11% of L-talose from L-lyxose [4], 43% of L-*glycero*-L-galactoheptose and 12% of L-*glycero*-L-taloheptose from L-mannose [5], 22% of D-altrose and 20% of D-allose from D-ribose [6], and 21% of D-*glycero*-L-mannoheptose and 17% of D-*glycero*-L-glucoheptose from D-galac-

* For Part XVI see Ref. [7].

tose [7]. During oxidative decomposition, sodium salts of nitroheptitols prepared from L-mannose were partially converted to starting L-mannose (8%) in a parallel elimination reaction. In the case of nitrohexitols prepared from D-ribose, this elimination reaction was even more pronounced (16% of ribose). In the present work we have focused on the preparation of D-*glycero*-D-guloheptose and D-*glycero*-D-idoheptose by oxidative decomposition of sodium salts of the corresponding nitroheptitols. The parallel elimination reaction leading back to starting D-glucose has also been examined.

Nitromethane synthesis with D-glucose in the medium of dimethyl sulfoxide—methanol in the presence of sodium methanolate gave a mixture of epimeric nitroheptitols in the ratio 1 1 and in 40% yield. After oxidative decomposition of the sodium salts of the epimeric nitroheptitols, deionization and fermentative removal of D-glucose, D-*glycero*-D-guloheptose was obtained on direct crystallization in 13.7% yield. Chromatographic fractionation on a cellulose column gave



Scheme 1

I. D-Glucose; *II.* 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol; *III.* D-*glycero*-D-guloheptose; *IV.* 1-deoxy-1-nitro-D-*glycero*-D-idoheptitol; *V.* D-*glycero*-D-idoheptose; Ox — oxidative decomposition.

further 4.6% of D-*glycero*-D-guloheptose and 9% of D-*glycero*-D-idoheptose. It was observed that oxidative decomposition of individual nitroheptitols afforded not only the corresponding aldoheptoses but also starting D-glucose formed in a side elimination reaction (Scheme 1). This elimination reaction is more significant with 1-deoxy-1-nitro-D-*glycero*-D-idoheptitol, since twice as much of D-glucose arose from this epimer than during oxidative decomposition of 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol. D-Glucose was determined by an enzymatic procedure [8] which was not interfered with D-*glycero*-D-guloheptose, D-*glycero*-D-idoheptose, sodium nitrate and nitrite present at equimolar ratios to D-glucose. The reactions catalyzed by catalase, glucosoxidase and peroxidase were inhibited by nitroheptitols and nitromethane, which were not present, however, in the reaction mixture after oxidative decomposition.

The effect of the parallel elimination reaction was enhanced by increase of the alkalinity of the reaction medium (Table 1). From this reason, in the preparation of

Table 1

Effect of alkalinity of the reaction medium on the formation of D-glucose during oxidative decomposition of sodium salts of nitroheptitols

1-Deoxy-1-nitro-heptitol		NaOH mmol	D-Glucose mmol	%
-D-*glycero*-D-ido-				
a		1.25	1.25	0.14	11.6
b		1.25	1.40	0.19	15.1
c		1.25	1.55	0.25	20.0
d		1.25	1.70	0.29	23.4
e		1.25	1.85	0.34	27.3
-D-*glycero*-D-gulo-				
a		1.25	1.25	0.07	6.0
c		1.25	1.55	0.12	9.9
e		1.25	1.85	0.15	12.3

aldoses, it is desirable to submit the aqueous solutions of sodium salts of nitroheptitols to oxidative decomposition as soon as possible, since oxidative decomposition is accompanied by a change of pH of the reaction medium from pH 11 to pH 6 [6].

In regard to the significance and different rate of the reverse elimination reaction of the two epimeric nitroheptitols to starting D-glucose as a consequence of the alkalinity of the medium, the ratio of epimeric nitroheptitols resulting from nitromethane synthesis varies depending on the nature and concentration of the base and on the properties of the solvent used.

Experimental

Preparation of D-*glycero*-D-*guloheptose and* D-*glycero*-D-*idoheptose*

Nitromethane synthesis and oxidative decomposition

D-Glucose (100 g) was dissolved in dimethyl sulfoxide (400 ml) and mixed with methanol (200 ml), nitromethane (200 ml), and a solution of sodium methoxide (25 g of sodium in 750 ml of methanol) added in portions. The reaction mixture was left to stand for 20 hrs at room temperature and sodium salts of nitroheptitols were filtered off. For the determination of the ratio of epimeric nitroheptitols, a part of the sodium salts (*ca.* 1 g) was deionized on a cation exchanger and subjected to paper chromatography on Whatman No. 3 paper in *n*-butanol : ethanol : water (5 : 1 : 4, v/v). After visualization under u.v. light, the separated nitroheptitols were eluted with methanol and their ratio was determined as 1 : 1 by measuring the optical density at 224 nm.

