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## Note

# A convenient synthesis of 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methanesulphonyl-β-L-idofuranose, and its conversion into 6-substituted L-idofuranose derivatives*

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In connection with other work, a convenient synthesis of 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methanesulphonyl-β-L-idofuranose (**3**) was required. The compound has previously been obtained[1] from 1,2-*O*-isopropylidene-3-*O*-methanesulphonyl-α-D-glucofuranose by sequential benzoylation and tosylation followed by treatment with sodium methoxide.

6-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) is readily available[2] from D-glucose, in moderate yield, in a single reaction sequence. Methanesulphonylation of **1** gave the crystalline dimesylate **2**, which gave the desired oxirane **3** on treatment with sodium isopropoxide. Both these last reactions proceeded in high yield, and the whole sequence thus provides a convenient synthesis of the oxirane **3** from D-glucose.

Reduction of the oxirane **3** with lithium aluminium hydride gave the known[3] 6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**4**) (isolated as its diacetate **5**), by reductive cleavage of both the oxirane ring at C-6 and of the mesyl group. The former cleavage evidently occurred more readily, for, with shorter reaction times, **4** was accompanied by the 3-mesylate **6**. Examples of C–O cleavage of secondary sulphonate groups in compounds bearing free hydroxyl groups have been reported[4], but no 3-deoxy compounds were encountered in the present reaction.

Two sulphur-containing products accompanied the expected 6-deoxy compound **4** when the reaction was performed with an old sample of lithium aluminium hydride. The n.m.r. spectrum of the first product contained a singlet (3 H) at δ 2.14, indicative of an *S*-methyl group, and desulphuration with Raney nickel gave the 6-deoxy derivative **4**, showing the precursor to be 1,2-*O*-isopropylidene-6-*S*-methyl-6-thio-β-L-idofuranose (**7**). This conclusion was confirmed by synthesis. The oxirane ring of **3** was opened at the 6-position by sodium methanethiolate to give the methylthio ether **8**. Cleavage of the mesyl group with sodium methoxide then afforded the diol **7**. It appears that, in contrast to the earlier reaction with fresh lithium aluminium hydride,

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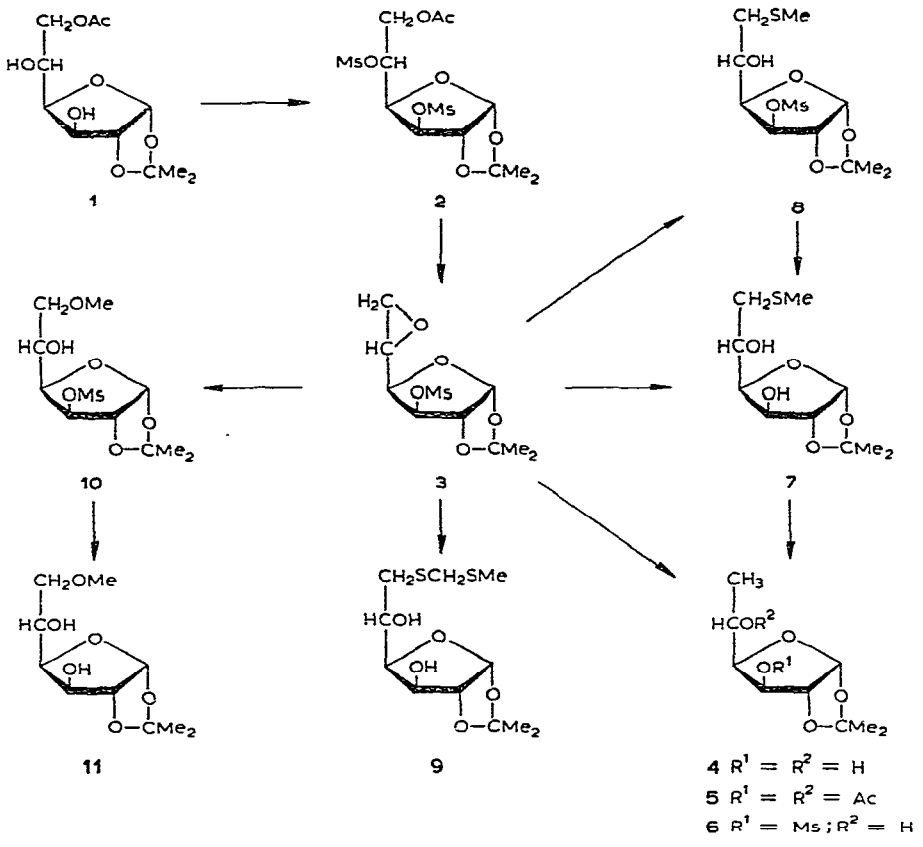


reduction occurred first at the sulphonate group of **3**, and that the methanethiol produced then opened the oxirane ring to give **7**. The n.m.r. spectrum of the second sulphur-containing by-product was, with the addition of a singlet (2 H) at $\delta$ 3.71, remarkably similar to that of **7**. The mass spectrum indicated an additional $CH_2S$ in the molecular formula. Desulphuration with Raney nickel gave, as with **7**, the 6-deoxy compound **4**, but, unlike **7**, the compound liberated methanethiol when heated with sulphuric acid. From these facts, the dithioacetal structure **9** is suggested for this compound, but its mode of formation is not clear at present.

