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Note

1,2-Anhydro-6-chloro-6-deoxy-D-mannitol and 1,2-anhydro-6-chloro-6-deoxygalactitol

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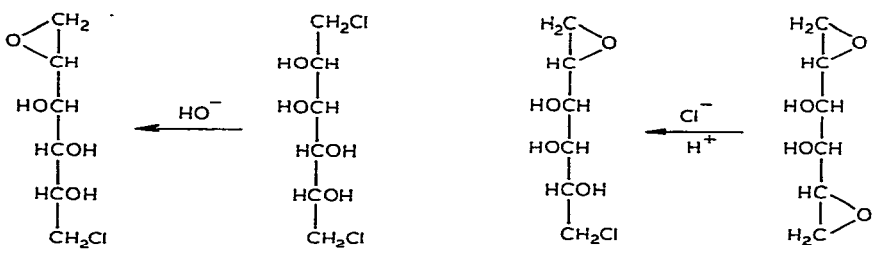
Terminally disubstituted hexitols possessing appropriate leaving-groups are converted into the corresponding 1,2:5,6-dianhydrohexitols by mild treatment with alkali. Derivatives that undergo this transformation include the *O*-methanesulphonyl[1,2], *O*-toluene-*p*-sulphonyl[2], chlorodeoxy[2], bromodeoxy[1,3], and deoxyiodo[2] derivatives of D-mannitol and galactitol. The corresponding monoepoxides are obligatory intermediates, and one such compound, 1,2-anhydro-6-*O*-methanesulphonyl-D-mannitol has been isolated[4] following titration of 1,6-di-*O*-methanesulphonyl-D-mannitol with 35% of the theoretical quantity of alkali needed for conversion into the diepoxide. We now report on the preparation of two halogenoepoxides in this category, namely, 1,2-anhydro-6-chloro-6-deoxy-D-mannitol (**1**) and 1,2-anhydro-6-chloro-6-deoxygalactitol (**3**).



1 2 3 4

The mannitol derivative **1** was prepared by titration of 1,6-dichloro-1,6-dideoxy-D-mannitol (**2**) with an equimolar quantity of aqueous alkali or by treating **2** with sodium methoxide, but the galactitol analogue (**3**) could not be similarly obtained because of the low solubility of 1,6-dichloro-1,6-dideoxygalactitol. It was prepared by treating 1,2:5,6-dianhydrogalactitol (**4**) with hydrochloric acid.

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The p.m.r. spectra of **1** and **3** displayed signals appropriate for the oxirane ring. The reaction of **1** with sodium thiosulphate[1] gave 86% of the theoretical yield of hydroxyl ion for a monoepoxide. On treatment with potassium iodide and titration of the liberated hydroxyl ion with acid, **1** afforded 1-chloro-1,6-dideoxy-6-iodo-D-mannitol. In contrast to 1,2-anhydro-6-*O*-methanesulphonyl-D-mannitol, the chloroepoxides **1** and **3** are stable compounds. The mannitol derivative **1** has been stored for 18 months at room temperature without decomposition. The biological properties of **1** and **3** will be reported elsewhere.

EXPERIMENTAL

P.m.r. spectra were recorded for 6–10% solutions in D_2O (DSS internal standard) with a Perkin–Elmer R-12 spectrometer operating at 60 MHz. R_F values are for descending p.c. on Whatman No. 1 paper with 1-butanol–water (86:14). Detection was effected with a solution of 4-(4-nitrobenzyl)pyridine in acetone. Sprayed chromatograms were heated above 90°, when a blue colour developed as a result of the alkali liberated on ring-opening of the epoxide. For column chromatography, Merck Kieselgel 60 (30–70 mesh) was used.

