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# THE FORMATION OF EPOXIDES FROM SUBSTITUTED HEXITOLS

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## ABSTRACT

1,6-Dibromo-1,6-dideoxygalactitol (**2**), 1-*O*-methanesulphonyl-D-mannitol (**5**), and 3,4-di-*O*-methanesulphonyl-D-mannitol (**8**) were respectively converted at nearly neutral pH into 1,2:5,6-dianhydrogalactitol (**4**), 1,2-anhydro-D-mannitol (**6**), and 2,3:4,5-dianhydro-D-iditol (**9**). Strongly alkaline conditions yielded 2,3:4,5-dianhydro-L-iditol (**7**) from 1,6-di-*O*-methanesulphonyl-D-mannitol (**1**). The structures of compounds **4**, **6**, **7**, and **9** were confirmed by p.m.r. spectroscopy, and by their reactivity towards thiosulphate and iodide ions.

The conversion of 1,2:5,6-dianhydro-D-mannitol (**3**) into 1,6-dideoxy-1,6-diiodo-D-mannitol, 1,6-dibromo-1,6-dideoxy-D-mannitol, and 1,6-di-*O*-benzoyl-D-mannitol, and 1,2:5,6-dianhydrogalactitol into 1,6-dideoxy-1,6-diiodogalactitol is described.

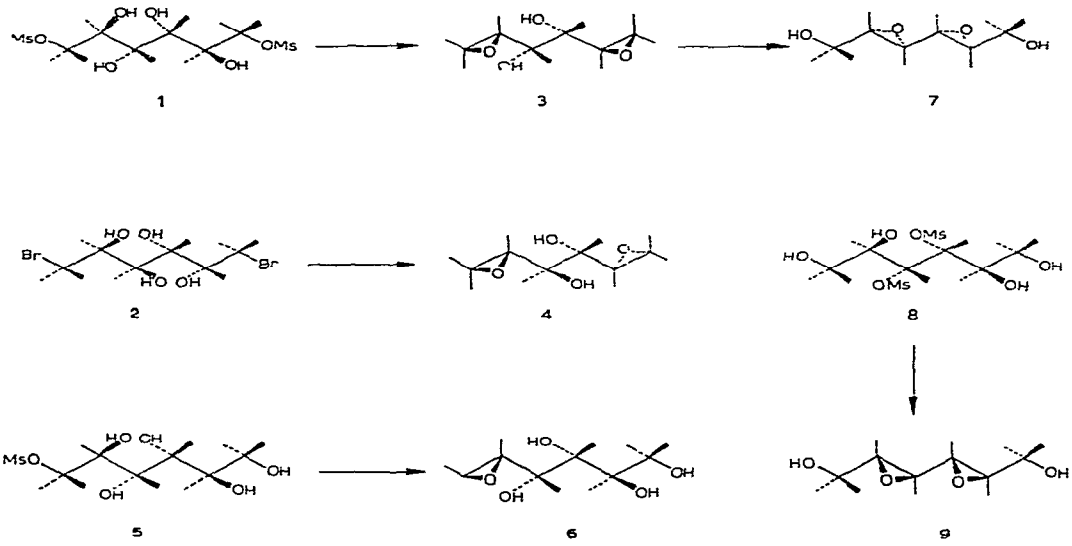
## INTRODUCTION

Until recently[1], anhydrohexitols containing the oxirane ring have been isolated only as derivatives[2]. However, their intermediacy in the formation of larger anhydro rings[3] and their existence in solution[4] have been postulated. The principle of the preparative method leading to 1,2:5,6-dianhydro-D-mannitol[1], namely very mild basic treatment of a suitably substituted hexitol, now promises to be generally applicable. Three further epoxide derivatives of hexitols have been prepared by this method, and the utility of the terminal diepoxides in the synthesis of terminally substituted hexitol derivatives is indicated.