In earlier experiments, the conversion of the disulphonate **2** into the oxirane **3** was effected by sodium methoxide. However, yields were diminished, because the oxirane **3** slowly reacted further with the methoxide to give the methyl ether **10** whose n.m.r. spectrum showed the hydroxyl hydrogen signal as a doublet at $\delta$ 2.90, confirming that ring opening had occurred at the primary position. The methyl ether **10** reacted further with sodium methoxide, affording the diol **11**. Better yields of **3** were achieved by using the more bulky isopropoxide ion, which decreased the rate of opening of the oxirane ring.

TABLE I

FIRST-ORDER CHEMICAL SHIFTS[a]

| *Compound* | *H-1* | *H-2* | *H-3* | *H-4* | *H-5* | *H-6* | *H-6'* | *$CMe_2$* | *Other signals* |
|---|---|---|---|---|---|---|---|---|---|
| **2** | 5.96 | 4.96 | 5.11 | 4.33 | 5.06 | 4.67 | 4.26 | 1.51,1.33 | 3.21, 3.14 (2 $MeSO_2$); 2.11 (MeCO) |
| **3** | 6.01 | 4.76 | 5.13 | 4.07 | 3.21 | 2.83 | 2.73 | 1.49,1.33 | 3.13 ($MeSO_2$) |
| **4** | 6.03 | 4.56 | 4.26 | 3.99 | 4.11 | | 1.38[b] | 1.53,1.37 | 3.76 (HO) |
| **5**[c] | 5.82 | 4.40 | 5.13 | 4.15 | 5.02 | | 1.16[b] | 1.51,1.30 | 2.10, 2.06 (2 MeCO) |
| **6** | 5.98 | 4.83 | 5.02 | ←3.9-4.2→ | | | 1.26[b] | 1.52,1.32 | 3.11 ($MeSO_2$); 2.35 (HO) |
| **7** | 5.99 | 4.54 | ←4.0-4.4→ | | | | 2.78[d] | 1.49,1.32 | 2.14 (MeS); 3.57 (HO) |
| **8** | 6.00 | 4.80 | 5.08 | 4.32 | 4.00 | 2.78 | 2.61 | 1.51,1.32 | 3.12 ($MeSO_2$); 2.14 (MeS) |
| **9** | 5.98 | 4.52 | ←4.0-4.4→ | | | | 2.93[d] | 1.49,1.39 | 3.71 ($SCH_2S$); 2.18 (MeS); 3.49 (HO) |
| **10** | 5.98 | 4.81 | 5.03 | 4.28 | 4.04 | | 3.51[d] | 1.51,1.33 | 3.37 (MeO); 3.10 ($MeSO_2$); 2.90 (HO) |
| **11**[c] | 5.83 | 4.39 | ←3.3-4.1→ | | | | | 1.41,1.26 | 3.49 (MeO); 3.9-4.2 (HO) |

[a] $\delta$ values. [b] Methyl doublet. [c] In $CCl_4$. [d] Doublet (2 H).

Details of the n.m.r. spectra of compounds **2–11** are given in Tables I and II. In all compounds except **11**, the H-6 signals were clearly distinguished. Those of the 6-deoxy compounds **4–6** appeared as the expected, upfield doublets. In the remaining compounds, H-6 and H-6′ were non-equivalent in **2**, **3**, and **8**, and equivalent in **7**, **9**, and **10**.

TABLE II

FIRST-ORDER COUPLING CONSTANTS[a]

| *Compound* | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6}$ | $J_{5,6'}$ | $J_{6,6'}$ |
|---|---|---|---|---|---|---|---|
| **2** | 3.5 | <0.5 | 2.8 | 8.8 | 2.2 | 6.0 | 12.4 |
| **3** | 3.8 | <0.5 | 3.2 | 5.0 | 4.4 | 2.6 | 5.0 |
| **4** | 3.6 | <0.5 | 2.8 | 4.0 | 6.5 | | |
| **5** | 3.8 | <0.5 | 3.4 | 8.4 | 5.6 | | |
| **6** | 3.6 | <0.5 | 2.2 | | 6.0 | | |
| **7** | 3.6 | <0.5 | | | 6.5 | | |
| **8** | 3.8 | <0.5 | 3.0 | 6.4 | 4.4 | 7.6 | 14.0 |
| **9** | 3.7 | <0.5 | | | 6.5 | | |
| **10** | 3.6 | <0.5 | 2.8 | 9.6 | 4.8 | | |
| **11** | 3.4 | <0.5 | | | | | |

[a]In Hz.

