

Synthesis of the 1,2:3,4-Di-*O*-isopropylidene Derivatives of *D*-xylo- and *D*-lyxo-3-Hexulose

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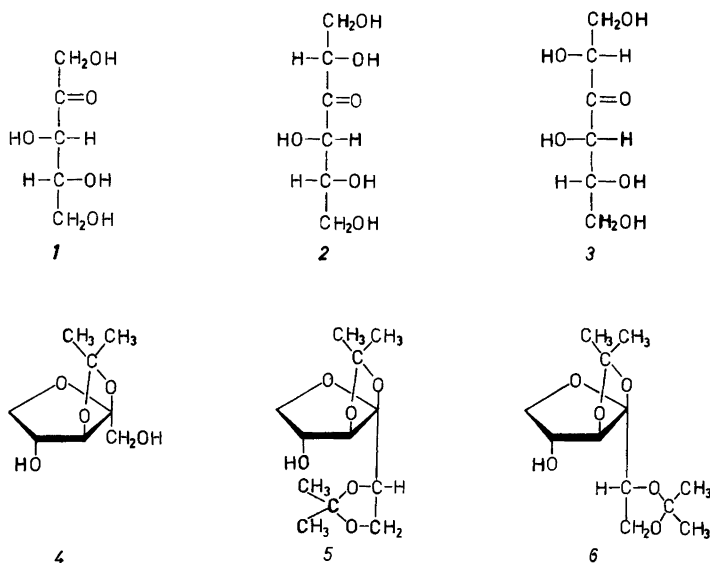
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In connection with analysis of product mixtures from aldol condensations, it was necessary to know the gas chromatographic behaviour and mass spectral data of the di-*O*-isopropylidene derivatives of the 3-hexuloses with the *xylo* and *lyxo* configurations. The preparation of 3-hexuloses by chromium trioxide oxidation in acetic acid of ethylidene or benzylidene derivatives of hexitols has been described.^{1,2} Other, less general methods have also been reported for the preparation of such compounds,^{3,4} but the need was felt for a more simple and rapid small-scale synthesis of the two required 3-hexuloses. It is known that the first step in the ribulose-monophosphate cycle of formaldehyde fixation in some methylotropic bacteria is the condensation of formaldehyde and *D*-erythro-pentulose 5-phosphate (*D*-ribulose 5-phosphate) to give *D*-arabino-3-hexulose 6-phosphate.⁵⁻⁸

The present paper reports on a method, elaborated with this formaldehyde fixation as a model, for the preparation of a mixture of the *D*-xylo- and *D*-lyxo-3-hexuloses and their separation as di-*O*-isopropylidene derivatives.

D-threo-Pentulose (1), easily prepared by isomerisation of *D*-xylose in hot pyridine,⁹ and also commercially available, was treated with formaldehyde in sodium hydroxide solution at room temperature to give, in addition to unchanged starting material, approximately equal amounts of *D*-xylo- (2) and *D*-lyxo-3-hexulose (3). Traces of xylose were also observed in the product mixture. The optimal reaction time was about 30 min, prolonged reaction caused diminished yields of 2 and 3, and several secondary products were formed. Treatment of the product mixture with acetone-sulfuric acid gave 2,3-*O*-isopropylidene- β -*D*-threo-pentulofuranose (4) from 1 and di-*O*-isopropylidene derivatives from 2 and 3. The di-*O*-isopropylidene derivatives were easily separated from 4 by partitioning between water and chloroform. A procedure involving partial hydrolysis to mono-*O*-isopropylidene derivatives and a second partitioning between chloroform and water followed by re-isopropylideneation of the compounds from the water phase, gave a mixture which except for traces of the di-*O*-isopropylidene derivative of xylose contained almost exclusively 1,2:3,4-di-*O*-isopropylidene- β -*D*-xylo-3-hexulofuranose (5) and 1,2:3,4-di-*O*-isopropylidene- β -*D*-lyxo-3-hexulofuranose (6). Compounds 5 and 6 were readily separated by column chromatography on aluminum oxide, due to a surprisingly high mobility of the former, and they were obtained in a combined yield of about 25%.

