Aldol Reaction between Small Sugars. Preparation of DL-*threo*-2-Pentulose and DL-*lyxo*-3-Hexulose and their Isolation as *O*-Isopropylidene Derivatives

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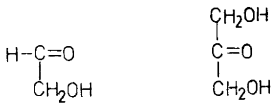
The improved diastereoselectivity obtained with strongly basic anion-exchange resins as catalysts in aldol condensations between two-, three- and four-carbon "sugars" has been utilized in the preparation of DL-*threo*-2-pentulose and DL-*lyxo*-3-hexulose, which were isolated as their *O*-isopropylidene derivatives. A possible reason for the observed preference of formation of the *lyxo*-diastereomer in condensation between glycolaldehyde and *glycero*-tetrulose is suggested.

During the last century considerable attention has been focused on the formation of pentoses, hexoses and higher sugars by the base-catalysed aldol condensation between unprotected two-, three- and four-carbon sugars.[1-5] When catalysed by hydroxides of alkali and alkaline-earth metals, the diastereoselectivity obtained normally does not satisfy the requirements for a synthetic application of these reactions. The finding that the use of strongly basic anion-exchange resins as catalysts improves the stereoselectivity markedly and shortens the reaction time significantly[6-8] has rendered these reactions more attractive for synthetic purposes.[9] This paper describes the utilization of these observations in the preparation of two ketoses as their racemic mixtures. DL-Sugars are expected to become more and more important in the preparation of pure enantiomers. This is due to the increasing use of microorganisms for conversion of one enantiomer in a racemic mixture at a selected stage in a multi-step synthesis.

Results and discussion

Aldol condensation between glycoaldehyde (**1**) and 1,3-dihydroxy-2-propanone (**2**) catalysed by anion-exchange resin gave, as previously reported,[7] a product mixture in which DL-*threo*-2-pentulose (**3**) predominated. A small amount of the diastereomer DL-*erythro*-2-pentulose was also formed, as well as tetroses formed by condensation between two molecules of **1**, and the branched ketohexose dendroketose formed by self-condensation of **2**.[10] After treatment of the product mixture with acetone/sulfuric acid, the isolation of 2,3-*O*-isopropylidene-β-DL-*threo*-2-pentulofuranose (**4**) was easily achieved by partitioning the products between chloroform and water; pure **4** was obtained from the water phase.



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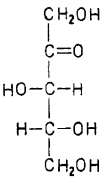

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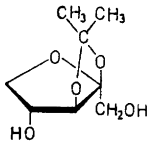

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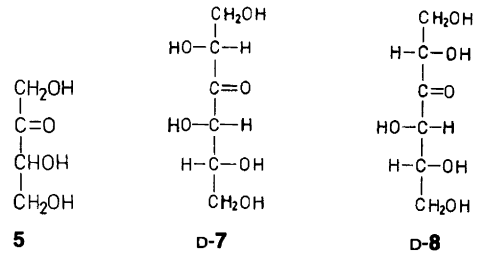
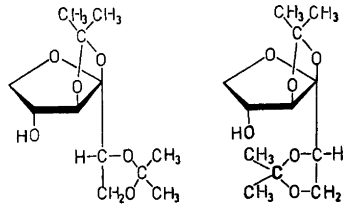


5 D-7 D-8



D-9 D-10

When compound **2** is replaced by DL-*glycero*-tetrulose (**5**) in condensation with **1**, 3-hexuloses and compounds formed by self aldolisation of **1** or **5** are the expected products. Compound **5** was prepared from erythritol by bromine oxidation,[11] and was isolated as its 3,4-*O*-isopropylidene derivative (**6**). The product mixture from the condensation of **1** with **5** contained as major component DL-*lyxo*-3-hexulose (**7**); in addition the *xylo*-diastereomer (**8**) was present. Compounds **7** and **8** were identified as their di-*O*-isopropylidene derivatives (**9** and **10**, respectively) by comparison with authentic samples of the corresponding D-enantiomers.[12] The gas chromatogram of the product mixture after acetonation (Fig. 1) also showed the presence of the 2,3-*O*- and 1,2-*O*-isopropylidene derivatives (**11** and **12**) of DL-erythrose and DL-threose, respectively.[7] Again, the isolation of the main product **9** was easily achieved, since it crystallised from a hexane extract of the product mixture.