## RESULTS AND DISCUSSION

The general procedure applied to the synthesis from substituted hexitols of anhydrohexitols containing the oxirane ring consisted in continuously titrating the appropriate *O*-methanesulphonyl, *O*-toluene-*p*-sulphonyl, or bromo derivative in aqueous solution or suspension with N sodium hydroxide, keeping the solution close to pH 8. When no further alkali was consumed, the solution was added dropwise to a stirred suspension of anhydrous sodium carbonate in ethyl acetate. Water was thus removed, and the anhydrohexitol was crystallised from the concentrated ethyl acetate solution. Thus, 1,6-di-*O*-methanesulphonyl-D-mannitol (**1**), and 1,6-dibromo-1,6-dideoxygalactitol[5] (**2**) gave crystalline 1,2:5,6-dianhydro-D-mannitol (**3**) and 1,2:5,6-

dianhydrogalactitol (4) in over 30% yield. These compounds had previously been obtained as their 3,4-*O*-isopropylidene derivatives[6,7], but the acid lability of the oxirane ring precluded selective cleavage of the isopropylidene group.



Similarly, 1-*O*-toluene-*p*-sulphonyl-D-mannitol and 1-*O*-methanesulphonyl-D-mannitol (5), prepared by acidic hydrolysis of their 3,4:5,6-di-*O*-isopropylidene derivatives, were converted into 1,2-anhydro-D-mannitol (6). This compound, isolated in 8–10% yield, was previously known only as its 3,4:5,6-di-*O*-isopropylidene derivative[8].

The nearly quantitative reactivity of terminal oxirane rings towards thiosulphate[9] and iodide[1] ions provided a method for estimating epoxide content. The liberated hydroxyl ion was continuously titrated with standard acid. The epoxide contents of the solutions obtained by the mild, basic treatment of compounds **1**[1], **2**, and **5** were found to be much higher than implied by the isolated yield of epoxide. This loss was attributable to incomplete extraction into ethyl acetate, but was unavoidable, since isolation procedures involving concentration of the aqueous solutions invariably caused extensive cleavage of the oxirane rings.

The reality of oxirane ring formation from terminally substituted hexitol derivatives was disputed by Institoris *et al.*[10]. In cases where the formation of the less strained five- or six-membered rings was possible, they claimed that these would form preferentially. Hence, the 67% conversion in solution of the methanesulphonate **5** into the epoxide **6** appears remarkable, since five ring-sizes (three- to seven-membered) could theoretically result. A closer examination of the problem of hydroxyl-ion catalysed anhydro-ring formation reveals the importance of distinguishing between the rate of formation of the ring and its stability to the reaction conditions. Thus, the rate constants $k$ ($l \cdot mole^{-1} \cdot min^{-1}$) for the formation in aqueous sodium hydroxide at 30° of ethylene oxide, tetrahydrofuran, and tetrahydropyran from the appropriate,

terminally substituted halohydrins were[11], respectively, 1.13, 0.172, and 0.0007, indicating that oxirane ring formation was kinetically preferred. Owing to the relatively greater degree of ionisation of the hydroxyl group adjacent to the electron-withdrawing leaving group, this preference for hydroxyl-ion catalysed oxirane ring formation would be enhanced at a less alkaline pH. The direct competition of oxirane ring formation with both tetrahydrofuran and tetrahydropyran ring formation has been investigated by studying the products of hydroxyl-ion catalysed ring-closure in various mono-*O*-toluene-*p*-sulphonylpentanetriols[12]. The products, where cyclic, were invariably derivatives of tetrahydrofuran and tetrahydropyran, but their stereochemistry was often consistent with the initial formation of an oxirane derivative, followed by a rearrangement involving attack of the oxirane ring by the remaining hydroxyl group. Again, tetrahydropyran ring formation was kinetically least favoured. It is clear from these studies that the present use of a nearly neutral pH for oxirane ring formation is the major factor permitting the isolation of the epoxides, rather than their rearrangement products.