The electron impact mass spectra of 5 and 6 are almost identical, and they show that the compounds are 1,2:3,4-di-*O*-isopropylidene derivatives. Primary fragmentation between C-2 and C-3 gives



rise to fragments with m/z 101 and 159, with a greater relative abundance of the latter than that usually observed for the corresponding m/z 159 fragment in the spectra of 1,2:5,6- or 2,3:5,6-di-*O*-isopropylidene aldoses.¹⁰ This is presumably due to the possibility of charge stabilisation by lone-pair electrons from O-3 and O-6 in the fragment from the 3-hexulose derivatives, whereas lone-pair electrons only from O-4 may participate in the aldose derivative fragments. The m/z 200 and 185 peaks in the spectra of 5 and 6 are obviously analogues of the m/z 130 and 115 peaks in the spectra of 2-ketoses carrying a 2,3-*O*-isopropylidene group.^{10,11} The fact that the two 3-hexuloses both form 1,2:3,4-di-*O*-isopropylidene derivatives confirms the expected *xylo* and *lyxo* configurations, since it has been shown that those with *ribo* and *arabino* configuration give 1,2:4,5- or 2,3:4,5-di-*O*-isopropylidene acetals under similar conditions.²

The compounds 4, 5 and 6 are readily separated by gas chromatography, and the condensation reaction thus may be monitored by isopropylidene-ation of aliquots withdrawn after different reaction times or under varying reaction conditions. Good separation of 5 and 6 is also obtained on TLC on silica gel, and again a high mobility is observed for the *xylo* isomer (5). A reason for the low polarity of compound 5 may be suggested on the basis of molecular model inspections; intramolecular hydrogen bonding between OH-5 and O-2 appears sterically possible in a favourable conformation with *anti*-periplanar arrangement of C-1 and C-4 around the C-2/C-3 bond in 5, whereas for the *lyxo* isomer (6), such hydrogen bonding is presumably less pronounced, since it would require an energetically less favourable *syn*-clinal orientation of C-1 and C-4 around the C-2/C-3 bond (Fig. 1).

In the infrared spectra of 5 and 6, recorded in tetrachloromethane, a relatively sharp OH stretching absorption band at 3460 cm^{-1} is observed, which is unchanged on dilution and thus

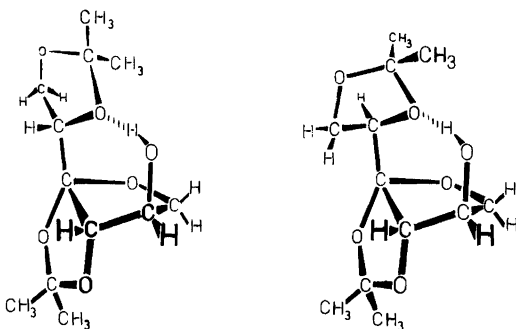


Fig. 1. Conformations of 5 (left) and 6 (right) allowing intramolecular hydrogen bonding.

is characteristic of intramolecular hydrogen bonding. This band is of considerably greater intensity in the spectrum of 5 than in that of 6, supporting the suggested difference in the intramolecular hydrogen bond formation.

Experimental. TLC was performed on silica gel G plates in chloroform – methanol 50:1, detection was effected with diphenylamine – aniline – phosphoric acid.¹² For GLC was used a Perkin-Elmer F 11 gas chromatograph, equipped with a flame ionisation detector and a glass column (2 m \times 1.5 mm i.d.) filled with 3% OV-225 on 100/120 Supelcoport. The temperature was programmed at $4^\circ/\text{min}$ from 90 to 210°C . Mass spectra were recorded with a Micromass 12 F mass spectrometer, operating at 70 eV, and IR spectra with a Perkin-Elmer infrared spectrophotometer 597.