In agreement with observations made with other similar aldol condensations,[2,7,8] sugars with *threo* configuration at the new chiral centres were the main products also in the condensation of **1** with **5**. Of the reaction mechanisms previously suggested[13] for aldol condensation, one involving a pericyclic transition state, formed from a *cis*-enediolate, explains the observed diastereoselectivity in the formation of 2-hexuloses and aldopentoses.[14] By inspection of the geometry of the

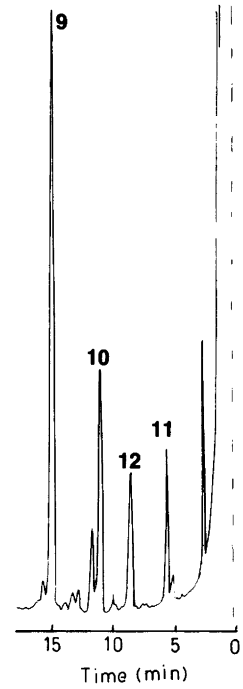
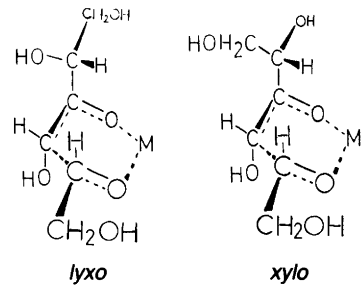


Fig. 1. Gas chromatogram of *O*-isopropylidene derivatives of the products formed by the aldol condensation between glycolaldehyde (**1**) and DL-*glycero*-tetrulose (**5**) catalysed by Dowex 1×4 (OH^-) resin. The derivatives are as follows: **9**: from DL-*lyxo*-3-hexulose, **10**: from DL-*xylo*-3-hexulose, **11**: from DL-erythrose, and **12**: from DL-threose.

transition states leading to the *lyxo* (**7**) and *xylo* (**8**) diastereomers in the present reaction according to this model (Fig. 2), a reason for the preference for the *lyxo* form may be suggested; the *xylo* transition state presumably adopts gauche con-



lyxo *xylo*

Fig. 2. Possible transition states leading to the *lyxo* and *xylo* diastereomers in the aldol condensation between glycolaldehyde and *glycero*-tetrulose.

formation about the C-2/C-3 bond to avoid a pseudo 1,3-parallel interaction between OH-2 and C-5, whereas the *lyxo* transition state may have the C-1/C-4-part of the carbon chain in the favourable zig-zag planar conformation.

D-*threo*-2-Pentulose is usually prepared by pyridine-catalysed isomerisation of D-xylose,[15] whereas the L-enantiomer of **9** is obtained via several steps from 3,4-*O*-ethylidene-D-mannitol,[16] and the D-enantiomer from condensation between D-*threo*-2-pentulose and formaldehyde.[12] When the ketoses are not required in one of the enantiomeric forms, the preparations described in this paper should provide useful synthetic alternatives.

Experimental

General methods. Solutions were concentrated under reduced pressure at temperatures below 40 °C. Gas chromatography (GLC) was performed on a Perkin-Elmer F11 gas chromatograph, equipped with a flame-ionisation detector and a glass column (1.83 m × 2 mm i.d.) filled with 3 % OV-225 on 100/120 Supelcoport. The temperature programming was 4° min^{-1} from 90 to 190 °C, or 5° min^{-1} from 110 to 200 °C. GLC–MS was recorded with a Varian Aerograph 2400 gas chromatograph in combination with a Micromass 12 F mass spectrometer. The ionisation energy was 70 eV, the ion-source temperature was 200 °C and the accelerating voltage was 4 kV. IR spectra were recorded with a Perkin-Elmer 597 infrared spectrophotometer, and NMR spectra with a 270 MHz Jeol JNM–GX 270 spectrometer.

