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Note

The synthesis and stereochemistry of D-*threo*-3,4-hexodiulose derivatives*

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From among the theoretically possible optically active hexodiuloses containing the oxo groups symmetrically distributed along the carbon chain, only D-*threo*-2,5-hexodiulose ("5-keto-D-fructose") has so far been described in the literature[1–7]. As this crystalline compound, obtained *via* biological oxidation of D-fructose, showed no carbonyl bands in the i.r. spectrum, a 1,5:2,6-diacetal structure was suggested for it[6], but neither the configuration of the anomeric centers, nor the conformation of the two fused pyranose rings was investigated.

In continuing our search for biologically active 1,4:3,6-dianhydro-hexitol derivatives[8] containing two fused oxolane rings, it was decided to synthesize D-*threo*-3,4-hexodiulose, which would presumably form a similar fused-ring system in its difuranose structure.

Oxidation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**) with Me_2SO–Ac_2O yielded the corresponding 3,4-diketo derivative **2** as a crystalline compound which could be satisfactorily hydrolyzed in methanol in the presence of sulfuric acid, affording the diulose **3**. The lack of any carbonyl band in the i.r. spectrum of **3** suggested the presence of a diacetal, which could possess either the $\alpha\alpha$ (**4**) or the $\beta\beta$ (**6**) difuranose structure. The aqueous solution of the crystalline compound showed a mutarotation of $-31 \rightarrow -15°$; therefore, presuming that Hudson's rule of rotation[9] is valid for difuranosides, the $\beta\beta$ structure **6** was suggested for the anomer present in the crystalline state whereas, in solution, an equilibrium mixture of the $\alpha\alpha$ (**4**) and the $\beta\beta$ (**6**) anomer should prevail. The presence of a mixed $\alpha\beta$ anomer can be excluded for steric reasons as this structure would contain two *trans*-fused five-membered rings, constituting an overstrained system.

A similar equilibrium between **4** and **6** also exists in pyridine as, on treatment with acetic anhydride, two tetraacetate isomers were obtained in the ratio of 1:2; these could be separated by crystallization. According to their optical rotations

*Dedicated to the memory of Karl Freudenberg on the centenary of his birth.

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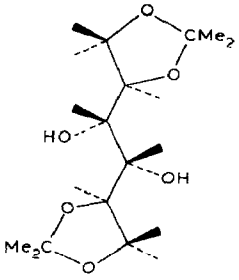
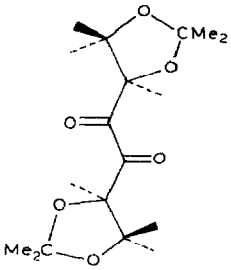


1



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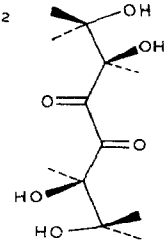

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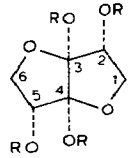
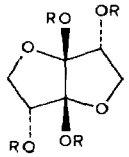


3S, 4S

4 R = H

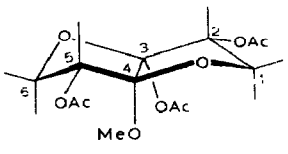
5 R = Ac



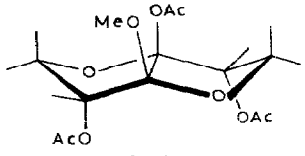
3R, 4R

6 R = H

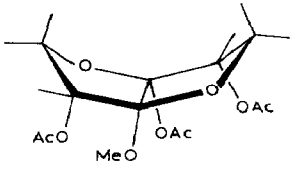
7 R = Ac



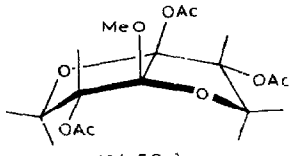
8 ($_6EE_1$)



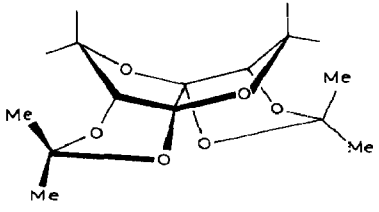
9 ($^6EE^1$)



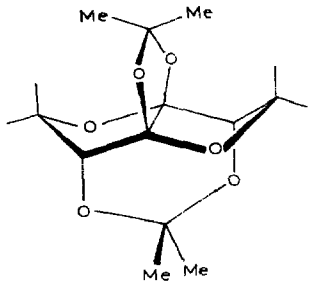
10 ($^6EE^1$)



11 ($_6EE_1$)



12



13

($[\alpha]_D^{20}$ −63.5° and −130°), their structures should correspond to the $\alpha\alpha$ (**5**) and $\beta\beta$ (**7**) forms, respectively, but this could not be unambiguously proved by study of their ^{1}H-n.m.r. spectra.