The lability of the terminal oxirane ring was further indicated by the isolation of a different type of rearrangement product. When the dimethanesulphonate **1** reacted with hydroxyl ion at a higher pH (not less than 12.6) than was employed for the preparation of the terminal diepoxide **3**, a new dianhydrohexitol was isolated. Its reaction with sodium thiosulphate gave 74% of the theoretical yield of hydroxyl ion from a diepoxide. The corresponding yield from the terminal diepoxide **3** was 93.5%. Comparison with the hydroxyl-ion yields[13] from 1,2:5,6-diepoxyhexane (98%) and its non-terminal analogue 2,3:4,5-diepoxyhexane (75%) strongly implied that the new product was a non-terminal diepoxide, an interpretation consistent with the finding of only four oxirane-ring CH protons in its p.m.r. spectrum. The initial production of the terminal diepoxide **3**, followed by hydroxyl-ion catalysed migration of the oxirane rings to the non-terminal position, would involve inversion of configuration at C-2 and C-5, and the formation of a non-terminal diepoxide, *viz.*, 2,3:4,5-dianhydro-L-iditol (**7**). Base-catalysed oxirane ring migration has been invoked to explain the formation in aqueous sodium hydroxide from 1-*O*-toluene-*p*-sulphonyl-*myo*-inositol of 1,2-anhydro-*myo*-inositol, whereas apparently milder basic treatment gives 1,2-anhydro-(±)-inositol[14].

The structure of the new diepoxide was confirmed by comparison with its supposed enantiomer. 3,4-Di-*O*-methanesulphonyl-D-mannitol (**8**) was prepared in two stages from 1,2:5,6-di-*O*-isopropylidene-D-mannitol. Hydroxyl-ion catalysed ring-closure at nearly neutral pH gave 2,3:4,5-dianhydro-D-iditol* (**9**). The D-iditol configuration arose from the general observation that the direct formation of anhydro rings from sulphonic esters proceeds with inversion of configuration at the carbon atoms carrying the leaving groups[15], in this case C-3 and C-4. That the compound

*Since this paper was submitted, a preparation of 3,4-di-*O*-methanesulphonyl-D-mannitol and its conversion into 2,3:4,5-dianhydro-D-iditol have been described [R. S. TIPSON AND A. COHEN, *Carbohyd. Res.*, 7 (1968) 240].

assigned the structure 7 was an enantiomer of compound 9 was shown by the coincidence of their physical properties (m.p., i.r. and p.m.r. spectra, and paper-chromatographic characteristics), with the exception that their specific rotations, though almost equal in magnitude, were opposite in sign.

The p.m.r. spectra (Table I) of the new anhydrohexitols were consistent with the structures assigned. Oxirane ring protons characteristically resonate at higher field ($\tau$ 6.5–7.3) than those adjacent to the oxygen atom of five- or six-membered anhydro rings, for which the characteristic range[16] is $\tau$ 6.3–6.7. In addition, the presence of five- or six-membered rings is excluded by their unreactivity towards thiosulphate ions. Oxetane rings react with thiosulphate ion[17], but are excluded by the absence in the p.m.r. spectrum of 1,3-anhydro-D-glucitol[18] of signals above $\tau$ 6.5.

TABLE I

THE 60-MHZ P.M.R. DATA FOR HEXITOL EPOXIDES

| *Compound* | *Solvent* | *Chemical shift* ($\tau$) | | |
|---|---|---|---|---|
| | | *H(1,6)* | *H(2,5)* | *H(3,4)* |
| 1,2:5,6-Dianhydro-D-mannitol (3) | $D_2O$ | 6.94–7.22 | 6.60–6.92 | 6.20–6.43 |
| 1,2:5,6-Dianhydrogalactitol (4) | $D_2O$ | 6.92–7.23 | 6.58–6.85 | 6.26–6.50 |
| 1,2-Anhydro-D-mannitol (6) | $D_2O$ | 7.00–7.16 | 6.60–6.90 | 6.20–6.43 |
| 2,3:4,5-Dianhydro-L-iditol[a] (7) | Acetone-$d_6$ + 10% $D_2O$ | 6.06–6.69[b] | 6.78–7.00 | 7.04–7.19 |

[a]The spectrum of 2,3:4,5-dianhydro-D-iditol (9) was identical. [b]The OH signal at $\tau$ 6.20 was distinguished from others in this region by its downfield shift relative to those of *ca.* 0.2 p.p.m. on raising the $D_2O$ content to 20%. The spectrum (in $D_2O$) of 1,3-anhydro-D-glucitol prepared[18] from 1,3-anhydro-6-*O*-benzyl-2,4-*O*-benzylidene-D-glucitol showed no signals at higher field than $\tau$ 6.5.

