Preparation of aldoses by ozonolysis of sodium salts of 1-deoxy-1-nitroalditols

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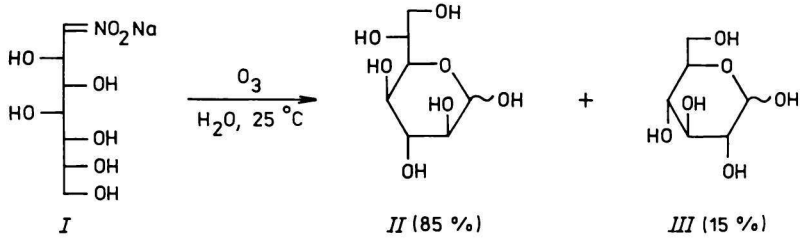
Treatment of aqueous solution of sodium salts of 1-deoxy-1-nitroalditols with ozone at room temperature results in high yields of the corresponding aldoses. By application of this new method L-glucose, L-mannose, D-*glycero*-D-*gulo*-heptose, D-*glycero*-D-*ido*-heptose, and D-*glycero*-L-*manno*-heptose have been prepared. Utilization of ozone in this conversion was 20 to 55 %.

Nitromethane synthesis is one of the most developed methods for elongation of the aldose chain. So far, usually two methods have been used for conversion of sodium salts of 1-deoxy-1-nitroalditols to the corresponding aldoses. They are disproportionation of the *aci*-nitro group with mineral acids under formation of aldose and nitrogen(I) oxide, known as the Nef reaction [1], and oxidation of the isonitro group with peroxo anions of transition metals, most advantageously of the six-valent molybdenum, under formation of aldose, nitrite, and nitrate, known as the oxidative decomposition [2]. In this contribution an alternative conversion of sodium salts of 1-deoxy-1-nitroalditols to aldoses has been achieved by treatment with ozone.



Scheme 1

Sodium salt of 1-deoxy-1-nitro-D-*glycero*-D-*ido*-heptitol [3] (*I*, Scheme 1) was rapidly converted to the corresponding aldose, *i. e.* D-*glycero*-D-*ido*-heptose (*II*), when treated with ozone in aqueous solution at 25 °C. The simultaneous formation of D-glucose (*III*) was a consequence of retroaldol reaction of *I* [3]. The advantage of ozonolysis, applied successively after nitromethane synthesis, is shown by the reaction of one of the conformationally least stable 1-deoxy-1-

Table 1

Conversion of 1-deoxy-1-nitro-D-*glycero*-D-*ido*-heptitol (*I*) to D-*glycero*-D-*ido*-heptose (*II*) and D-glucose (*III*)[a]

t/min	$m(I):m(II):m(III)$[b]	Unreacted amount of *I* / %	Utilization of ozone/%
2	1.7 : 6.0 : 0.8	20.0	53
4	0.3 : 7.0 : 1.0	3.6	27
6	0.0 : 7.2 : 1.2	0.0	22

a) Ozonolysis of *I* (0.2 g) in NaOH (2.4 cm^3; $c = 0.5$ mol dm^{-3}) at 25 °C and 40 mg min^{-1} flow rate of ozone.

b) Determined by liquid chromatography: column (95 cm × 1.2 cm) of Dowex 50 W × 8 (Ba^{2+} form), water elution at 15 cm^3 h^{-1} flow rate, elution volumes R_G are relative to that of D-glucose, $R_G(II) = 1.61$, $R_G(I) = 2.40$. Resolution (R_s of pairs of polyols) was calculated from the equation $R_s = 2(t_2 - t_1)/(w_1 + w_2)$, where t_1 and t_2 are retention times and w_1 and w_2 are the widths of the peaks. $R_s(III—II) = 3.2$ and $R_s(II—I) = 2.6$.

-nitroalditols, namely compound *I*. While in nitromethane synthesis of D-glucose, followed by oxidative decomposition, 18 % of D-*glycero*-D-*gulo*-heptose and 9 % of D-*glycero*-D-*ido*-heptose were obtained [3], by using ozonolysis in the second step the yields increased to 23 and 18 %, respectively. On application of the Nef reaction these saccharides were prepared in 10 and 9 % yields [4]. Utilization of ozone, followed in dependence on the degree of conversion of *I* to *II*, varied from 20 to 55 % (Table 1). During ozonolysis the *aci*-nitro group of nitroalditol is converted to nitrate anion. The presence of sodium nitrate in the resulting reaction mixture was confirmed by comparison of its IR spectrum with that of the commercial product. Due to simple composition of the reaction mixture after ozonolysis, the isolation of the prepared aldoses is very simple. The reaction mixture is exposed to vacuum or bubbling through with nitrogen for a few minutes to remove the ozone residues and then deionized with cation- and anion-exchangers. From the starting 1-deoxy-1-nitro-D-*glycero*-D-*gulo*--heptitol [3] after ozonolysis in aqueous solution of sodium hydroxide it was possible to obtain as much as 76 % crystalline D-*glycero*-D-*gulo*-heptose. Formation of acid derivatives of saccharides in ozonolysis of sodium salts of 1-deoxy-1-nitroalditols with ozone generated from pure oxygen has not been observed.

