Comparison of Three Methods of the Conversion of 1-Deoxy-1-nitroalditols to the Corresponding Aldoses

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Ozonolysis, peroxomolybdate oxidation, and the treatment with sulfuric acid as three relatively simple methods of the conversion of 1-deoxyalditol-1-nitronates to the corresponding aldoses were mutually compared. The yields and complexity of the methods applied to the synthesis of D-*glycero*-D-*galacto*-heptose and D-*glycero*-D-*talo*-heptose from D-mannose are presented and discussed.

One of the best developed and most often used methods of the elongation of the carbon chain of aldoses is a method introduced by and named according to Sowden [1]. The method consists of the addition of the nitromethylide nucleophile usually generated by methoxide ions to an aldose affording a pair of the epimeric 1-deoxyalditol-1-nitronates. The intermediate nitronates subsequently are being transformed to the corresponding aldoses. For this purpose the author of the method adopted the Nef reaction and, until recently, the method has been used most frequently for the transformation. The treatment with a moderately concentrated strong mineral, usually sulfuric acid has been most often utilized.

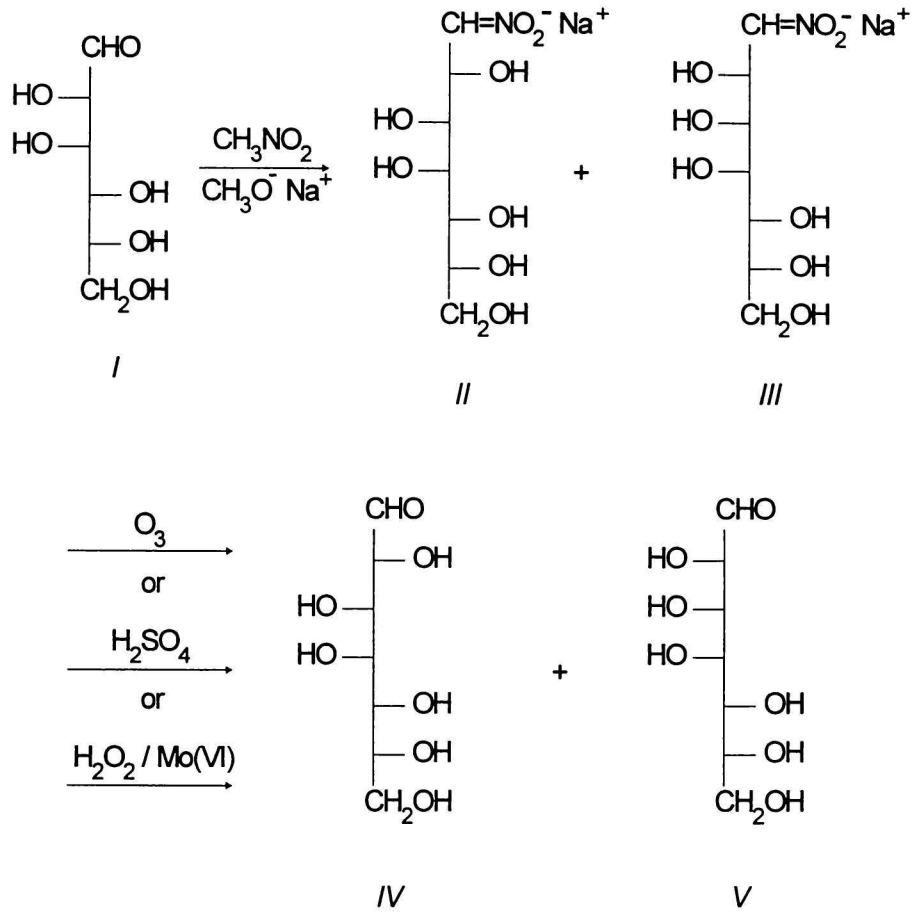
An alternative method of the conversion to the corresponding aldoses has been introduced in 1974 by *Bílik* [2]. His method employs for the conversion the treatment with hydrogen peroxide in the presence of a catalytic amount of anions of some transient metals, best of molybdate. Also this method has been generalized and was exploited for synthesis of hexoses [2, 3], heptoses [4—7], and octoses [8, 9]. Due to avoiding acidic reaction conditions this peroxomolybdate method, known in literature also as an oxidative decomposition, is safely applicable also for the elongation of the carbon chain of reducing disaccharides [10].