The 60 MHz p.m.r. spectrum of the anhydrohexitols showed the required signal intensities in the oxirane ring-proton region, equivalent to six protons for the terminal diepoxides 3 and 4, three protons for the monoepoxide 6, and four protons for the non-terminal diepoxides 7 and 9. In each case, three distinct absorption regions were present (Table I). The lowest field signals were attributed to CH protons in the acyclic portion of the molecules, and the two higher field regions to oxirane ring protons. In the spectra of the terminal epoxides 3, 4, and 6, the oxirane ring-proton signals at higher and lower field (intensity ratio, 2:1) were respectively assigned to the methylene and to the methine protons. The higher and the lower field signals for the non-terminal diepoxides 7 and 9 could not be assigned on the basis of their intensity ratio, since the signal intensities were equal. However, a similar assignment of the lower field signals to H-2 and H-5 was favoured, since a similar chemical shift was observed in the spectrum of compound 3 in the same solvent for the environmentally similar methine protons[1].

Although the individual signals were too complex to permit further unequivocal elucidation, the foregoing examination of the p.m.r. spectra of the epoxides, considered with their chemical reactions, sufficed to prove their structures.

The high reactivity of the terminal diepoxides **3** and **4** towards anions was exploited in the preparation of various terminally di-substituted hexitol derivatives. Thus, treatment of aqueous solutions of compounds **3** or **4** with sodium iodide and acidic titration of the liberated hydroxyl ion gave 1,6-dideoxy-1,6-diiodo-D-mannitol and its galactitol analogue. The analogous reaction of compound **3** with lithium bromide, the solubility of which permitted an optimal concentration of the less nucleophilic bromide ion, gave 1,6-dibromo-1,6-dideoxy-D-mannitol, an interesting reversal of the conversion[1] of the latter compound into the diepoxide **3**. The reaction of compound **3** with sodium benzoate and benzoic acid gave 1,6-di-*O*-benzoyl-D-mannitol.

This reactivity towards anions may be highly relevant to the toxic and tumour-inhibitory properties of terminally substituted diepoxides. Preliminary results on the biological activity of the mannitol derivative **3** have been reported elsewhere[1].

## EXPERIMENTAL

P.m.r. spectra were measured on *ca.* 10% w/v solutions with a Perkin–Elmer R10 spectrometer, operating at 60 MHz. *tert*-Butyl alcohol (in $D_2O$ solutions) and tetramethylsilane (in acetone-$d_6$ solutions) were used as internal standards; *ca.* 10% v/v of $D_2O$ was added to acetone-$d_6$ solutions to exchange hydroxyl protons.

Ascending paper chromatography was conducted on Whatman No. 1 paper in butyl alcohol–water (86:14). Spots were detected by three spray tests: periodate–benzidine for *cis*-diol groups; aqueous sodium iodide–phenolphthalein, with which epoxides gave pink spots owing to the liberation of hydroxyl ion in the presence of iodide ion; and potassium permanganate in acetone, which gave yellow spots against a purple background. The last reagent gave a positive reaction with 1,4:3,6-dianhydro-D-mannitol ($R_F$ 0.35) which lacks both epoxide and *cis*-diol groupings, as well as with all compounds having such groupings.

Thin-layer chromatography (t.l.c.) was conducted on microscope slides coated with Merck Kieselgel G. Spots were detected by spraying with sulphuric acid, followed by heating at 150°.

All melting points are corrected.

