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Note

The formation of 1,6-thioanhydrohexitols from the 1,6-di-*O*-mesyl derivatives of D-mannitol and galactitol

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As part of an investigation into the use of sodium sulphide as a trapping agent for bifunctional alkylating agents possessing antitumour activity[1,2], we have investigated the reaction between sodium sulphide and terminally disubstituted hexitols in this category[3], exemplified by 1,6-di-*O*-methanesulphonyl-D-mannitol (mannitol myleran, **1**) and the galactitol analogue (**2**).

The D-mannitol derivative **1** and related, terminally substituted D-mannitol and galactitol derivatives afforded[4,5] the corresponding 1,2:5,6-dianhydrohexitols when their aqueous solutions were maintained at pH <10 by controlled titration with aqueous sodium hydroxide. At higher pH values, the mannitol derivatives yielded 2,3:4,5-dianhydro-L-iditol, owing to hydroxyl ion-catalysed migration of the oxirane substituents to the non-terminal positions[5], and this compound is also reactive towards nucleophiles. Therefore, in order to limit the reactive species derived from the dimethanesulphonates **1** and **2** to those possessing terminally situated alkylating substituents, the reactions with sodium sulphide were conducted at pH 8–10 by controlled addition of aqueous sodium sulphide to a stirred solution or suspension of **1** or **2**. From each reaction mixture, a crystalline product was isolated. Elemental analysis indicated replacement of the two mesyloxy substituents by one sulphur atom, and mass spectrometry (molecular ion at m/e 180) confirmed that each product was a thioanhydrohexitol.

The attachment of the sulphur in the thioanhydro derivatives to C-1 and C-6 was established by reduction, which gave 1,6-dideoxy-D-mannitol[6] (**3**) and 1,6-dideoxygalactitol[7] (**4**), respectively. The products of the reaction between sodium sulphide and **1** and **2** were therefore 1,6-thioanhydro-D-mannitol (**5**) and 1,6-thioanhydrogalactitol (**6**), respectively.

Since the conditions of alkalinity and temperature employed in the foregoing reactions with sodium sulphide promote the abundant formation of 1,2:5,6-dianhydrohexitols[8], epoxides are likely intermediates in the reactions leading to the 1,6-thio-

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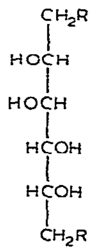

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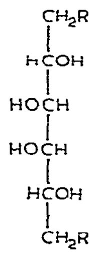
3 R = H



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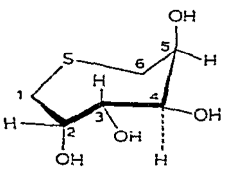

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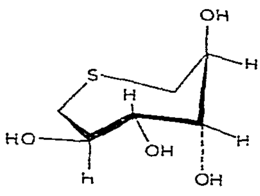

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anhydrohexitols. Either direct displacement of the mesyloxy groups or attack on epoxide intermediates could yield the observed products, by way of a two-stage process involving an intermolecular reaction between sulphide ion and the hexitol derivative followed by intramolecular cyclization with displacement of the remaining terminal substituent. Epoxide intermediates must be cleaved[5] at the primary carbon atom in an intermolecular displacement reaction. The relatively low yields of **5** and **6** are probably attributable to the low recovery of the relatively polar thioanhydrohexitols from aqueous solutions rather than to abundant side-reactions. Thus, paper and thin-layer chromatography of the reaction solution containing the thioanhydro-D-mannitol **5** revealed mannitol as the sole, additional, organic constituent, and even in the absence of competing nucleophiles (*e.g.*, sulphide ion), the proportion of the starting material (**1**) hydrolysed at pH 8 and 60° is only 35%, whereas epoxide formation accounts for 65% of **1** transformed under these conditions[8]. Attempts to improve the yields of the thioanhydro derivatives **5** and **6** by more-prolonged extraction with ethyl acetate resulted in an increasing proportion of unidentified decomposition products in the extracts which prevented crystallization of the required products.

1,6-Thioanhydrohexitols, which are formal analogues of the 1,6-anhydrohexitols first described by Vargha and Kasztreiner[9], have previously been described as derivatives in which the thioanhydrohexitol ring was part of a bicyclic system[10]. The present preparations appear to be the first reported for any unsubstituted monothioanhydrohexitols.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are corrected. P.m.r. spectra were measured on 10% solutions in D_2O (DSS internal standard) with a Perkin–Elmer R-10 spectrometer operating at 60 MHz. Mass spectra were determined with an AEI MS-12 spectrometer operating at an ionizing voltage of 70 eV and a source temperature of 120–160°. R_F values are for descending p.c. on Whatman No. 1 paper with 1-butanol–water (86:14), and for t.l.c. on Kieselgel G (Merck) with chloroform–methanol (3:1). Detection was effected with potassium permanganate in acetone (hexitols and their derivatives gave yellow spots on a purple background), potassium dichromate–silver nitrate (for bivalent sulphur compounds[11]), and iodine vapour (t.l.c.).

