INVESTIGATIONS IN THE FIELD OF SUBSTITUTED FURANURONALDEHYDES

STERIC DIRECTIVITY OF THE NITROMETHANE CONDENSATION

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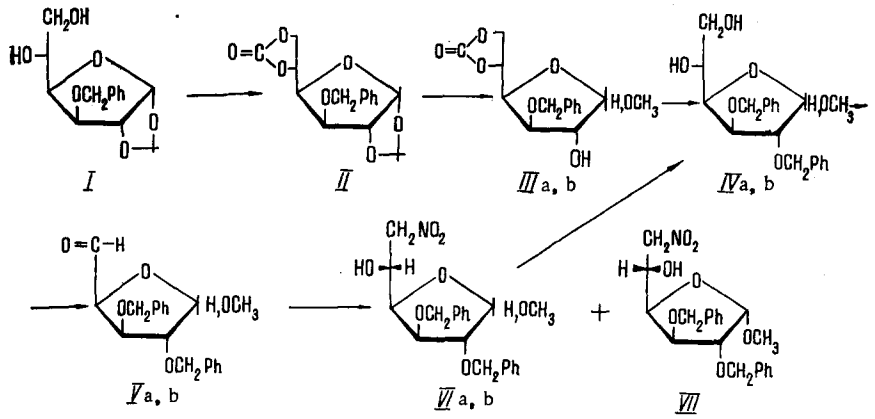
The present paper gives the results of a study of the steric directivity of the condensation of substituted D-xylofuranuronaldehydes with nitromethane. Interest in the nitromethane condensation is due to the fact that the compounds formed in this reaction are convenient intermediates in the synthesis of derivatives of cyclitols of the natural structure. As is well-known, the reaction of D-xylofuranuronaldehydes with nitromethane gives a mixture of 6-nitro-6-deoxyhexofuranoses with the D-gluco and the L-ido configurations which is difficult to separate [1-3], the ratio of the epimers depending on the nature and position of the substituents. We have shown previously [4] that the introduction of a voluminous substituent into position 3 leads to an increase in the amount of the gluco isomer in the mixture formed. Thus, in the case of 1,2-O-isopropylidene-α-D-xylofuranuronaldehydes the ratio of the gluco and ido epimers is 3.5:1, while for the corresponding 3-O-benzyl derivative it is 9:1.

From this point of view, it appeared of interest to investigate the influence of the nature and position of substituents at the glycosidic center on the configuration of the new center of asymmetry arising as a result of this reaction using as examples methyl α- and β-2,3-di-O-benzyl-D-xylofuranosiduronaldehydes (Va and b, respectively).

The initial uronaldehydes (Va) and (Vb) were obtained from 3-O-benzyl-1,2-O-isopropylidene-α-D-glycofuranose [5], which was converted by the action of diethyl carbonate in the presence of a catalytic amount of potassium carbonate into 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose 5,6-carbonate (II). The methanolysis of the latter led to a mixture of the anomeric methyl glycosides (IIIa, b), which could be separated chromatographically on silica. The anomers (IIIa) and (IIIb) were benzylated with benzyl bromide in the presence of silver oxide and were then subjected to alkaline hydrolysis. The resulting methyl α- and β-2,3-di-O-benzyl-D-glucofuranosides (IVa, b) were oxidized with lead tetraacetate to the corresponding D-xyluronaldehydes (Va) and (Vb).



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The reaction of the β anomer (Vb) with nitromethane led to the formation of practically a single isomer with the gluco configuration (VIb), as was to be expected in accordance with Cram's rule [6]. The nitromethane condensation of the α anomer (Va) gives a mixture of the gluco and ido epimers (Va) and (VII), respectively, approximately in a ratio of 6:1, the epimers being capable of chromatographic separation on silica gel impregnated with boric acid. The increase in the amount of ido isomer in the latter case can probably be explained by the conformation of the aldehyde (Va), in which the aldehydic and 3-O-benzyl groups are separated by a greater distance than in the more rigid structure of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranuronaldehydes. The gluco configuration of the 6-nitro-6-deoxyhexofuranoses (VIa) and (VIb) is confirmed by their conversion into the corresponding methyl D-glucofuranosides (IVa) and (IVb) by reduction with lithium tetrahydroaluminate and subsequent deamination with nitrous acid.

EXPERIMENTAL

The NMR spectra were taken on a Varian Chart S-100 A instrument with a working frequency of 100 MHz. Tetramethylsilane was used as internal standard. The IR spectra were obtained on a Perkin-Elmer model 257 recording spectrophotometer (paraffin oil, and also chloroform solutions with concentrations of $5 \cdot 10^{-2}$ to $5 \cdot 10^{-3}$ M).

The elementary analyses of substances (VIa, VIb, and VII) and of the semicarbazones of compounds (Va and b) corresponded to the calculated figures.