Sodium salts of nitroheptitols were dissolved in water (1000 ml), sodium molybdate (5 g) was added followed by addition of 15% hydrogen peroxide in water (200 ml) at a rate to keep the temperature of the reaction mixture below 30°C. After standing for 24 hrs, the excess of hydrogen peroxide was decomposed by 24 hr treatment with 5% Pd/C (*ca.* 0.5 g) at room temperature. Finally acetic acid was added (25 ml) and the solution was bubbled with air for 4 hrs to decompose the present nitrites.

Isolation of aldoheptoses

The solution obtained after oxidative decomposition of nitroheptitols was deionized on columns of Wofatit KPS (H^+ form, 5 × 130 cm) and Wofatit SBW (acetate form, 3 × 130 cm). Water eluate (7 l) was evaporated *in vacuo* to a syrup which was dissolved in tap water (3 l) and fermented with yeast (25 g) until complete removal of D-glucose (2—3 days). The mixture was then filtered, concentrated to about 300 ml, mixed with methanol (300 ml) under heating, purified with charcoal and evaporated again. Resulting syrup (40 g) was crystallized from a mixture water (40 ml)—methanol (80 ml) to give D-*glycero*-D-guloheptose (16 g). A half of the mother liquor was chromatographed on a cellulose column (4 × 130 cm) with the system *n*-butanol—ethanol—water (5 : 1 : 4, v/v) to give D-*glycero*-D-idoheptose (4.7 g, in the elution volume 2300—2900 ml), a mixture of D-*glycero*-D-idoheptose and D-*giycero*-D-guloheptose in the ratio 1 : 1 (1.1 g, in the elution volume 2900—3200 ml) and D-*glycero*-D-guloheptose (2.1 g, in the elution volume 3200—3900 ml).

Chromatography of individual reaction components on Whatman No. 1 paper in *n*-butanol : ethanol : water for about 90 hrs showed following R_{Gl} values (D-glucose, 1.00): for D-*glycero*-D-guloheptose 0.85, D-*glycero*-D-idoheptose 1.32, 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol 1.98 and 1-deoxy-1-nitro-D-*glycero*-D-idoheptitol 1.72.

Recrystallization of the aldoheptoses from a mixture methanol—water or from methanol gave D-*glycero*-D-guloheptose, m.p. 190—198°C (Kofler), $[\alpha]_D^{23}$ −25° (4 min) → −22° (15 min) → −21° (30 min) → −19.5° (1 hr) → −19° (equil.) (*c* 2, water), and D-*glycero*-D-idoheptose, m.p. 121—124°C (Kofler), $[\alpha]_D^{23}$ −6.2° (3 min) → −2.2° (15 min) → −0.8° (20 min) → −0.4° (30 min) → −0.2° (1—3 hrs) (*c* 5, water).

Ref. [2] gives for D-*glycero*-D-guloheptose m.p. 193—194°C, $[\alpha]_D$ −22° → −18.5° (*c* 2.5, water). Ref. [9] gives for the same compound m.p. 195°C (decomp.), $[\alpha]_D^{20}$ −29° → −20° (equil.) (*c* 4, water) and for D-*glycero*-D-idoheptose m.p. 121°C, $[\alpha]_D^{20}$ −0.1° → −6° (18 min) → −0.1° (equil., 24 hrs) (*c* 5, water).

Effect of alkalinity during oxidative decomposition of nitroheptitols on reverse reaction to D-*glucose*

1-Deoxy-1-nitro-D-*glycero*-D-idoheptitol and 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol were isolated from the mixture of nitroheptitols prepared by nitromethane synthesis by fractional crystallization [2]. Oxidative decomposition of both nitroheptitols was carried out on a small scale under the conditions of the preparative reaction (*a*) and under increased basicity of the medium (*b*—*e*). D-Glucose was determined in the reaction mixtures (Table 1).

Nitroheptitol (1.25 mmole), sodium hydroxide (1.25—1.85 mmole) and sodium molybdate dihydrate (15 mg) were dissolved in water (3.0 ml) and 15% aqueous solution of hydrogen peroxide (0.6 ml) was added to the solution kept at 25°C. After standing for 24 hrs, the solution was treated with 5% Pd/C for 24 hrs. After addition of 10% acetic acid (0.75 ml), the mixture was filtered and adjusted to 25 ml by water. An aliquot (40 µl) diluted with 0.1 M phosphate buffer, pH 7 (5 ml) was mixed with a solution of beef liver catalase (EC 1.11.1.6, Boehringer) (3900 U in 0.02 ml), incubated for 1 hr and then heated at 100°C for 3 min. After cooling to 25°C, the solution was mixed with solutions of 30 U of glucoseoxidase of *Aspergillus niger* (EC 1.1.3.4, Sigma) (0.01 ml), 30 U of horse radish peroxidase (EC 1.11.1.7) (0.01 ml) and *o*-dianisidine (0.066 mg in 1 ml of 0.1 M phosphate buffer, pH 7). Samples were incubated at 25°C for 30 min and their absorbance at 346 nm was measured in 1 cm cells. D-Glucose in the concentration range 25—250 µg in the same phosphate buffer was used as a standard.

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