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Note

A novel mode of reductive elimination from a 2-deoxy-2-iodo-α-D-altropyranoside

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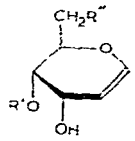
It is well-established[1–4] that D-allal derivatives (**1**) are formed when methyl 2-deoxy-2-iodo-α-D-altropyranosides having an unsubstituted hydroxyl group at the 3-position (**2**, R = H) are treated with alkyl-lithium reagents. On the other hand, if a reasonable leaving-group is present at C-3, as, for example, in a 3-*O*-tosyl derivative[1] or a 3,4-*O*-isopropylidene system[5], an alternative, reductive elimination can occur in the presence of anionic reagents, to give a methyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside of type **3**. We now report that, in certain structural circumstances, a third mode of reductive elimination can occur in these systems, which can be related to the conformation of the starting material.



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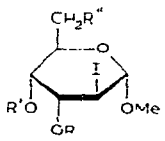
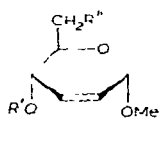


2

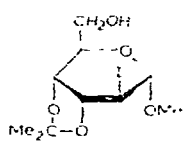
4 R = R' = H, R'' = OH



3

6 R' = H, R'' = OH

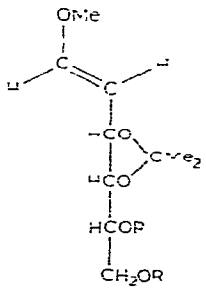
7 R' = Bz, R'' = OBz



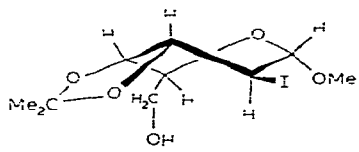
5

When methyl 2-deoxy-2-iodo-α-D-altropyranoside (**4**) was treated with acetone and sulphuric acid, the major isopropylidene derivative **5** could be isolated by chromatography as a syrup in 89% yield. The expected 3,4-position of the isopropylidene grouping was confirmed by the ^{13}C-n.m.r. spectrum[6] (see Experimental). On treatment of **5** with methyl- or butyl-lithium, two products were produced in comparable yields, and these could be separated by chromatography. The slower-moving component was identified by n.m.r. spectroscopy as a predictable[5] product, namely, methyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**6**), and this was confirmed by formation of the crystalline dibenzoate[7] in 51% overall yield. The faster-moving material was shown by n.m.r. spectroscopy to have retained both the *O*-methyl and *O*-isopropylidene functions, but with the appearance of a prominent, 1-proton doublet

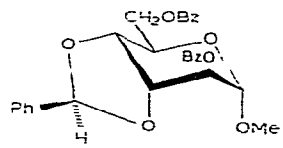
(J 12 Hz) at δ 6.4. The postulated structure, (*E*)-2-deoxy-3,4-*O*-isopropylidene-1-*O*-methyl-D-*ribo*-hex-1-enitol (**8**), was confirmed by characterisation of the diacetate (**9**) obtained by conventional acetylation (35% overall yield) from **5**. The 360-MHz, ^{1}H-n.m.r. spectrum of **9** showed singlets for two acetate groups, an isopropylidene group, and an *O*-methyl group. The presence of the enol-ether linkage was indicated by a 1-proton doublet (J 12.5 Hz) at δ 6.58 and a 1-proton double-doublet (J 12.5 and 9.5 Hz) at δ 4.73; these chemical shifts and the coupling constant of 12.5 Hz are typical of a *trans*-enol ether[8]. Signals for five other protons were present in the range δ 4.0–5.1; complete assignments are given in the Experimental section.



8 R = H
9 R = Ac



10



11

Compound **5** was treated with methylmagnesium iodide or with lithium aluminium hydride, because structurally related compounds were reported[5] to give only the hex-2-enopyranoside with these reagents. The ring-opened product **8** was again produced, but in lower yield relative to the hex-2-enopyranoside system. No glycal of type **1** was produced.