Combination of nitromethane synthesis with ozonolysis as a general method for elongation of the carbon chain of aldoses was shown to be advantageous also in preparation of some other aldoses. Thus, from L-arabinose 37 % of L-mannose and 19 % of L-glucose, and from 1-deoxy-1-nitro-D-*glycero*-L--*manno*-heptitol [5] 57 % of D-*glycero*-L-*manno*-heptose were prepared.

Experimental

Melting points were measured on a Kofler block, optical rotations were taken with a Perkin—Elmer 140 polarimeter, and IR spectra with a Perkin—Elmer 457 spectrophotometer. Ozone was generated from gaseous oxygen in a Fischer 502 generator. Liquid chromatography of the reaction mixtures was performed in a closed system composed of a peristaltic VCM 300 pump (Czechoslovak Academy of Sciences, Prague), six-way valve [6], a column (95 cm × 1.2 cm) of Dowex 50 W × 8 (bead size 75—150 μm; Ba^{2+} form), and of a Knauer 5100 refractometer.

Ozonolysis of 1-deoxy-1-nitro-D-*glycero*-D-*ido-heptitol (I)*

The compound *I* (0.2 g) was dissolved in aqueous solution of sodium hydroxide (2.4 cm^3, $c = 0.5$ mol dm^{-3}) and the solution was bubbled through with ozone at 40 mg min^{-1} flow rate and 25 °C for 2, 4, or 6 min. The reaction mixture was deionized (strongly acidic cation exchanger in H^+ form, strongly basic anion exchanger in HCO_3^- form) and evaporated at reduced pressure to give a sirup which, after dissolution in water (0.4 cm^3), was analyzed by liquid chromatography (water elution at 15 $cm^3 h^{-1}$ flow rate). The results of analysis are presented in Table 1.

D-*Glycero*-D-*gulo-heptose and* D-*glycero*-D-*ido-heptose*

Into the solution of D-glucose (5 g) in dimethyl sulfoxide (20 cm^3) methanol (10 cm^3), nitromethane (10 cm^3), and methanolic solution of sodium methoxide (1.3 g of sodium, 35 cm^3 of methanol) were added at stirring. After 1 h reaction 1-butanol (25 cm^3) was added to the formed precipitate, the mixture was stirred and allowed to stay in the dark for 24 h. The precipitate was filtered off, washed with the mixture of 1-butanol—methanol ($\varphi_r = 2:1$; 3 × 10 cm^3), and added into water (70 cm^3) saturated with ozone. Then at 20—25 °C ozone (30 mg min^{-1}) was introduced into the mixture for 3 h. The unreacted ozone was captured in 10 % aqueous solution of potassium iodide. The reaction mixture was made neutral by deionization with strongly acidic cation exchanger in H^+ form and strongly basic anion exchanger in HCO_3^- form. The deionized solution was evaporated under reduced pressure to a sirup which was dissolved in tap water (200 cm^3) and treated with baker's yeast (1 g) at 30 °C for 48 h. The solution was filtered off and after addition of a small amount of 1-hexadecanol it was evaporated under reduced pressure to a sirup. This was dissolved at heating in the mixture of water—methanol ($\varphi_r = 1$ 1; 30 cm^3), charcoal (0.3 g) was added and the solution was filtered off. The last operation was repeated thrice. The obtained sirup (3.5 g) was crystallized from the mixture of water—methanol ($\varphi_r = 1:3$) to give the first portion of D-*glycero*-D-*gulo*-heptose (0.68 g; 11.7 %). Column separation using water as eluent at 15 $cm^3 h^{-1}$ flow rate resulted in the second portion of D-*glycero*-D-*gulo*-heptose (0.7 g; 12 %) of m. p. = 194—197 °C, $[\alpha]$ (D, 20 °C, water, $\varrho = 20$ g dm^{-3}) = −18.5° (Ref. [3] gives m. p. = 190—198 °C and $[\alpha]$ (D,

20 °C, water, $\varrho = 20\ \mathrm{g\,dm^{-3}}$) = −19.0°) and D-*glycero*-D-*ido*-heptose (1.1 g; 18.9 %) of m. p. = 124—126 °C, [α](D, 20 °C, water, $\varrho = 20\ \mathrm{g\,dm^{-3}}$) = −0.1° (Ref. [3] gives m. p. = 121—124 °C and [α] (D, 20 °C, water, $\varrho = 50\ \mathrm{g\,dm^{-3}}$) = −0.2°).