*1,2:5,6-Dianhydrogalactitol.* — A stirred suspension of 1,6-dibromo-1,6-dideoxygalactitol[5] (1.23 g, 0.004 mole) in water (5 ml) at 35–40° was continuously titrated with N sodium hydroxide, with phenolphthalein as internal indicator, keeping the solution just pink, until no more acidity had developed; 6.4 ml of alkali was added*, corresponding to a development of 80% of the theoretical acidity. The

*Addition of potassium iodide (2 g) at this stage, and titration of the liberated alkali at 35–40° with N hydrochloric acid, using phenolphthalein as internal indicator, and keeping the solution just pink, allowed an estimate of the epoxide content of the solution. The hydroxyl ion liberated corresponded to 5.6 ml of acid. Hence, 70% of the starting material was converted into epoxide. Simultaneous separation of crude 1,6-dideoxy-1,6-diiodogalactitol (1.02 g) occurred (Found: I, 58.30. $C_6H_{12}I_2O_4$ calc.: I, 63.14%). Owing to its insolubility in common crystallisation solvents, the pure compound was best prepared from crystalline 1,2:5,6-dianhydrogalactitol.

solution was added dropwise to a stirred suspension of anhydrous sodium carbonate (30 g) in ethyl acetate (150 ml). The filtered solution was concentrated under diminished pressure below 30° to 25 ml, redried over anhydrous magnesium sulphate, and concentrated to 5 ml. The title compound separated as colourless plates (0.21 g, 36%), m.p. 96.5–98.5°, $[\alpha]_D^{25}$ +2° (*c* 1.25, water) (Found: C, 49.19; H, 6.75. $C_6H_{10}O_4$ calc.: C, 49.28, H, 6.89%).

Paper chromatography showed a single spot, $R_F$ 0.39, which gave a positive reaction with *cis*-diol reagents and with epoxide reagents.

*1,2:5,6-Dianhydro*-D-*mannitol*[1] (3). — By essentially the above procedure, 1,6-di-*O*-methanesulphonyl-D-mannitol was converted into diepoxide 3 (31%), m.p. 64–66°, $[\alpha]_D$ +40° (*c* 1.25, water) (Found: C, 49.45; H, 6.97. $C_6H_{10}O_4$ calc.: C, 49.28; H, 6.89%).

*1*-O-*Toluene*-p-*sulphonyl*-D-*mannitol*. — To an ice-cooled solution of 1,2:3,4-di-*O*-isopropylidene-D-mannitol[21] (5 g, 0.019 mole) in dry benzene (7 ml) was added dropwise a solution of toluene-*p*-sulphonyl chloride (3.8 g, 0.020 mole) in dry pyridine (7 ml) with stirring during 1 h. After 16 h at 5°, the solution was evaporated below 30° under diminished pressure. The residue was partitioned between chloroform (25 ml) and water (25 ml). The organic phase was washed (dilute hydrochloric acid, water, and saturated, aqueous sodium hydrogen carbonate) and evaporated. The residue was dissolved in 1:5 water–acetic acid (50 ml). After 18 h at room temperature, the solution was evaporated below 30° under diminished pressure. Co-evaporation with toluene, followed by crystallisation of the solid residue from ethanol (50 ml), yielded the title compound (3.0 g, 47%) as colourless prisms, m.p. 130–131° (Found: C, 46.22; H, 5.98; S, 9.69. $C_{13}H_{20}O_8S$ calc.: C, 46.37; H, 5.99; S, 9.53%).

*1*-O-*Methanesulphonyl*-D-*mannitol*. — 1,2:3,4-Di-*O*-isopropylidene-D-mannitol (5 g, 0.019 mole) was treated with methanesulphonyl chloride (2.29 g, 0.020 mole) by the foregoing procedure. Identical treatment of the intermediate gave the title compound (1.75 g, 35%) as colourless needles from ethanol (50 ml), m.p. 133–135°, $[\alpha]_D^{25}$ +3° (*c* 2.5, water) (Found: C, 32.57; H, 6.01; S, 12.00. $C_7H_{16}O_8S$ calc.: C, 32.45; H, 6.20; S, 12.31%).