Examination of the 360-MHz, ^{1}H-n.m.r. spectrum of **5** revealed that all vicinal coupling constants for the ring protons were quite large ($\geqslant$6 Hz) (see Experimental). This implies that the compound exists in a skew conformation, most probably as shown in **10**: since the spectrum remains unchanged on cooling to −90°, interconverting chair-forms are ruled out. The tendency to adopt a skew conformation is presumably due to the steric bulk of the iodine atom, coupled with the steric restrictions imposed by the 3,4-*O*-isopropylidene ring, since 2-deoxy-2-iodo-altropyranosides without a 3,4-*O*-isopropylidene ring adopt the $^4C_1$ conformation[2,4], and methyl 2,6-di-*O*-benzoyl-3,4-*O*-(*S*)-benzylidene-α-D-altropyranoside (**11**) exists predominantly as the $^4C_1$ conformer[9]. A methyl 2-deoxy-2-iodo-altropyranoside in the $^4C_1$ conformation has the iodine atom trans-coplanar with both MeO-1 and O-3, so that concerted eliminations to glycals and hex-2-enopyranosides are stereoelectronically favourable. Examination of a molecular model of **10** indicates that all the inter-proton dihedral angles are such that relatively large couplings should be observed[10], and also that the iodine atom and the C-1–O-5 bond are approximately trans-coplanar, so that concerted, reductive elimination should lead stereospecifically to **8**.

EXPERIMENTAL

General methods. — Solutions were evaporated under diminished pressure; solvent extracts were dried with anhydrous sodium sulphate. Optical rotations were measured at room temperature with a Bendix–NPL 143D automatic polarimeter (pathlength, 1 cm). N.m.r. spectra were recorded on solutions in $CDCl_3$ with a JEOL MH-100 or Bruker WH-360 spectrometer. Column chromatography was performed on Silica Gel (Merck). Melting points are uncorrected.

*Methyl 2-deoxy-2-iodo-3,4-*O*-isopropylidene-α-*D*-altropyranoside* (**5**). — To a solution of methyl 2-deoxy-2-iodo-α-D-altropyranoside[3] (**4**, 1.0 g) in acetone (15 ml) was added conc. sulphuric acid (0.01 ml). The mixture was maintained at 40° for 30 min, after which it was poured into cold, aqueous sodium carbonate and extracted with dichloromethane (3 × 100 ml). The washed and dried organic layer was evaporated, to yield a syrup which was chromatographed on silica gel with ethyl acetate to yield **5** as a colourless syrup (1.0 g, 89%), $[\alpha]_D$ +44° (*c* 0.7, chloroform). P.m.r. data (360 MHz): δ 1.31, 1.44 (2 s, 6 H, CMe_2), 2.2 (br.s, 1 H, exchangeable, OH), 3.39 (s, 3 H, OMe), 3.70 (dd, 1 H, *J* 11.5 and 4.9 Hz, H-6a), 3.80 (m, 1 H, H-5), 3.84 (dd, 1 H, *J* 11.5 and 2.9 Hz, H-6b), 3.97 (dd, 1 H, $J_{2,3}$ 8.8, $J_{1,2}$ 6.0 Hz, H-2), 4.25 (dd, 1 H, $J_{4,5}$ 8.5, $J_{3,4}$ 6.6 Hz, H-4), 4.40 (dd, 1 H, $J_{2,3}$ 8.8, $J_{3,4}$ 6.6 Hz, H-3), and 4.98 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1). ^{13}C-N.m.r. data ($CDCl_3$): 25.2, 27.1, and 110.5 p.p.m. (isopropylidene group)[6].

Anal. Calc. for $C_{10}H_{17}IO_5$: C, 34.88; H, 4.94; I, 36.92. Found: C, 34.44; H, 5.06; I, 36.10.