## EXPERIMENTAL

*General methods.* — Silica gel was used for t.l.c. (Gelman, I.T.L.C. Type SA) and column chromatography (Merck Kieselgel). Optical rotations were determined for solutions in dichloromethane, and n.m.r. spectra were recorded for solutions in deuteriochloroform.

*6-O-Acetyl-1,2-O-isopropylidene-3,5-di-O-methanesulphonyl-α-D-glucofuranose* (**2**). — 6-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[2] (**1**) (10.5 g) was dissolved in dry pyridine (40 ml), and the solution was cooled to 0° while methanesulphonyl chloride (11 ml) was added slowly with stirring. The mixture was kept at 0° for a further hour and then left at room temperature overnight. Work-up in the usual manner, with crystallisation of the product from ethanol, yielded the disulphonate **2** (16.0 g), m.p. 95–97°, $[\alpha]_D$ −13° (*c* 1.8) [Found: C, 37.55; H, 5.2; ($M^+$ − 15), 403.0374. $C_{13}H_{22}O_{11}S_2$ calc.: C, 37.3; H, 5.3%; ($M^+$ − 15), 403.0369].

*5,6-Anhydro-1,2-O-isopropylidene-3-O-methanesulphonyl-β-L-idofuranose* (**3**). — A solution of sodium isopropoxide [from sodium (2.3 g)] in isopropyl alcohol (125 ml) was added to a solution of the disulphonate **2** (21.0 g) in dichloromethane (150 ml). The resulting slurry was mixed well, and kept overnight at 0° before being neutralised ($CO_2$) and evaporated to dryness. The residue was partitioned between dichloromethane and dilute, aqueous potassium hydrogen carbonate. The organic extract was dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was

crystallised from ethanol to give the oxirane **3** (12.5 g), m.p. 96–98°, $[\alpha]_D$ −16° (*c* 1.0); lit.[1], m.p. 96.5–98.5°, $[\alpha]_D$ −7.4°.

*Reduction of the oxirane* **3** *with lithium aluminium hydride.* — (*a*) *With fresh reagent.* A solution of **3** (0.65 g) in tetrahydrofuran (7.5 ml) was added slowly to a stirred suspension of lithium aluminium hydride (0.4 g) in the same solvent (7.5 ml). When the addition was complete, the mixture was stirred and boiled under reflux for 4 h. Any excess of reagent was decomposed with ethyl acetate, and the mixture was evaporated to dryness. Water and dichloromethane were added to the residue, and the mixture was filtered. The organic extract was separated, and the aqueous layer re-extracted with more dichloromethane. The combined extracts were dried and evaporated to a syrup (0.08 g) which, when dissolved in a mixture of ether and isopropyl ether, gave crystals of the sulphonate **6** (25 mg), m.p. 131–133°, $[\alpha]_D$ −30° (*c* 1.0) [Found: C, 42.7; H, 5.9; ($M^+ - 15$), 267.0536. $C_{10}H_{18}O_7S$ calc.: C, 42.5; H, 6.4%; ($M^+ - 15$), 267.0538].

The residue from the mother liquors was bulb-distilled (110°/0.2 mmHg), and the distillate was acetylated in the usual way with acetic anhydride in pyridine to give the diacetate **5** (0.11 g), m.p. 120–121°, $[\alpha]_D$ −22° (*c* 1.1); lit.[3], m.p. 122–123°, $[\alpha]_D$ −27°.

(*b*) *With aged reagent.* Repetition of the reduction in (*a*) with an old sample of lithium aluminium hydride gave a syrup (0.15 g) which contained (t.l.c.) three major components. The syrup was dissolved in benzene and chromatographed on silica gel (5 g). Elution with ether–benzene (3:7) gave first the dithioacetal **9** (60 mg), m.p. 79–81° (from isopropyl ether), $[\alpha]_D$ −40° (*c* 1.0) (Found: C, 45.8; H, 7.3; $M^+$, 296.0766. $C_{11}H_{20}O_5S$ calc.: C, 44.55; H, 6.8%; $M^+$, 296.0752). Further elution with the same solvent gave the thioether **7** (15 mg), m.p. 112–114° (from isopropyl ether), $[\alpha]_D$ −18° (*c* 1.0) (Found: C, 48.4; H, 7.0; $M^+$, 250.0875. $C_{10}H_{18}O_5S$ calc.: C, 48.0; H, 7.2%; $M^+$, 250.0857). Finally, elution with ether–benzene (3:2) gave the diol **4** (15 mg), m.p. 82–84°, $[\alpha]_D$ −10° (*c* 1.3); lit.[3], m.p. 88–89°, $[\alpha]_D$ −7°. Acetylation of **4** gave the diacetate **5**, m.p. 121–122°, identical with the product obtained in the previous experiment.