Base-catalysed condensation of D-threo-pentulose and formaldehyde. To D-threo-pentulose⁹ (1, 10 mg) in water (2 ml) were added 3.5% formaldehyde solution (0.3 ml) and 0.2 M sodium hydroxide (2.2 ml). The solution was kept at room temperature, and aliquots (0.5 ml) were withdrawn at intervals, neutralised with Dowex 50 W (H^+) ion exchange resin and concentrated to dryness under reduced pressure. The residues were treated with 2% sulfuric acid in acetone (1 ml) for 90 min, the acetone solutions were neutralised with solid sodium hydrogencarbonate and subjected to GLC. Three major components, 4, 5 and 6, were observed, with retention times 10.10, 8.05 and 10.45 min, respectively.

Preparation of 1,2:3,4-di-O-isopropylidene- β -D-xylo-(5) and -lyxo-(6)-3-hexulofuranose. To D-threo-pentulose (1, 100 mg) in water (20 ml) were added 3.5% formaldehyde solution (3 ml) and 0.2 M sodium hydroxide (23 ml). The solution was kept at room temperature for 30 min and then neutralised with Dowex 50 W (H^+) ion exchange resin. After filtration of the solution, the solvent was removed under diminished pressure, and the residue was treated with 2% sulfuric acid in acetone (10 ml) for 90 min. The solution was neutralised with solid sodium hydrogencarbonate and, following filtration, the solvent was removed. The residue was dissolved in chloroform (10 ml), the chloroform solution extracted with water (10 ml) and the chloroform removed at reduced pressure. The residue was dissolved in 70% aqueous acetic acid (10 ml) and the solution kept at 55°C for 90 min. After removal of the solvents under reduced pressure, the residue was dissolved in water (10 ml), the water solution was extracted with chloroform (5 ml) and the chloroform extract re-extracted with water (5 ml). From the combined water solutions the solvent was removed under reduced pressure, and the residue was stirred with 0.2% sulfuric acid in acetone (10 ml) for 1 h. The acetone solution was

neutralised with solid sodium hydrogencarbonate and then it was filtered. TLC showed that the solution contained traces of a compound (R_F 0.56), indistinguishable from 1,2:3,5-di-*O*-isopropylidene- α -D-xylofuranose, and two major components (R_F 0.52 and 0.29), giving a brown-to-red colour with the spray reagent. After removal of the solvent, the residue was dissolved in chloroform (1 ml) and subjected to chromatography on a column (20 cm \times 1.4 cm i.d.) filled with neutral aluminum oxide, activity grade II. Hexane-chloroform 5:1 (v/v) eluted the compound with R_F (TLC) 0.52, crystallisation from hexane gave 5 (19 mg, 11%), m.p. 103–105 °C, $[\alpha]_D^{20} +12^\circ$ (c 2, chloroform) (Lit.² m.p. 104–105 °C, $[\alpha]_D -16.6^\circ$ for the L-enantiomer). MS [IP 70 eV; m/z (% rel. int.)]: 245 (31), 200 (20), 187 (9), 185 (14), 159 (40), 127 (21), 101 (41), 85 (12), 71 (13), 59 (89), 43 (100). The compound with R_F (TLC) 0.29 was eluted with chloroform, evaporation of the solvent gave crystalline 6 (23 mg, 13%), m.p. 119–122 °C, $[\alpha]_D^{20} +10^\circ$ (c 2, chloroform) (Lit.² m.p. 122–123 °C, $[\alpha]_D -14.7^\circ$ for the L-enantiomer). MS [IP 70 eV; m/z (% rel. int.)]: 245 (26), 200 (12), 187 (7), 185 (18), 159 (49), 127 (24), 101 (49), 85 (12), 71 (17), 59 (90), 43 (100).

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