Note

Enolization of hexodiulose acetals. Synthesis of derivatives of D-psicose by reduction of a hex-3-enulopyranose*†**

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Previous papers from this laboratory have reported the synthesis of isopropylidene acetals of D-*erythro*-pentulose[2], D-*threo*-pentulose[2], D-fructose[3], and D-psicose[4], and have demonstrated their utility in the synthesis and purification of rare ketoses. The present work describes an attempt to synthesize similar acetals of D-tagatose (D-*lyxo*-hexulose). 1,2:4,5-Di-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexodiulo-2,6-pyranose (**1**), an intermediate previously used[4], was converted into a 3,4-enediol acetate, namely, 1,2:4,5-di-*O*-isopropylidene-*β*-D-*glycero*-hex-3-enulopyranose (**2**). Reduction of **2** with hydrogen over palladium gave, however, only 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*β*-D-psicopyranose (**3**), and none of the D-tagatose derivative.

The synthesis and synthetic applications of fully protected aldosuloses and diuloses have received much attention[5], but the chemistry of enediol acetates, as obtained from these compounds by the action of acetic anhydride–triethylamine[6], is largely unexplored. Stereospecific reduction or addition reactions of these unsaturated derivatives offer attractive possibilities for the synthesis of rare and unusual sugars.

DISCUSSION

Diulose **1** is obtainable in 78% overall yield from D-fructose by condensation with acetone to produce (in 80% yield[3]) 1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose, which may be oxidized[4] by ruthenium tetraoxide[7] to give **1** in 98% yield.

Treatment of diulose **1** with an acetic anhydride–triethylamine reagent[6] for 3 days at 50° gave 46% of a new, crystalline compound whose i.r. spectrum showed bands at 1770 and 1746 cm^{-1}, indicative of a O–C=C–O–C=O system[6], and whose elemental analysis was consistent with the formula $C_{14}H_{20}O_7$. The n.m.r. spectrum showed the presence of two isopropylidene acetal groups and one acetyl group; two 1-proton doublets for the protons on C-1 and a well-defined, eleven-line, AMX pattern representing the protons on C-5 and C-6 were also readily identifiable. These

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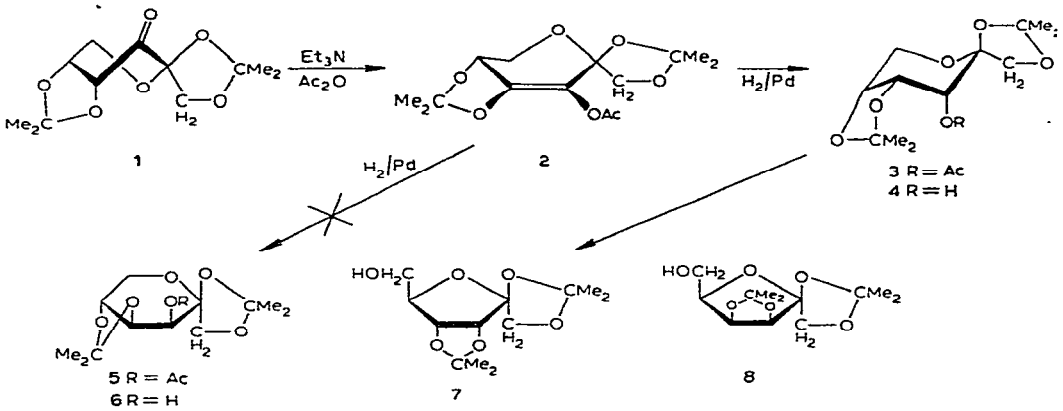
data, and the fact that diulose **1** has a proton on C-4 but not on C-2, establish that the product is 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-β-D-*glycero*-hex-3-enulopyranose (**2**).



Attempts to prepare enediol acetate **2** by treating diulose **1** with acetic anhydride and pyridine (*a*) at room temperature for 16 h, (*b*) under prolonged heating at 80 or 125°, or (*c*) under reflux for 1 h, were successful. Treatment of diulose **1** in carbon tetrachloride solution with an acetic anhydride–perchloric acid reagent[8] did not give the desired product **2**. Treatment of diulose **1** in tetrahydrofuran solution with an acetic anhydride–sulfuric acid reagent[9], or slow distillation of the solvent from a solution of diulose **1** in acetic anhydride containing *p*-toluenesulfonic acid[10], also failed to produce enediol acetate **2**. Earlier attempts, by using acidic conditions, to prepare an enediol acetate from a precursor ketone having acid-labile blocking groups were also unsuccessful[6], in contrast to the successful outcome when basic conditions were used.