D-*Glycero*-D-*gulo*-heptose was prepared also by the following procedure: Into the solution of 1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol ([3]; 0.3 g) in aqueous solution of sodium hydroxide (3.6 $\mathrm{cm^3}$; $c = 0.5\ \mathrm{mol\,dm^{-3}}$) ozone was introduced at 30 $\mathrm{mg\,min^{-1}}$ flow rate. The reaction mixture was deionized, concentrated, and crystallized. The obtained D-*glycero*-D-*gulo*-heptose (0.2 g; 76 %) had m. p. = 194—198 °C (H_2O—MeOH, $\varphi_r = 1:4$), [α] (D, 20 °C, water, $\varrho = 20\ \mathrm{g\,dm^{-3}}$) = −17.6°

L-*Glucose and* L-*mannose*

The reaction mixture obtained from the starting L-arabinose (5 g) and the other components by the above-mentioned procedure for preparation of heptoses from D-glucose was bubbled through with nitrogen for 10 min. Then phenylhydrazine (3.6 $\mathrm{cm^3}$) and ethanol (10 $\mathrm{cm^3}$) were added and the mixture was allowed to stay for 24 h. The crystalline precipitate was filtered off and washed with water ($3 \times 2\ \mathrm{cm^3}$). The obtained L-mannose phenylhydrazone (3.5 g; 38 %) had m. p. = 186—187 °C (Ref. [7] gives m. p. = 186—188 °C).

L-Glucose was obtained from the supernatant in the following way: To the supernatant benzaldehyde (3 $\mathrm{cm^3}$), pyridine (1.2 $\mathrm{cm^3}$), and ethanol (4.2 $\mathrm{cm^3}$) were added and the mixture was heated at 100 °C for 3 h. The cool mixture was filtered, the supernatant was washed with ethyl acetate ($3 \times 10\ \mathrm{cm^3}$) and about a tenth of it was distilled off at reduced pressure. The solution was decolorized with charcoal (0.1 g), filtered, and evaporated at reduced pressure. The sirupy mixture of L-glucose and L-arabinose (2.8 g) was fractionated by column chromatography using water as the eluent at 5 $\mathrm{cm^3\,h^{-1}}$ flow rate. Concentration of the first fraction and crystallization from methanol gave L-glucose (1.15 g; 19 %) of m. p. = 145—146 °C, [α] (D, 20 °C, water, $\varrho = 20\ \mathrm{g\,dm^{-3}}$) = −51.6° Ref. [7] gives m. p. = 145—146 °C and [α] (D, 22 °C, water, $\varrho = 26\ \mathrm{g\,dm^{-3}}$) = −52.6°

L-Mannose was released from phenylhydrazone by the already mentioned reaction with benzaldehyde (3.5 g of L-mannose phenylhydrazone, 2 $\mathrm{cm^3}$ of benzaldehyde, 3.5 $\mathrm{cm^3}$ of ethanol, 1 $\mathrm{cm^3}$ of pyridine, and 20 $\mathrm{cm^3}$ of water). The obtained supernatant was concentrated *in vacuo* and the residue was crystallized from methanol to give L-mannose (2.2 g; 37 %) of m. p. = 129—131 °C and [α](D, 20 °C, water, $\varrho = 20\ \mathrm{g\,dm^{-3}}$) = = −14.2° Ref. [7] gives m. p. = 128—132 °C and [α] (D, 20 °C, water, $\varrho = 34\ \mathrm{g\,dm^{-3}}$) = = −14.5°

D-*Glycero*-L-*manno-heptose*

Into the solution of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol ([5], 1 g) in aqueous solution of sodium hydroxide (12 $\mathrm{cm^3}$; $c = 0.5\ \mathrm{mol\,dm^{-3}}$) ozone was introduced at the flow rate 30 $\mathrm{mg\,min^{-1}}$ After bubbling through the reaction mixture with nitrogen for 10 min, chromatographically pure sirupy D-*glycero*-L-*manno*-heptose (0.5 g; 57 %) of [α]

(D, 20 °C, water, $\varrho = 10\ \mathrm{g\,dm^{-3}}$) = −14.2° was obtained (Ref. [8] gives [α](D, 23 °C, water, $\varrho = 20\ \mathrm{g\,dm^{-3}}$) = −14° ± 0.5°) *via* D-*glycero*-L-*manno*-heptose phenylhydrazone [8].

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