When a solution of tetrol **6** in 1.5M methanolic hydrochloric acid was boiled for 2 h and subsequently acetylated, a crystalline tri-*O*-acetylmono-*O*-methyl acetal derivative (**8**) was obtained. The asymmetry of the molecule introduced by the presence of the methoxyl group made its extensive n.m.r. investigation possible, and, by applying the NOESY technique, both the $\alpha\alpha$ configuration and the $_6EE_1$ conformation of **8** were established.

As may be seen from formulas **8–11**, the bicyclic skeleton of both anomers can theoretically adopt the same extreme conformations in which C-1 and C-6 are out of the respective plane of the other atoms ($_6EE_1$ for **8** and **11**, and $^6EE^1$ for **9** and **10**). According to the NOESY spectrum (see Fig. 1) the methoxyl group interferes with only two of the three acetoxyl groups and with both of the axially oriented protons of the methylene groups (H-1*a*,6*a*); that excludes the presence of the $\beta\beta$ anomer, as, in its conformer **9**, the methoxyl group would interfere only with the acetoxyl group at C-3, as those at C-2 and C-5 are placed too far away from each other. In the other $\beta\beta$ conformer **11** where, besides the acetoxyl group at C-3, that at C-5 is situated close enough to the methoxyl group to produce a proper interaction, the two axial protons at C-1 and C-6 are bent away, and therefore no effect on them could be expected. The same holds for these protons in the $^6EE^1$ conformer **10** of the $\alpha\alpha$ anomer whereas, in the corresponding $_6EE_1$ conformer **8**, all of the steric requirements indicated in the spectrum are fulfilled and consequently the molecule adopts this conformation. The value of the optical rotation, $[\alpha]_D^{20}$ −61.5°, of **8** is also in good agreement with that of the $\alpha\alpha$-tetraacetate **5**, suggesting for the latter a similar conformation. The formation of **8** under equilibrium conditions means that the all-*cis* arrangement of the substituents in the $\alpha\alpha$ anomers is not unfavorable, compared to their *trans–cis–trans* arrangement in the $\beta\beta$ anomers.

When the tetrol **6** was treated with acetone in the presence of sulfuric acid, the 2,3:4,5-di-*O*-isopropylidene derivative **12** was obtained in high yield; according to its ^{13}C-n.m.r. spectrum it has a completely symmetrical structure and must therefore adopt a conformation analogous to that of compound **10**, with an all-*cis* arrangement of the functional groups. The other theoretically-possible symmetrical 2,5:3,4-diacetal **13**, which would represent the $\beta\beta$ anomer, could be excluded, as the acetal carbon atoms of the two dioxolane rings had identical shifts whereas, in **13**, due to the presence of a dioxolane and a dioxepane ring, they should differ. The rather high value of their shift (115.89 p.p.m.) is somewhat outside the interval given in the literature[10] for the shifts of the acetal carbon atoms of dioxolane rings fused to furanoid rings (111.3–115.7 p.p.m.). This is probably due to the fact that, in compound **12**, the four five-membered fused-rings form a quite rigid system in which the acetal carbon atoms of the sugar skeleton appear similarly downfield (117.18 p.p.m.). The rather small shift-difference ($\Delta\delta$ 0.98 p.p.m.) of the two *exo*-