1,2-Anhydro-6-chloro-6-deoxy-D-*mannitol* (**1**). — (*a*) To a suspension of 1,6-dichloro-1,6-dideoxy-D-mannitol (**2**; 5.45 g, 25 mmol) in water (10 ml) at 55° was added, dropwise with stirring during 15 min, 5M sodium hydroxide (5 ml) using phenolphthalein as internal indicator and keeping the solution just pink. The solution was added slowly to a stirred suspension of anhydrous sodium carbonate (50 g) in ethyl acetate (200 ml). The filtered solution was concentrated to 25 ml under reduced pressure, precipitated solid (mainly unreacted **2**, 1.84 g) was filtered off, and the filtrate, after further concentration to 5 ml, was left at room temperature overnight; **1** (0.325 g, 7.2%) then separated as a white solid, m.p. 111–113°, $[\alpha]_D^{18}$ +5.6° (*c* 1, methanol), R_F 0.56 (p.c.) (Found: C, 39.45; H, 6.00; Cl, 19.79. $C_6H_{11}ClO_4$ calc.: C, 39.46; H, 6.07; Cl, 19.41%). P.m.r. data: δ 2.90–3.18 (m, 2 H, H-1,1′), 3.18–3.48 (m, 1 H, H-2), and 3.68–4.28 (m, 5 H, H-3,4,5,6,6′).

(*b*) To a solution of **2** (2.19 g, 0.01 mol) in methanol (15 ml) was added M methanolic sodium methoxide (10 ml). The solution remained alkaline after 1 h, but was neutral after 3 h at room temperature. It was then concentrated to dryness, the residue was triturated with ethyl acetate (25 ml), and crude **2** (0.42 g) was removed by filtration. The filtrate was concentrated to 10 ml, seeded with authentic **1** [preparation (*a*)], and set aside at 0° overnight, to yield **1** (0.14 g, 7.7%) as a white solid that was identical with the product described in (*a*).

1-Chloro-1,6-dideoxy-6-iodo-D-*mannitol*. — To a solution of 1,2-anhydro-6-chloro-6-deoxy-D-mannitol (**1**; 91 mg, 0.5 mmol) in water (10 ml) at 45° was added a solution of potassium iodide (0.644 g, 4 mmol) in water (1 ml). Continuous titration of the liberated hydroxyl-ion with acid, using phenolphthalein as internal indicator, required 3.0 ml of 0.1M hydrochloric acid, corresponding to the development of 60% of the theoretical alkalinity. The solution was extracted with ethyl acetate (25 ml),

and the dried (sodium sulphate) extract was concentrated to dryness. The residue (0.044 g) was crystallised from ethanol (1 ml) to give the title compound (26 mg, 17%) as colourless plates, m.p. 172° (dec.) (Found: C, 23.44; H, 4.04; Cl, 11.62; I, 40.62. $C_6H_{12}ClIO_4$ calc.: C, 23.21; H, 3.90; Cl, 11.42; I, 40.87%).

1,2-Anhydro-6-chloro-6-deoxygalactitol (3). — To a solution of 1,2:5,6-dianhydrogalactitol[1] (4; 1.46 g, 0.01 mol) and sodium chloride (1.755 g, 0.03 mol) in water (8 ml) was added, dropwise with stirring at room temperature, 0.5M hydrochloric acid (20 ml, 0.01 mol), using 4-nitrophenol as internal indicator and keeping the solution just yellow (pH 5–7). The precipitate (1,6-dichloro-1,6-dideoxygalactitol[2], 0.632 g) was filtered off and the filtrate was added dropwise to a stirred suspension of sodium sulphate (40 g) in ethyl acetate (160 ml). The filtered solution was concentrated to 100 ml, dried with sodium sulphate, concentrated to 50 ml (when crystallisation commenced), and then kept at 4° overnight. A solution of the crude product (0.6 g) in chloroform–ethyl acetate (4:1) was applied to a column (2-cm diam.) of silica gel (30 g) which was eluted (15-ml fractions) with ethyl acetate saturated with water. Dichlorogalactitol appeared in fractions 22–45, and the chloroepoxide 3 in fractions 70–85. Crystallisation of 3 from ethyl acetate gave a white solid (0.2 g, 14%), m.p. 112–118° (dec.), R_F 0.60 (p.c.) (Found: C, 38.94; H, 6.52; Cl, 19.44. $C_6H_{11}ClO_4$ calc.: C, 39.46; H, 6.07; Cl, 19.41%) P.m.r. data: δ 2.76–3.10 (m, 2 H, H-1,1'), 3.24–3.50 (m, 1 H, H-2), and 3.60–4.35 (m, 5 H, H-3,4,5,6,6').

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