*2,3-*O*-Isopropylidene-β-*DL*-*threo*-2-pentulofuranose* (**4**). To a solution of **1** (200 mg) and **2** (240 mg) in water (20 ml) was added freshly regenerated Amberlite IRA 400 (OH^-) anion-exchange resin (20 ml). After 15 min at room temperature, the solution was filtered, the resin washed with 40 % aqueous acetic acid (4×20 ml), and the combined filtrate and washings were concentrated to dryness. The residue was stirred with acetone (15 ml) containing conc. sulfuric acid (0.3 ml) for 90 min at room temperature. After neutralisation with solid sodium hydrogencarbonate, the solution was filtered and analysed by GLC–MS as described earlier.[7] Next, the solution was concentrated, and the residue was partitioned between water (15 ml) and chloroform (15 ml). The water solution was extracted with chloroform (10 ml) and concentrated to give chromatographically homogeneous (GLC), syrupy **4** (185 mg, 37 %). The mass spectrum (*m/z* 175, 35 %, M−15) was identical with that of authentic D-enantiomer.[8] IR ($CHCl_3$): 3600 (w, OH free), 3360 (s, OH bonded), 3005, 2980, 2930 and 2880 (m), 1375 and 1385 cm^{-1} (m, CH_3–*–CH_3) ^{1}H–NMR (270 MHz, $CDCl_3$): δ 1.35 (s, 3H, Me), 1.50 (s, 3H, Me), 3.70 (d, 1H, H-1), 3.88 (d, 1H, H-1′), 3.92 (broad, 2H, OH), 3.96 (d, 1H, H-5), 4.19 (dd, 1H, H-5′), 4.21 (d, 1H, H-4) and 4.43 (s, 1H, H-3). $J_{1,1'}$ 11.7, $J_{3,4} \sim 0$, $J_{4,5} \sim 0$, $J_{4,5'}$ 2.2 and $J_{5,5'}$ 9.7 Hz.

*3,4-*O*-Isopropylidene-DL-*glycero*-tetrulose* (**6**). To erythritol (400 mg) in saturated bromine-water (25 ml) was added $CaCO_3$ (2 g). The mixture was stored at 25 °C in a closed flask in the dark for 20 h. The suspension was then filtered and treated with a mixture of Dowex 1 (HCO_3^-) and Dowex 50 W (H^+) ion-exchange resins. After filtration and washing of the resin with water, the combined filtrate and washings were concentrated. The resulting residue was stirred with acetone (20 ml) containing conc. sulfuric acid (0.2 ml) for 50 min. The solution was neutralised with solid sodium hydrogencarbonate, filtered, and concentrated. The product mixture was partitioned between hexane (10 ml) and water (20 ml). The water solution was extracted with dichloromethane (6×10 ml) and the dichloromethane solution was concentrated to give syrupy **6** (110 mg, 21 %), MS: *m/z* 145 (20 %), 101 (100 %). The compound had GLC-mobility and mass spectrum indistinguishable from those of authentic D-enantiomer.[7]

*1,2:3,4-di-*O*-Isopropylidene-β-*DL*-lyxo-3-hexulofuranose* (**9**). To DL-*glycero*-tetrulose (**5**, 65 mg), prepared from **6** by hydrolysis in 50 % aqueous acetic acid at 60 °C for 4 h, were added glycolaldehyde (**1**, 40 mg) in water (5 ml) and freshly regenerated Dowex 1×4 (OH^-) ion-exchange resin (10 ml). After 15 min at room temperature, 30 % aqueous acetic acid (20 ml) was added, the solution was filtered and the resin washed with aqueous acetic acid (4×10 ml). The combined filtrate and washings were concentrated and the residue was stirred with acetone (15 ml) containing conc. sulfuric acid (0.25 ml) for 2 h. The so-

lution was neutralised with solid sodium hydrogen carbonate, filtered, and subjected to analysis by GLC–MS. The compounds **9**, **10**, **11** and **12** were chromatographically indistinguishable from the corresponding authentic D- or L-enantiomers, and the mass spectra were identical with those of the corresponding reference compounds.[7,8,12] The solution was then concentrated and the residue was extracted with hot hexane (4×10 ml), from which **9** crystallised. Yield 35 mg (26 %), m.p. 160–161 °C. IR (CCl_4): 3600 (w, OH free) 3460 (m, OH bonded), 2980, 2930 and 2880 (m), 1370 and 1380 cm^{-1} (s, CH_3–*–CH_3). ^{1}H–NMR (270 MHz, $CDCl_3$): δ 1.38 (s, 3H, Me), 1.40 (s, 3H, Me), 1.489 (s, 3H, Me), 1.494 (s, 3H, Me), 3.35 (d, 1H, OH), 3.94 (d, 1H), 3.97 (d, 1H, H-6), 4.21 (m, 3H), 4.42 (s, 1H, H-4), 4.46 (d, 1H). $J_{4,5} \sim 0$, $J_{6,6'}$ 9.2 Hz. Found: C 55.93; H 7.87. Calc. for $C_{12}H_{20}O_6$: C 55.36; H 7.76.

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