*1,2-Anhydro*-D-*mannitol*. — A stirred suspension of 1-*O*-toluene-*p*-sulphonyl-D-mannitol (1.01 g, 0.003 mole) in water (4 ml) at 35–40° was continuously titrated with N sodium hydroxide, with phenolphthalein as internal indicator, keeping the solution just pink, until no more acidity had developed; 2.65 ml of alkali was added*, corresponding to development of 88% of the theoretical acidity. The solution was

*Addition of potassium iodide (2 g) at this stage, and titration of the liberated alkali at 35–40° with N hydrochloric acid, using phenolphthalein as internal indicator and keeping the solution just pink, allowed an estimate of the epoxide content of the solution. The liberated hydroxyl ion corresponded to 1.30 ml of acid. Hence 43% of the starting material was converted into epoxide. The title compound was similarly isolated (0.026 g, 8%) from a titrated solution of 1-*O*-methanesulphonyl-D-mannitol (0.52 g, 0.002 mole) in water (1 ml); 1.8 ml of alkali was consumed, corresponding to development of 90% of the theoretical acidity. Addition of potassium iodide at this stage, as above, showed 67% conversion of the starting material into epoxide.

added dropwise to a stirred suspension of anhydrous sodium carbonate (20 g) in ethyl acetate (100 ml). After further drying over anhydrous calcium sulphate ("Drierite"), the filtered solution was concentrated under diminished pressure below 30° to 5 ml. The title compound separated as colourless needles (0.050 g, 10%), m.p. 102–104°, $[\alpha]_D^{25}$ −16° (*c* 2.5, water) (Found: C, 43.83; H, 7.19. $C_6H_{12}O_5$ calc.: C, 43.89; H, 7.37%).

Paper chromatography showed a single spot, $R_F$ 0.20, which gave a positive reaction with *cis*-diol reagents and with epoxide reagents.

*2,3:4,5-Dianhydro-*L*-iditol.* — A solution of 1,6-di-*O*-methanesulphonyl-D-mannitol (6.65 g, 0.0197 mole) in N sodium hydroxide (35 ml) was added dropwise after 15 min (pH 12.6) to a stirred suspension of anhydrous sodium carbonate (100 g) in ethyl acetate (500 ml). The filtered solution was concentrated below 30° under diminished pressure to 100 ml, re-dried with anhydrous magnesium sulphate, and evaporated to 5 ml. The title compound separated as colourless, rectangular prisms (0.678 g, 24%), m.p. 98–99°, $[\alpha]_D^{25}$ −72° (*c* 1.25, water) (Found: C, 49.06; H, 6.74. $C_6H_{10}O_4$ calc.: C, 49.28; H, 6.89).

Paper chromatography showed a single spot, $R_F$ 0.39, which gave no reaction with *cis*-diol reagents, but a positive reaction with epoxide reagents.

*Treatment with sodium thiosulphate.* — (*a*) *2,3:4,5-Dianhydro-*L*-iditol.* To a solution of the diepoxide (0.073 g, 0.0005 mole) in water (10 ml) at 50–55° was added sodium thiosulphate (5 g). The liberated alkali was continuously titrated with 0.1N hydrochloric acid, using phenolphthalein as internal indicator and keeping the solution just pink. The total hydroxyl ion liberated (in 3 h) consumed 7.40 ml of acid, corresponding to development of 74% of the theoretical alkalinity for a diepoxide.

(*b*) *1,2:5,6-Dianhydro-*D*-mannitol.* — To a solution of the diepoxide (0.146 g, 0.001 mole) in water (20 ml) at 35–40° was added sodium thiosulphate (5 g). Titration of the liberated alkali was conducted as in (*a*); 18.7 ml of acid was required in 30 min, corresponding to a development of 93.5% of the theoretical alkalinity for a diepoxide.