On reduction of **2**, *cis*-addition of hydrogen at C-3 and at C-4 might result in formation of the corresponding derivative of D-tagatose or D-psicose, or both. Inspection of a molecular model of compound **2** revealed that the molecule could assume either an H_6^0(D) conformation or that sofa conformation[11] having the oxygen atom of the pyranoid ring exoplanar to the plane of the carbon atoms of this ring. Reduction of **2** at either side of either conformation appeared possible.

One possible reduction product, namely, 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**3**), would be formed by *cis*-addition of hydrogen at that side of the plane, defined by C-2–C-3–C-4–C-5, on which O-2 is located. By analogy with the conformation[12] of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose, compound **3** may be expected to assume a conformation, intermediate between ^1C(D) and H_0^2(D), in which that part of the molecule containing C-4, C-5, and C-6 is slightly flattened from the ideal chair conformation because of the presence of the 1,3-dioxolane ring involving C-4 and C-5. The unacetylated compound **4** has been prepared and found to be stable[4].

The other possible reduction product, namely, 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-β-D-tagatopyranose (**5**), would be formed by *cis*-addition of hydrogen to that side of the plane on which C-1 is located. Diacetal **5** would contain an isopropylidene group *trans*-fused to the equatorially attached hydroxyl groups on C-4 and C-5. Although several hexulopyranose derivatives containing a *trans*-fused isopropylidene group have been reported[13], isopropylidene groups *trans*-fused to six-membered rings generally cause steric strain[14] in these rings, and are thus disfavored. Neither diacetal **5** nor the unacetylated compound **6** has yet been reported. In view of the steric strain in compound **5**, similar strain in the transition state in the reduction of **2** to **5** could also be anticipated.

Experimentally, it is found that reduction of **2** is stereospecific and that only diacetal **3** is formed. Hydrogenation of compound **2** at atmospheric pressure in the presence of 5% palladium-on-carbon catalyst gave a syrup that was shown to be 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**3**). Acetate **3** was deacetylated with methanolic barium methoxide[15] to afford crystalline 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**4**). Diacetal **4** was converted into a furanose derivative by treatment with acetone containing 0.5% of sulfuric acid to effect rearrangement, giving a chromatographically homogeneous, levorotatory, crystalline compound, identified as 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose (**7**). The corresponding derivative of D-tagatose, 1,2:3,4-di-*O*-isopropylidene-D-tagatofuranose (**8**), is a strongly dextrorotatory, crystalline solid[16].

Reduction of the enediol acetate **2** with sodium borohydride in ethanolic solution is complete after 18 h, and affords diacetal **4** in high yield. This reaction evidently proceeds by reductive deacetylation of **2**, with intermediate formation of the enolate anion; this ketonizes, and is protonated by the alcoholic solvent, forming diulose **1**, which is subsequently reduced to diacetal **4**. Although the reduction of **2** to **4** with sodium borohydride is much slower than similar borohydride reduction of an enediol acetate prepared by Horton and Just[6], the product obtained in both cases is the same as that obtained when the diulose is reduced by borohydride directly. This suggests that the reduction proceeds through the diulose in each case. Compound **4** has also been obtained[4] by direct reduction of diulose **1** with borohydride.

As a synthetic route to isopropylidene acetals of D-psicose, the reduction of compound **2** is not preferred, because direct reduction of diulose **1** with borohydride gives diacetal **4** in 99% yield[4]. However, this synthesis of derivatives of D-psciose may prove valuable for the synthesis of acetals made with other aldehydes and ketones, in which the reduction of the diulose analogous to **1** would not be stereospecific because of bulkier alkylidene acetal groups.