In early 90s the third simple and universal method of the transformation of 1-deoxy-1-nitroalditols to aldoses with the same number of carbon atoms has been published [11]. The method utilizes the treatment of aqueous solution of the intermediate nitronates with ozone at room temperature. Also this method affords moderate yields and similarly as the peroxomolybdate one is applicable for synthesis of reducing disaccharides [12]. The paper describes the application of the ozone method of the transformation of 1-deoxyalditol-1-nitronates to the synthesis of D-*glycero*-D-*galacto*-heptose and D-*glycero*-D-*talo*-heptose and compares yields of the aldoses with those obtained by both preceding methods in such a manner that the other experimental procedures, *i.e.* preparation of epimeric 1-deoxyalditol-1-nitronates and isolation of product aldoheptoses have been performed at the same conditions. This aldoheptose example was chosen as both sugars are readily separable from each other to ensure their unambiguous determination. Another, practical reason was that they occur in nature [13, 14] what could make the procedures preparatively more useful.

Sodium 1-deoxyheptitol-1-nitronates *II* and *III* (Scheme 1) obtained by a classical nitromethane synthesis from D-mannose (*I*) in methanol at homogeneous conditions and dissolved in water were subsequently treated with ozone at room temperature. The treatment caused their rapid conversion to D-*glycero*-D-*galacto*-heptose (*IV*) and D-*glycero*-D-*talo*-heptose (*V*). After a fermentational removal of D-mannose also present in reaction mixture the heptoses were conveniently resolved by chemisorption chromatography on cation-exchange resin in the Ba^{2+} form [8, 15] and were obtained in respective 27.7 % and 18.0 % yields.

Intermediates *II* and *III* were converted to respective aldoses *IV* and *V* also by the classical Nef reaction [16]. Under identical isolation conditions the sugars *IV* and *V* were obtained in practically the same yields (26.6 % and 18.1 %, respectively). Another comparative treatment of intermediates *II* and *III* with hydrogen peroxide in the presence of molybdate and again the same isolation procedure afforded aldoheptoses *IV* and *V* in respective 25.5 % and 17.6 % yields.

From view of the yields obtained all the three methods gave practically the same results. However, taking into account simplicity of the alditolnitronate to aldose conversion step, ozonolysis was found to be the most convenient method. Although it requires an ozone-generating equipment, the other isolation procedure is simple as the unreacted agent (ozone) and



Scheme 1

the only by-product, an equimolar amount of sodium nitrate [11], are easily removable so that the method as a whole is simple, fast, and efficient. Also relatively simple is the classical Nef reaction, however, the removal of a large but necessary excess of reaction agent (sulfuric acid) is a major disadvantage of the method. The third, peroxomolybdate method is relatively most laborious as there is necessary an additional removal of the excessive oxidizing agent (hydrogen peroxide) as well as of the by-product (nitrite).

In summary, of the three methods of the alditol-nitronate to aldose conversion studied, the most convenient procedure due to its simplicity is ozonolysis provided that there is available an ozone generator. Otherwise two other available methods, the Nef reaction and the peroxomolybdate oxidation are approximately equally material- and time-demanding.

EXPERIMENTAL

Melting points were measured on a Kofler stage. Optical rotations were obtained using a Perkin—Elmer 141 polarimeter. Ozone was generated from gaseous oxygen in a Fischer 502 generator. Chromatography of reaction mixtures was performed on column C_1 (100 cm × 1.6 cm, flow rate = 15 cm^3 h^{-1}) of the Dowex 50W X-8 (37—75 μm) resin in the Ba^{2+} form by elution with water. The individual 1 h fractions were monitored by paper chromatography on Whatman No. 1 sheets eluted with butan-1-ol—ethanol—water (volume ratio = 5 1 4) and detected with alkaline silver nitrate. Solvents were evaporated under diminished pressure at temperature below 40 °C. The chemicals used were commercial products.

Nitromethane Synthesis

Powdery D-mannose (5 g) was dissolved in methanol (80 cm^3) at 50 °C, then to the solution cooled to 20 °C nitromethane (10 cm^3) and sodium methoxide solution (2 g of sodium in 40 cm^3 of methanol) were added under stirring. An amorphous precipitate began to appear after a few minutes while vigorous stirring was continued for 4 h. After the addition of butan-1-ol (50 cm^3) the reaction mixture was left to stand overnight at 4 °C. The solid precipitate was then filtered off and washed with a mixture of butan-1-ol—methanol (volume ratio = 1 1).