*Desulphurations with Raney nickel.* — (*a*) The thioether **8** (30 mg) was stirred and boiled under reflux with a suspension of Raney nickel (0.3 ml) in 80% alcohol (2 ml) for 1 h. The mixture was then filtered and the filtrate evaporated to dryness to give material that was chromatographically indistinguishable from the diol **4**. Acetylation with acetic anhydride in pyridine gave the diacetate **5** (11 mg), m.p. and mixture m.p. 121–123°.

(*b*) Treatment of the dithioacetal **9** (30 mg) by the procedure in (*a*) similarly gave the diacetate **5** (10 mg), m.p. and mixture m.p. 121–123°.

*1,2-O-Isopropylidene-3-O-methanesulphonyl-6-S-methyl-6-thio-β-*L*-idofuranose* (**8**). — A stock solution of M sodium methanethiolate was prepared by adding methanethiol (5 ml) to a solution of sodium methoxide [from sodium (0.7 g)] in methanol (30 ml). A portion (3 ml) of this solution was added to the oxirane **3** (0.56 g) dissolved in dichloromethane (1 ml). The resulting solution was kept overnight

at 0°, and then neutralised ($CO_2$) and evaporated to dryness. The residue was partitioned between dichloromethane and dilute, aqueous potassium hydrogen carbonate. The organic extract was dried ($MgSO_4$) and evaporated to dryness, and crystallisation of the residue from ethanol or isopropyl ether gave the thioether **8** (0.54 g), m.p. 73–75°, $[\alpha]_D$ −34° (*c* 1.1) [Found: C, 40.5; H, 6.7; ($M^+-15$), 313.0407. $C_{11}H_{20}O_7S_2$ calc.: C, 40.2; H, 6.15%; ($M^+-15$), 313.0416].

*1,2-O-Isopropylidene-6-S-methyl-6-thio-β-*L*-idofuranose* (**7**). — The sulphonate **8** (0.19 g) was boiled under reflux in methanol (5 ml) containing sodium methoxide [from sodium (0.20 g)] for 1.5 h. The reaction was neutralised ($CO_2$) and worked-up, as described in the preceding experiment, to give the thioether **7** (0.14 g), m.p. 114–116°, mixture m.p. (with material obtained in the earlier experiment) 113–115°.

*1,2-O-Isopropylidene-3-O-methanesulphonyl-6-O-methyl-β-*L*-idofuranose* (**10**). — Solutions of the oxirane **3** (2.58 g) in dichloromethane (15 ml) and sodium methoxide [from sodium (0.30 g)] in methanol (5 ml) were mixed, and kept at room temperature for 2 days. The reaction mixture was neutralised ($CO_2$), and worked-up as described in the previous experiment. The product was crystallised from ethanol to give the methyl ether **10** (1.20 g), m.p. 112–114°, $[\alpha]_D$ −23° (*c* 1.2) (Found: C, 42.1; H, 6.3; ($M^+-15$), 297.0660. $C_{11}H_{20}O_8S$ calc.: C, 42.3; H, 6.5%; ($M^+-15$), 297.0644). T.l.c. of the mother liquors indicated the presence of the oxirane **3** and the diol **11**, in addition to the ether **10**.

*1,2-O-Isopropylidene-6-O-methyl-β-*L*-idofuranose* (**11**). — The sulphonate **10** (0.62 g) was boiled under reflux in methanol (30 ml) containing sodium methoxide [from sodium (0.70 g)] for 2 h. The mixture was neutralised ($CO_2$), and evaporated to dryness, and the residue was taken up in dilute, aqueous potassium hydrogen carbonate. This solution was exhaustively extracted with dichloromethane, and the extract was dried and evaporated to give the diol **11** (0.47 g) as a syrup, b.p. 110° 0.2 mmHg (bulb distillation), $[\alpha]_D$ +41° (*c* 0.9) [Found: C, 50.6; H, 7.5; ($M^+-15$), 219.0864. $C_{10}H_{18}O_6$ calc.: C, 51.3; H, 7.7%; ($M^+-15$), 129.0869].

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