3-O-Benzyl-1,2-O-isopropylidene-α-D-glucopyranose 5,6-Carbonate (II). A solution of 25.0 g of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucopyranose [5] in 150 ml of freshly distilled diethyl carbonate was treated with 0.25 g of anhydrous potassium carbonate. The mixture was stirred at the boil for 2 h, and then 500 ml of diethyl carbonate was added to it dropwise over 4 h with the simultaneous elimination of the solvent by distillation until the temperature of the vapors had reached 125°C. After the completion of the reaction, the mixture was cooled to 20°C and was treated with 5 g of KU-2 resin (H^+ form), and then it was filtered and the solvent was driven off. Crystallization of the residue from 100 ml of methanol gave 23.2 g (85.6%) of (II) with mp 119-120.5°C, $[\alpha]_D^{20}$ −53.0° (c 3.7; chloroform). Literature data: mp 119-120.5°C, $[\alpha]_D^{25}$ −53.7° (c 3.7; chloroform) [7].

Methyl α- and β-3-O-Benzyl-D-glucopyranoside 5,6-Carbonates (IIIa, b). A mixture of 12.0 g of (II), 6 g of KU-2 resin (H^+ form), and 250 ml of absolute methanol was stirred at 60-65°C for 8 h, cooled to 20°C, and filtered, and the solvent was driven off. Chromatography of the residue on a column containing 250 g of silica [chloroform−methanol (99.5:0.5) and (98:2), 600 and 1500 ml, respectively] gave 3.90 g (35.2%) of (IIIa) and 7.05 g (63.7%) of (IIIb).

Methyl α-3-O-Benzyl-D-glucopyranoside 5,6-Carbonate (IIIa). The substance had mp 62-62.5°C (ethanol−petroleum ether), $[\alpha]_D^{20}$ +94.0° (c 2.7; methanol). Literature data: mp 62-63°C, $[\alpha]_D^{20}$ +93.3° (c 2.7; methanol) [7].

Methyl β-3-O-benzyl-D-glucopyranoside 5,6-Carbonate (IIIb). Syrupy substance with $[\alpha]_D^{25}$ −61.3° (c 3.3; methanol). Literature data: $[\alpha]_D^{30}$ −61.2° (c 3.3; methanol) [7].

Methyl α- and β-2,3-Di-O-benzyl-D-glucofuranosides (IVa, b). With stirring, a solution of 5.5 ml of freshly distilled benzyl bromide in 10 ml of dimethyl formide was added to a mixture of 3.90 g of (IIIa), 7.5 g of silver oxide, and 25 ml of dimethyl formamide. The reaction mixture was kept at 20°C for five days and was filtered and evaporated at 80-100°C (5-7 mm), and then 200 ml of chloroform was added to the residue, the resulting mixture was filtered, and the solvent was driven off. The residue was dissolved in 200 ml of acetone, and this solution was treated with 50 ml of 0.3 N barium hydroxide solution, stirred for 2 h, and filtered. The filtrate was concentrated to a volume of 50 ml and extracted with ether (200 ml), and the extract was dried with anhydrous magnesium sulfate. After elimination of the solvent, a syrupy residue was obtained which was chromatographed on a column containing 200 g of silica [chloroform−petroleum ether (1:1), 500 ml; chloroform, 600 ml; chloroform−methanol (97.5:2.5), 900 ml]. The yield of (IVa) was 3.87 g (85.5%). Amorphous substance with $[\alpha]_D^{20}$ +75.2° (c 3.4; chloroform). Literature data: $[\alpha]_D^{20}$ +75.3° (c 3.4; chloroform).

Similarly, 6.0 g of (IIIb) gave 6.85 g (90%) of (IVb) with mp 60-61°C (ether−petroleum ether), $[\alpha]_D^{20}$ −59.8° (c 2.7; chloroform). Literature data: mp 59-61°C, $[\alpha]_D^{27}$ −59.8° (c 2.7; chloroform).

Methyl α- and β-2,3-Di-O-benzyl-D-xylofuranosiduronaldehydes (Va, b). With stirring, 3.75 g of lead tetraacetate and, after 15 min, 2-3 drops of ethylene glycol were added to a solution of 3.00 g of (IVa) in 50

ml of dry benzene heated to 50-55°C, after which the mixture was cooled to 20°C and filtered. The filtrate was washed with water (25 ml), dried with anhydrous magnesium sulfate, and the solvent was eliminated in vacuum (10 mm). This gave 2.68 g (97.6%) of (Va) (syrupy substance). The semicarbazone had the composition $C_{21}H_{25}N_3O_5$, mp 128-129°C (ether—hexane), $[\alpha]_D^{20}$ +59.6° (c 2.10; chloroform).

Similarly, 2.57 g of (IVb) gave 2.32 g (98.7%) of (Vb) (syrupy substance), semicarbazone $C_{21}H_{25}N_3O_5$, mp 161.6-162.5°C (ether—hexane), $[\alpha]_D^{20}$ −1.7° (c 1.18; chloroform).