Ozonolysis

The washed solid precipitate of sodium 1-deoxyheptitol-1-nitronates was dissolved at 25 °C in 4 M-NaOH solution (120 cm^3) presaturated with ozone for 5 min. An ozone stream (flow rate = 40 mg min^{-1}) was introduced into the mixture until the neutral reaction of the solution was reached. (The excessive ozone was being trapped in a saturated aqueous solution of sodium iodide.) The reaction mixture was then bubbled with nitrogen for 10 min to remove unreacted ozone. Afterwards the reaction mixture was separately treated first with Amberlite IR 120 resin in the H^+ form and then with Amberlite IRA 400 resin in the HCO_3^- form. The neutral solution was evaporated under diminished pressure to a sirup which was dissolved in tap water (2 dm^3) and baker's yeast (0.5 g) was added to remove D-mannose by a three-week fermentation. The mixture was then concentrated to 200 cm^3 and methanol (200 cm^3) and charcoal (1 g) were added. After filtration of precipitate, the filtrate was deionized by separate treatment with ion-exchange resins (H^+ form, HCO_3^- form) and evaporated. The residue was fractionated on column C_1. Evaporation of the first sugar-containing fraction and crystallization from methanol afforded D-*glycero*-D-*galacto*-heptose monohydrate (1.76 g, 27.7 %), m.p. = 136—138 °C and $[\alpha]$(D, 20 °C, ρ = 20 g dm^{-3}, water) = + 63.3° Ref. [16] gives m.p. = 135—137 °C and $[\alpha]$(D, 25 °C, ρ = 35 g dm^{-3}, water) = + 68.1° and Ref. [4] for L-enantiomer gives m.p. = 131—134 °C and $[\alpha]$(D, 21 °C, ρ = 30 g dm^{-3}, water) = −62.0°

Evaporation of the second sugar-containing fraction and crystallization from methanol afforded D-*glycero*-D-*talo*-heptose (1.05 g, 18.0 %), m.p. = 105—107 °C and $[\alpha]$(D, 20 °C, ρ = 20 g dm^{-3}, water) = + 15.2° Ref. [16] gives m.p. = 83—84 °C and $[\alpha]$(D, 25 °C, ρ = 35 g dm^{-3}, water) = + 15.8° and Ref. [4] for L-enantiomer gives m.p. = 108—110 °C and $[\alpha]$(D, 21 °C, ρ = 30 g dm^{-3}, water) = −13.3°

Nef Reaction

The washed solid precipitate of sodium 1-deoxyheptitol-1-nitronates was dissolved in 0.5 M-NaOH (10 cm^3) and the mixture was added at room temperature to a stirred solution of 4.5 M-H_2SO_4 (28 cm^3). After stirring for 4 h the reaction mixture was diluted with water (600 cm^3), barium carbonate (40 g) was added and the mixture was stirred for 1 h. The neutral mixture was filtered and combined filtrate and washing solutions were further worked up (deionization, fermentation of D-mannose, *etc.*) as described in the ozonolysis section. The procedure afforded D-*glycero*-D-*galacto*-heptose monohydrate (1.69 g, 26.6 %) and D-*glycero*-D-*talo*-heptose (1.06 g, 18.1 %).

Peroxomolybdate Oxidation

The washed solid precipitate of sodium 1-deoxyheptitol-1-nitronates was dissolved in 1 M-NaOH (3 cm^3) and water (40 cm^3) and mixed with a solution of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (0.25 g) in water (10 cm^3). Hydrogen peroxide (30 %; 15 cm^3) was being added to the stirred mixture at a rate to keep the temperature below 35 °C. After standing at room temperature overnight the mixture was treated with 5 % Pd/C (0.1 g) for 24 h. Finally, acetic acid (2 cm^3) was added and the reaction mixture was vigorously bubbled with air for 4 h. The subsequent working up (deionization, fermentation of D-mannose, *etc.*) as described in the ozonolysis section afforded D-*glycero*-D-*galacto*-heptose monohydrate (1.62 g, 25.5 %) and D-*glycero*-D-*talo*-heptose (1.03 g, 17.6 %).

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