(*c*) *Larger ring anhydrohexitols.* — 1,4-Anhydro-D-mannitol[22], 1,5-anhydro-D-glucitol, and 1,4:3,6-dianhydro-D-mannitol failed to react with thiosulphate ions under either of the above conditions.

*3,4-Di-*O*-methanesulphonyl-*D*-mannitol.* — 1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-methanesulphonyl-D-mannitol[23] (0.25 g, 0.006 mole) was dissolved at room temperature in a mixture of chloroform (1 ml) and 5M HCl in methanol (1 ml). The reaction, monitored by t.l.c. (methanol–chloroform, 3:25), was complete within 5 min. The solution was evaporated below 30° under diminished pressure, and the residue, after standing *in vacuo* overnight over potassium hydroxide, was crystallised from hot ethanol (1.5 ml) to give the title compound (0.13 g, 64%) as colourless needles, m.p. 110–112°, $[\alpha]_D^{25}$ +27° (*c* 1.3, water) (Found: C, 28.28; H, 5.35; S, 18.89. $C_8H_{18}O_{10}S_2$ calc.: C, 28.40; H, 5.36; S, 18.95%).

*2,3:4,5-Dianhydro-*D*-iditol.* — A stirred solution of 3,4-di-*O*-methanesulphonyl-D-mannitol (0.13 g, 0.39 mole) in water (0.5 ml) at 35–40° was continuously titrated with N sodium hydroxide, with phenolphthalein as internal indicator, and keeping

the solution just pink, until no more acidity developed; 0.76 ml of alkali was added, corresponding to the development of 97.5% of the theoretical acidity. The solution was added dropwise to a stirred suspension of anhydrous sodium carbonate (3 g) in ethyl acetate (25 ml). The filtered solution was evaporated below 30° under diminished pressure to a solid residue. Crystallisation from ethyl acetate (5 ml) gave the title compound (0.032 g, 57%) as colourless plates, m.p. 98–99°, $[\alpha]_D^{25}$ +74° (*c* 1.0, water) Found: C, 49.60; H, 6.85. $C_6H_{10}O_4$ calc.: C, 49.28; H, 6.89. Paper chromatography showed a single spot, $R_F$ 0.39, which gave no reaction with *cis*-diol reagents, but a positive reaction with epoxide reagents.

*1,6-Dideoxy-1,6-diiodo-*D*-mannitol.* — To a solution of 1,2:5,6-dianhydro-D-mannitol (0.585 g, 0.004 mole) in water (5 ml) at 35–40° was added potassium iodide (2 g). Continuous acidic titration of the liberated hydroxyl ion, using phenolphthalein as internal indicator, required 6.0 ml of N hydrochloric acid, corresponding to the development of 75% of the theoretical alkalinity. There was simultaneous separation of the title compound as a white solid (0.75 g, 47%), m.p. 165° (decomp.); lit.[6] m.p. 165–167° (decomp.) (Found: C, 17.7; H, 3.16; I, 63.05. $C_6H_{12}I_2O_4$ calc.: C, 17.9; H, 3.01; I, 63.14%).

*1,6-Dideoxy-1,6-diiodogalactitol.* — To a solution of 1,2:5,6-dianhydrogalactitol (0.0625 g, 0.00043 mole) in water (5 ml) was added potassium iodide (1 g). Acidic titration (as above) required 0.66 ml of N hydrochloric acid, corresponding to development of 77% of the theoretical alkalinity. There was simultaneous separation of the highly insoluble, title compound (0.11 g, 64%), a white solid that decomposed at 181° (Found: C, 18.16; H, 3.12; I, 63.01. $C_6H_{12}I_2O_4$ calc.: C, 17.93; H, 3.01; I 63.14%).

A stirred mixture of 1,6-di-*O*-methanesulphonyl-D-mannitol (1.33 g, 0.039 mole) and water (1 ml) at 35–40° was continuously titrated with N sodium hydroxide, with phenolphthalein as internal indicator, keeping the solution just pink, until no more alkalinity developed; 7.2 ml of alkali was added, corresponding to the development of 90% of the theoretical acidity. Such a solution of 1,2:5,6-dianhydro-D-mannitol was used for the following two preparations.