Methyl β-2,3-Di-O-benzyl-6-nitro-6-deoxy-D-glucofuranoside (VIb), $C_{21}H_{25}NO_7$. A solution of 1.29 g of (Vb) in a mixture of 40 ml of 96% ethanol and 5 ml of nitromethane was brought to pH 8.5 with a 0.5 N solution of sodium methoxide in methanol and was stirred at 20°C for 1 h. Then it was treated with 4 g of KU-2 resin (H^+ form), filtered, and evaporated in vacuum (10 mm). The residue was dissolved in 10 ml of ether, and the solution was washed with water (20 ml) and dried with anhydrous magnesium sulfate. Elimination of the solvent gave a syrupy residue (1.48 g), from which chromatography on a column containing 30 g of KSK silica gel containing 1 g of boric acid [petroleum ether—ether (19:1), 100 ml, and (9:1), 600 ml] isolated 1.19 g (80.1%) of (VIb) with mp 63.5-64.5°C (ether—hexane), $[\alpha]_D^{20}$ −52.4° (c 0.65; chloroform). NMR spectrum (CCl_4; δ; ppm): 3.27 — OCH_3; 4.76 (singlet) — 1 H; 7.20 and 7.23 (C_6H_5). IR spectrum ($CHCl_3$; cm^{-1}): 1558 (NO_2 group), 3540 (OH group).

Methyl α-2,3-Di-O-benzyl-6-nitro-6-deoxy-D-glucofuranoside (VIa) and Methyl β-2,3-Di-O-benzyl-6-nitro-6-deoxy-L-idofuranoside (VII). As described for (Vb), 2.58 g of (Va) yielded a syrupy residue (2.77 g) chromatography of which on a column containing 60 g of silica gel with 2 g of boric acid [petroleum ether—ether (19:1), 200 ml; (9:1), 900 ml; (7:1), 500 ml] gave 2.01 g (71.6%) of (VIa) and 0.33 g (11.8%) of (VII).

Methyl α-2,3-Di-O-benzyl-6-nitro-6-deoxy-D-glucopyranoside (VIa), $C_{21}H_{25}NO_7$. Syrupy substance with $[\alpha]_D^{20}$ +52.1° (c 0.87; chloroform). NMR spectrum (CCl_4; δ; ppm): 3.34 — OCH_3; 4.77 (doublet) — 1 H (4 Hz); 7.27 and 7.31 ppm (C_6H_5). IR spectrum ($CHCl_3$; cm^{-1}): 1558 (NO_2 group) and 3520 (OH group).

Methyl β-2,3-Di-O-benzyl-6-nitro-6-deoxy-L-idofuranoside (VII), $C_{21}H_{25}NO_7$. Mp 95-96°C (ether—hexane), $[\alpha]_D^{20}$ +40.6° (c 0.40; chloroform). NMR spectrum (CCl_4; δ; ppm): 3.34 — OCH_3; 4.79 (doublet) — 1 H (4 Hz); 7.29 and 7.32 (C_6H_5). IR spectrum ($CHCl_3$; cm^{-1}): 1558 (NO_2 group) and 3530 (OH group).

Proof of the Gluco Configuration of the 6-Nitro-6-deoxyhexofuranosides (VIa) and (VIb). A solution of 0.10 g of (VIb) in 10 ml of absolute ether was treated with 0.05 g of lithium tetrahydroaluminate, and the mixture was stirred at 20°C for 1 h, after which the excess of reagent was decomposed by the addition of 2-3 drops of water and, after filtration, the solvent was driven off. The residue was treated with a solution of 0.05 g of sodium nitrite and 0.25 g of p-toluenesulfonic acid in 20 ml of 80% methanol, followed by stirring at 20°C for 3 h. Then the reaction mixture was concentrated to a volume of 4 ml and extracted with ether (15 ml), and the extract was washed with water (5 ml) and dried with anhydrous magnesium sulfate. After elimination of the solvent, a syrupy residue (0.07 g) was obtained from which by preparative thin-layer chromatography on silica (chloroform—methanol, 20:1) 32 ml (34.4%) of (IVb) was isolated with mp 59.5-61°C, $[\alpha]_D^{20}$ −59.9° (c 2.7; chloroform).

Similarly, (VIa) gave 33.1% of (IVa) in the form of an amorphous substance, $[\alpha]_D^{20}$ +75.4° (c 3.4; chloroform).

SUMMARY

1. The condensation of the anomeric methyl 2,3-di-O-benzyl-D-xylofuranosiduronaldehydes with nitromethane has been studied.

2. It has been shown that the position of the substituent at the glycosidic center has an influence on the steric directivity of this reaction.

3. The structure of the 6-nitro-6-deoxyhexofuranosides synthesized has been confirmed by their conversion into known derivatives of methyl D-glucofuranosides.

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