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Melting points were determined in a silicone-oil bath, and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer Model 257 grating i.r.

spectrophotometer*. Solution spectra were obtained by using 10% solutions in sodium chloride cells having a path-length of 0.1 mm; an identical cell containing only solvent was placed in the reference beam. Optical rotations were determined, for solutions in 1-dm tubes, with a Perkin–Elmer Model 141 photoelectric polarimeter. N.m.r. spectra were recorded at ~40° with Bruker (90 MHz) and Varian (60 MHz) n.m.r. spectrometers for solutions (15–20%) in acetone-d_6 containing tetramethylsilane ($\tau = 10.00$) as the internal standard. The first-order coupling-constants were measured from a spectrum recorded at 90 MHz and a sweep-width of 240 Hz, and the measurements are considered accurate to within ± 0.1 Hz. T.l.c. was performed with Silica Gel G (E. Merck, Darmstadt, Germany), activated at 110°, as the adsorbent, and 3:1 (v/v) ethyl acetate–pentane as the developer; indication of zones was effected with sulfuric acid. Analyses were made by W. P. Schmidt of this Institute.

1,2:4,5-Di-O-isopropylidene-β-D-erythro-2,3-hexodiulo-2,6-pyranose (**1**). — Compound **1** was prepared from D-fructose by a method previously described[3,4]. Recrystallized from hexane (4 ml/g), it had m.p. 102–103°, $[\alpha]_D^{25}$ −104.7° (*c* 1.0, acetone); R_F 0.89 (one component); i.r. spectrum identical with that of authentic[4] **1**.

3-O-Acetyl-1,2:4,5-di-O-isopropylidene-β-D-glycero-hex-3-enulopyranose (**2**). — A solution of the diulose **1** (10.0 g, 382 mmoles) in a mixture of acetic anhydride (200 ml, 2.12 moles) and triethylamine (50 ml, 360 mmoles) was kept for 3 days at 50° under a reflux condenser closed with a drying tube containing Drierite. The resulting dark-brown solution was evaporated to a syrup that was dissolved in 150 ml of 1:1 (v/v) ethyl acetate–pentane and chromatographed on a column (48 × 5 cm) of Florisil (300 g) (The Floridin Company, Berkeley Springs, W. Va.). The product was eluted with the same solvent; 50-ml fractions were collected and evaporated. Fractions 11–15, each completely crystalline, were combined, and recrystallized from pentane, giving the enediol acetate **2** as fine, colorless needles; yield 5.3 g (46%), m.p. 107–108°, $[\alpha]_D^{25}$ −92.9° (*c* 0.9, acetone); R_F 0.42; ν_{max}^{KBr} 3005, 2955, 2905 (all C–H stretches), 1770 and 1746 (doublet, O–C=C–O–C=O), 1463, 1455, 1435 (all C–H bends), 1395, 1380 and 1370 (doublet, CMe_2), 1368, 1316, 1286, 1262, 1248, 1208 (C–O stretch, acetic ester), 1180, 1145 and 1132 (doublet, CMe_2), 1108, 1070, 1062, 1052, 1011, 992, 986, 978, 914, 872, 851, 814, 806, 797, 757, and 670 cm^{-1}; n.m.r. data (90 MHz): τ 5.20 (1-proton quartet, $J_{5,6}$ 5.2 Hz, $J_{5,6'}$ 9.6 Hz, H-5), 5.79 (1-proton quartet, $J_{6,6'}$ 9.9 Hz, H-6), 6.00 (1-proton doublet, $J_{1,1'}$ 9.2 Hz, H-1), 6.15 (1-proton doublet, H-1), 6.51 (1-proton triplet, H-6'), 7.84 (3-proton singlet, Ac), 8.50, 8.52, and 8.69 (6-, 3-, and 3-proton singlets, two CMe_2 groups).

Anal. Calc. for $C_{14}H_{20}O_7$: C, 56.0; H, 6.7. Found: C, 56.2; H, 6.9.

When kept without desiccation, compound **2** decomposed within 3 months to a brown syrup having the odor of acetone, but it appeared to be stable indefinitely when stored under anhydrous conditions.

*Certain commercial products and instruments are identified in order to specify the experimental procedures adequately. In no case does such identification imply recommendation or endorsement by the National Bureau of Standards, nor does it imply that the product or equipment identified is necessarily the best available for the purpose.