*1,6-Dibromo-1,6-dideoxy-*D*-mannitol.* — Anhydrous lithium bromide (15 g) was added portionwise to the solution maintained at 35–40°. Continuous acidic titration to consume the liberated hydroxyl ion required 6 ml of N hydrochloric acid. Simultaneous separation of the title compound occurred as a white solid (0.525 g, 43%), m.p. 173–175° (decomp.); lit.[5] m.p. 174–176° (decomp.) (Found: C, 23.41; H, 4.30; Br, 51.70. $C_6H_{12}Br_2O_4$ calc.: C, 23.40; H, 3.95; Br, 51.88%).

*1,6-Di-*O*-benzoyl-*D*-mannitol.* — To the stirred diepoxide solution at 35–40° was added benzoic acid (0.98 g, 0.008 mole) and sodium benzoate (9 g). Complete dissolution within 3 h was followed by overnight precipitation of the title compound (0.475 g, 32%) as colourless needles, m.p. 173–175°, $[\alpha]_D^{25}$ +13° (*c* 2.0, pyridine), unchanged by recrystallisation from ethanol; lit.[24] m.p. 182°, $[\alpha]_D^{20}$ +15.9° in pyridine (Found: C, 61.42; H, 6.06. $C_{20}H_{22}O_8$ calc.: C, 61.53; H, 5.68%).

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REFERENCES

1 M. JARMAN AND W. C. J. ROSS, *Chem. Ind.* (London), (1967) 1789.
2 L. F. WIGGINS, *Advan. Carbohyd. Chem.*, 5 (1950) 191.
3 J. KUSZMANN, personal communication.
4 W. DAVIS AND W. C. J. ROSS, *Biochem. Pharmacol.*, 12 (1963) 915.
5 L. INSTITORIS, I. P. HORVATH, AND E. CSANYI, *Arzneimittel-Forsch.*, 17 (1967) 149.
6 L. F. WIGGINS, *J. Chem. Soc.*, (1946) 384.
7 L. VARGHA AND E. KASZTREINER, *Ber.*, 92 (1959) 2506.
8 L. F. WIGGINS, *J. Chem. Soc.*, (1946) 388.
9 W. C. J. ROSS, *J. Chem. Soc.*, (1950) 2257.
10 A. DAVID, G. HORVATH, I. P. HORVATH, L. INSTITORIS, A. NESZMELYI, AND L. RADICS, *Experientia*, (1967) 512.
11 B. CAPON, *Quart. Rev.* (London), 18 (1964) 45.
12 F. C. HARTMAN AND R. BAKER, *J. Org. Chem.*, 29 (1964) 875.
13 J. L. EVERETT AND G. A. R. KON, *J. Chem. Soc.*, (1950) 3131.
14 S. J. ANGYAL, V. BENDER, AND J. H. CURTIN, *J. Chem. Soc.* (*C*), (1966) 798.
15 F. H. NEWTH, *Quart. Rev.* (London), 13 (1959) 30.
16 N. S. BHACCA AND D. H. WILLIAMS, *Applications of NMR Spectroscopy in Organic Chemistry*, Holden–Day, San Francisco, 1964, p. 99.
17 S. SEARLES, *J. Amer. Chem. Soc.*, 73 (1951) 4515.
18 E. HASLAM AND T. RADFORD, *Carbohyd. Res.*, 2 (1966) 301.
19 N. S. BHACCA AND D. H. WILLIAMS, *ref. 16*, p. 46.
20 E. L. SNYDER, *J. Amer. Chem. Soc.*, 88 (1966) 1155.
21 L. F. WIGGINS, *J. Chem. Soc.*, (1946) 13.
22 L. F. WIGGINS, *J. Chem. Soc.*, (1945) 4.
23 P. BLADON AND L. N. OWEN, *J. Chem. Soc.*, (1950) 598.
24 P. BRIGL AND H. GRÜNER, *Ber.*, 65 (1932) 641.