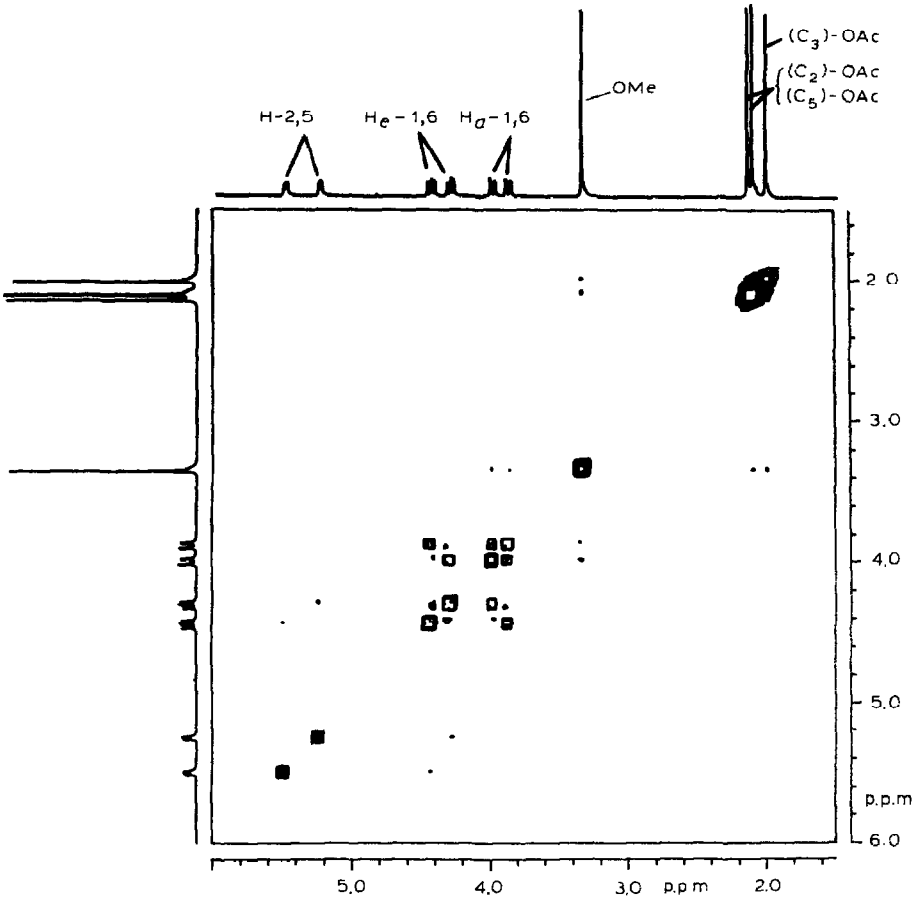


Fig. 1. The NOESY spectrum of **8** in $CDCl_3$ obtained at 300 MHz.

and *endo*-situated isopropylidene methyl groups means that the four fused rings must adopt a rather "flat" conformation in which the two dioxolane acetal carbon atoms are bent away from each other occupying a "*diexo*" position, and consequently, the methyl groups attached to them are far enough away from each other for them to avoid any stronger interference.

EXPERIMENTAL

General methods. — Organic solutions were dried (Na_2SO_4) and evaporated under diminished pressure. T.l.c. was performed on Kieselgel G with carbon tetrachloride–ethyl acetate 3:1 (*A*) and 1:1 (*B*), and 9:1 ethyl acetate–ethanol (*C*). For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Melting points are uncorrected. Optical rotations were determined on 1% solutions in chloroform, if not stated otherwise. I.r. spectra of compounds in KBr pellets were recorded with a Bruker-IFS-85 spectrometer. ^{1}H-N.m.r. spectra (90 and 300

MHz) were recorded with a Varian EM 390 and a Bruker AC 300 instrument, and ^{13}C-n.m.r. spectra (25.2 MHz) with a Varian XL-100 spectrometer, respectively, for solutions in chloroform-*d* with tetramethylsilane as the internal standard.

1,2:5,6-Di-O-*isopropylidene*-D-threo-*3,4-hexodiulose* (**2**). — A solution of **1** (ref. 11; 70 g) in dry dimethyl sulfoxide (600 mL) and acetic anhydride (150 mL) was kept for 1 h at 70° and then evaporated below 60°. The semisolid residue obtained was filtered with the aid of ethanol (50 mL), to give **2** (36 g, 52%); R_F 0.8 (solvent *B*), 0.35 (solvent *A*); m.p. 124–126°, $[\alpha]_D^{20}$ +113°; ν_{max} 1726 cm^{-1} (CO); ^{1}H-n.m.r. (90 MHz) data: δ 4.91 (dd, 2 H, *J* 5 Hz, H-2,5), 4.15 (m, 4 H, H-1,6), and 1.43 (s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.0. Found: C, 55.8; H, 7.1.

ββ-Di-D-threo-*3,4-hexodiulofuranose* (**6**). — A slurry of **2** (10 g) in methanol (100 mL) and M sulfuric acid (10 mL) was stirred for 2 h at 60°, the solution obtained cooled, and the acid neutralized with calcium carbonate. The solid material was filtered off and the filtrate was evaporated. The residue crystallized on being kept overnight at room temperature, and was filtered off with the aid of ethanol, to give **6** (5.9 g, 85.5%); R_F 0.5 (solvent *C*); m.p. 164–166°, $[\alpha]_D^{20}$ −31.6 (5 min) → −14.8° (24 h, water).

Anal. Calc. for $C_6H_{10}O_6$: C, 40.4; H, 5.7. Found: C, 40.3; H, 5.8.