(E)-*5,6-Di-*O*-acetyl-2-deoxy-3,4-*O*-isopropylidene-1-*O*-methyl-*D*-ribo-hex-1-enitol* (**9**) *and methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-α-*D*-erythro-hex-2-enopyranoside* (**7**). — A solution of butyl-lithium (4 mmol) in tetrahydrofuran was added dropwise to a stirred solution of **5** (0.704 g, 2.04 mmol) in tetrahydrofuran (30 ml) at 0° under nitrogen. The mixture was allowed to attain room temperature and then kept thereat for 1.5 h. Excess of reagent was decomposed with ice, and the mixture partitioned between ethyl acetate and water. Evaporation of the dried, organic extracts left a gum which was chromatographed on silica gel. Elution with ethyl acetate yielded, first, compound **8** (0.28 g) as a gum; p.m.r. data (100 MHz): δ 1.40, 1.48 (2 s, 6 H, CMe_2), 3.56 (s, 3 H, OMe), and 6.45 (d, 1 H, *J* 12 Hz, =C*H*-OMe). A portion (0.10 g) of this material was dissolved in pyridine (20 ml) containing acetic anhydride (0.6 ml), and the mixture was kept at room temperature for 18 h. A standard work-up, followed by chromatography on silica gel with dichloromethane–ethyl acetate, yielded the diacetate **9** (72 mg, 35% from **5**) as a syrup, $[\alpha]_D$ +6° (*c* 1.3, chloroform); p.m.r. data (360 MHz): δ 1.35, 1.45 (2 s, 6 H, CMe_2), 1.99, 2.04 (2 s, 6 H, OAc), 3.53 (s, 3 H, OMe), 4.08 (dd, 1 H, *J* 12.3 and 6.1 Hz, H-6a), 4.19 (dd, 1 H, $J_{4,5}$ 8.1, $J_{3,4}$ 6.4 Hz, H-4), 4.55 (dd, 1 H, *J* 12.1 and 2.4 Hz, H-6b), 4.61 (dd, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 6.3 Hz, H-3), 4.73 (dd, 1 H, $J_{1,2}$ 12.5, $J_{2,3}$ 9.5 Hz, H-2), 5.07 (ddd, 1 H, *J* 8.1, 5.9, and 2.4 Hz, H-5), and 6.58 (d, 1 H, *J* 12.5 Hz, H-1).

Anal. Calc. for $C_{14}H_{22}O_7$: C, 55.63; H, 7.28. Found: C, 55.73; H, 7.58.

Further elution of the original chromatography column yielded **6** (0.22 g), a portion (0.08 g) of which was treated for 18 h with pyridine (15 ml) containing benzoyl chloride (0.19 g). The solvent was then evaporated, the residue was partitioned between ethyl acetate and water, and the dried, organic layer was evaporated. Crystallisation of the residue from ethanol yielded the dibenzoate **7** (0.14 g, 51% from **5**), m.p. 74–75°; lit.[7] m.p. 74.5–75.5°. The n.m.r. data were identical with those published[7].

Use of methyl-lithium in ether in place of the butyl-lithium gave a very similar result.

Reactions of **5**. — (*a*) *With lithium aluminium hydride*. To a suspension of lithium aluminium hydride (38 mg, 1 mmol) in dry ether (10 ml) was added, dropwise, a solution of **5** (120 mg, 0.35 mmol) in ether (10 ml). After 10 min, the reaction mixture was processed as described above, to yield **9** (11 mg, 11%) and **7** (81 mg, 63%).

(*b*) *With methylmagnesium iodide*. The Grignard reagent was formed in the usual way from magnesium (0.44 g) and methyl iodide (0.41 ml) in ether (10 ml). A solution of **5** (120 mg) in ether (10 ml) was added and, after 2 h, the reaction mixture was processed as above, to yield **9** (5 mg, 5.5%) and **7** (90 mg, 70%).

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