*1,6-Thioanhydro-*D*-mannitol* (**5**). — To a stirred solution of 1,6-di-*O*-methanesulphonyl-D-mannitol (**1**; 5 g, 14.8 mmol) in water (30 ml) at 60°, a solution of sodium sulphide (nonahydrate, 10 g) in water (20 ml) was added gradually, using phenolphthalein as an internal indicator and keeping the solution just pink. When the pink colour was no longer discharged (~10 ml of sodium sulphide solution), addition was terminated. The solution was continuously extracted with ethyl acetate during 3 days. The residue (0.75 g), obtained on concentration of the extract, was crystallized from acetonitrile (6 ml), after removal of a small, insoluble residue by filtration, to give **5** (0.205 g, 7%), as colourless needles, m.p. 121–122°, $[\alpha]_D^{25}$ $-119.5°$ (*c* 1, water); R_F 0.29 (p.c.), 0.27 (t.l.c.) (Found: C, 40.02; H, 6.94; S, 17.83. $C_6H_{12}O_4S$ calc.: C, 39.98; H, 6.72; S, 17.79%). The mass spectrum contained, *inter alia*, peaks at *m/e* 180 ($M^{+\cdot}$, 2% of base peak at *m/e* 57), 162 (5, $[M-H_2O]$), 146 (6.5, $[M-H_2S]$). P.m.r. data: δ 2.37–3.20 (m, 4 H, H-1,1',6,6'), 3.95–4.40 (m, 4 H, H-2,3,4,5).

1,6-Thioanhydrogalactitol (**6**). — By essentially the above procedure, 1,6-di-*O*-methanesulphonylgalactitol (**2**, 5 g) afforded a crude product (1 g) which, on crystallization from ethanol, gave **6** as colourless granules (0.55 g, 19%), m.p. 129.5–130°, $[\alpha]_D^{25}$ $-0.4°$ (*c* 1, water), with R_F values identical with those reported for **5** (Found: C, 39.83; H, 6.86; S, 17.60%). The mass spectrum contained, *inter alia*, peaks at *m/e* 180 ($M^{+\cdot}$, 0.2% of base peak at *m/e* 57), 162 (20, $[M-H_2O]$), 144 (16, $[M-2H_2O]$). P.m.r. data: δ 2.50–3.25 (m, 4 H, H-1,1',6,6'), 3.87–4.36 (m, 4 H, H-2,3,4,5).

*1,6-Dideoxy-*D*-mannitol* (**3**). — A solution of **5** (0.18 g, 1 mmol) in methanol (20 ml) was heated under reflux with a large excess of Raney nickel[12] (~4 g) for 40 min. The cooled mixture was filtered, and the filtrate (which still contained some finely divided catalyst) was mixed with silicic acid (5 g) and concentrated, and the residue was applied to a dry column (2-cm diam.) of Kieselgel 60 (30 g), which was eluted with chloroform–methanol (3:1, 400 ml). The eluate was concentrated and the residue was crystallized from acetonitrile (1 ml) to yield **3** (27 mg, 18%) as colourless prisms, m.p. 144–146°, $[\alpha]_D^{20}$ $-21°$ (*c* 0.7, water); R_F 0.54 (p.c.), 0.24 (t.l.c.); lit.[6] m.p. 147–148°, $[\alpha]_D^{20}$ $-22.5°$ (*c* 0.7, water). The mass spectrum contained, *inter alia*, peaks at *m/e* 132 ($[M-H_2O]$, 1% of base peak at *m/e* 58), 117 (2.5, $[M-CH_3-H_2O]$), 105 $\{3.5, [M-CH_3\cdot CH(OH)]\}$. On oxidation with 0.25M sodium metaperiodate (2 ml), **5** (15 mg) consumed 2.94 mol. of oxidant.

1,6-Dideoxygalactitol (**4**). — By essentially the foregoing procedure, **6** (0.18 g) afforded **4** (40 mg, 27%), as colourless prisms from ethanol (1 ml); m.p. 185°; R_F 0.54 (p.c.), 0.27 (t.l.c.); lit.[7] m.p. 183–184°. The mass spectrum contained, *inter alia*, peaks at *m/e* 132 ($[M-H_2O]$, 0.3% of base peak at *m/e* 58), 117 (2, $[M-CH_3-H_2O]$), 105 $\{1.5, [M-CH_3\cdot CH(OH)]\}$. The dideoxy derivative consumed 3.0 mol. of sodium metaperiodate.

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