2,3,4,5-Tetra-O-*acetyl-αα-di*-D-threo-*3,4-hexodiulofuranose* (**5**) *and its ββ isomer* (**7**). — To an ice-cooled solution of **6** (7.2 g) in pyridine (100 mL) was added acetic anhydride (25 mL) and the mixture was kept for 2 days at room temperature. Thereafter it was poured into water to give, after the usual processing, a syrup which was treated with ethanol (30 mL). The crystals formed were filtered off to give, after recrystallization from ethanol (15 vol.), the ββ anomer **7** (5.2 g, 37%); R_F 0.8 (solvent *B*); m.p. 198–199°, $[\alpha]_D^{20}$ −130°; ^{1}H-n.m.r. (90 MHz) data: δ 5.6 (dd, 2 H, *J* 5 and 1.2 Hz, H-2,5), 4.43 (dd, 2 H, *J* 8.3 and 5 Hz, H-1,6), 4.03 (dd, 2 H, *J* 8.3 and 1.2 Hz, H-1,6), and 2.17 and 2.07 (2 s, 2 × 6 H, 4 OAc).

On treatment with ethanol (15 mL), the residue obtained on evaporation of the mother liquor gave the αα anomer **5** (2.5 g, 18%); R_F 0.8 (solvent *B*); m.p. 118–119°, $[\alpha]_D^{20}$ −63.5°; ^{1}H-n.m.r. (90 MHz) data: δ 5.58 (dd, 2 H, *J* 5 and 7.5 Hz, H-2,5), 4.57 (dd, 2 H, *J* 10 and 5 Hz, H-1,6), 3.89 (dd, 2 H, *J* 10 and 7.5 Hz, H-1,6), and 2.13 and 2.07 (2 s, 2 × 6 H, 4 OAc).

Anal. Calc. for $C_{14}H_{18}O_{10}$: C, 48.6; H, 5.2. Found for **5**: C, 48.5; H, 5.4. Found for **7**: C, 48.6; H, 5.4.

Methyl 2,3,5-tri-O-*acetyl-αα-di*-D-threo-*3,4-hexodiulose-3,6-furanose-1,4-furanoside* (**8**). — A solution of **6** (2.7 g) in 1.5M methanolic hydrochloric acid was boiled for 3 h. The solution was cooled, the acid neutralized with solid sodium hydrogencarbonate, the salts filtered off, and the filtrate evaporated. Benzene was added to, and evaporated from, the residue, which was dissolved in dry pyridine (25 mL) to which acetic anhydride (8 mL) was then added. The mixture was kept overnight at room temperature, to give, after the usual processing, a syrup which crystallized from ethanol (10 vol.), to yield **8** (2 g, 41.5%); R_F 0.65 (solvent *B*);

m.p. 189–190°, $[\alpha]_D^{20}$ −61.5°; ^{1}H-n.m.r. (300 MHz) data: δ 5.53 and 5.28 (2 ddd, 2 H, J_{cis} 5.5 and 6.0 Hz, J_{trans} 1.5 and 2.8 Hz, $J_{2,5}$ 1 Hz, H-2,5), 4.47 and 4.33 (2 dd, 2 H, J_{gem} 11 Hz, H_e-1,6), 4.03 and 3.92 (2 dd, 2 H, H_a-1,6), 3.39 (s, 3 H, OMe), 2.18 and 2.15 (2 s, 2 × 3 H, 2 OAc), and 2.03 (s, 3 H, OAc-3).

Anal. Calc. for $C_{13}H_{18}O_9$: C, 49.1; H, 5.7. Found: C, 49.1; H, 5.7.

*2,3:4,5-Di-O-isopropylidene-αα-di-*D-threo-*3,4-hexodiulofuranose* (**12**). — A slurry of **6** (1.8 g) in acetone (60 mL) and conc. sulfuric acid (0.3 mL) was stirred at room temperature until complete dissolution occurred (26 h). The solution was then made neutral with calcium carbonate, the precipitate filtered off, and the filtrate evaporated. The residue was purified by chromatography on a column of Kieselgel 40 using solvent *B* for elution. On evaporation, the fractions having R_F 0.85 (solvent *B*) gave **12** as syrup (1.8 g, 70%); $[\alpha]_D^{20}$ −45°; ^{1}H-n.m.r. (90 MHz) data: δ 4.49 (t, 2 H, *J* 4.5 Hz, H-2,5), 4.02 (d, 4 H, *J* 4.5 Hz, H-1,6), 1.52 (s, 6 H, CMe_2), and 1.47 (s, 6 H, CMe_2); ^{13}C-n.m.r. data: δ 117.18 (C-3,4), 115.89 (acetal-C), 81.24 (C-2,5), 71.56 (C-1,6), and 26.98 and 26.00 (acetal-Me).

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.8; H, 7.0. Found: C, 55.6; H, 7.0.

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