3-O-Acetyl-1,2:4,5-di-O-isopropylidene-β-D-psicopyranose (**3**). — A suspension of 120 mg of 5% palladium-on-carbon catalyst in a solution of enediol acetate **2** (1.51 g, 5.03 mmoles) in 100 ml of 95% ethyl alcohol was stirred magnetically under hydrogen at one atmosphere pressure for 6 h at room temperature, The suspension was filtered with suction through sintered glass, and the solids were washed with 10 ml of 95% ethyl alcohol. The filtrate and washings were combined, and evaporated to a colorless syrup, which was distilled at 106–108°/0.1 torr. A colorless syrup was obtained; yield 1.16 g (76%), $[\alpha]_D^{25}$ −115.7° (*c* 0.6, acetone), −115.9° (*c* 0.7, ethanol); [lit.[17] syrup, b.p. 106°/0.1 torr, $[\alpha]_D$ −116° (*c* 0.8, ethanol)]; R_F 0.40; $\nu_{max}^{CHCl_3}$ 2990, 2940, (C–H stretches), 1740 (C=O stretch), 1455, 1425 (C–H bends), 1385 and 1375 (doublet, CMe_2), 1230 (C–O stretch of acetic ester), 1140, 1090, 1070, 1025, 1000, 985, 930, 905, 868 (CMe_2), 800, and 720 cm^{-1}; n.m.r. data (60 MHz): τ 4.82 (1-proton multiplet), 6.05 (6-proton multiplet), 7.90 (3-proton singlet, Ac), 8.52, 8.63, and 8.70 (3-, 6-, and 3-proton singlets, two CMe_2 groups).

1,2:4,5-Di-O-isopropylidene-β-D-psicopyranose (**4**). — To a solution of compound **3** (350 mg, 1.16 mmoles) in 10.0 ml of abs. methanol, cooled to 0°, was added 0.03 ml (34 mmoles, 0.033 equivalent) of 0.56M barium methoxide in abs. methanol, and the solution was kept for 24 h at 0°. Finely powdered Dry Ice was then added until the solution was saturated with carbon dioxide. Water (2.0 ml) was added, followed by additional amounts of finely divided Dry Ice until the solution was again saturated with carbon dioxide. Decolorizing carbon (0.5 g) was added, and the suspension was brought to a gentle boil, and filtered through sintered glass. The filtrate was evaporated, and the resulting syrup was dried overnight at 25°/0.1 torr over phosphorus pentaoxide, giving a syrup (249 mg, 83%), which was dissolved in hexane (2.5 ml) under reflux and cooled. Crystallization ensued on nucleation with authentic **4**, yielding **4** as short needles, yield 209 mg (68%), m.p. 68–69°, $[\alpha]_D^{25}$ −116.2° (*c* 1.1, acetone); lit.[4] m.p. 68–69°, $[\alpha]_D^{25}$ −116.4° (*c* 0.7, acetone). The i.r. and n.m.r. spectra of diacetal **4** were identical with those of an authentic sample[4].

1,2:3,4-Di-O-isopropylidene-D-psicofuranose (**7**). — To a solution of diacetal **4** (130 mg, 0.5 mmole) in acetone (2 ml) was added 2.00 ml of a solution made by diluting 1.00 ml of concentrated sulfuric acid with acetone to 100.00 ml in a volumetric flask. The resulting solution was protected from moisture and kept for 4 h at room temperature; calcium hydroxide (2.0 g) was then added, and the suspension was stirred magnetically for 4 h, and kept overnight at room temperature. The suspension was filtered with suction through a layer of calcium hydroxide on a sintered-glass plate; the solids were washed with 5 ml of acetone, and the filtrate and washings were combined and evaporated to a syrup, which was dried overnight at 25°/0.1 torr over phosphorus pentaoxide; yield 110 mg (85%). This material was dissolved in 1.0 ml of boiling hexane and the solution was cooled; crystallization ensued when this solution was nucleated with authentic **7**, yielding **7** as hexagonal plates, wt. 87 mg (67%), m.p. 56–57°, $[\alpha]_D^{25}$ −97.8° (*c* 0.1, acetone); lit.[18] m.p. 57–58°, $[\alpha]_D$ −98.2° (acetone).

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