THE SYNTHESIS OF 1L-1,2-ANHYDRO-*myo*-INOSITOL AND 1L- AND DL-1,2-ANHYDRO-*chiro*-INOSITOL

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ABSTRACT

Two optically active inositol epoxides have been synthesised as potential glycosidase inhibitors. 1L-1,2-Anhydro-*myo*-inositol was prepared from 1L-1-*O*-toluene-*p*-sulphonyl-*chiro*-inositol and 1L-1,2-anhydro-*chiro*-inositol was prepared from 1L-1-*O*-toluene-*p*-sulphonyl-*myo*-inositol in good yield and without epoxide migration. DL-1,2-Anhydro-*chiro*-inositol was also prepared, by a novel route. The anhydroinositols were given preliminary tests for biological activity.

INTRODUCTION

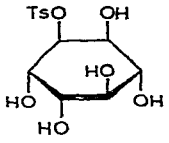
The synthesis of 1L-1-*O*-toluene-*p*-sulphonyl-*chiro*-inositol[1,2] has opened the way to the synthesis of many optically active derivatives of inositols. We now report on the preparation of two optically active epoxides, **2** and **6**. These are of importance as potential intermediates for the synthesis of other optically active inositol derivatives and are of considerable interest as potential specific and irreversible glycosidase inhibitors[3,4].

DISCUSSION

Treatment of 1L-1-*O*-toluene-*p*-sulphonyl-*chiro*-inositol (**1**) with an equivalent amount of sodium methoxide in methanol at room temperature readily gave 1L-1,2-anhydro-*myo*-inositol (**2**). The structure of epoxide **2** was shown by acid hydrolysis which gave, preponderantly, the axial product, 1L-*chiro*-inositol, together with a trace of *scyllo*-inositol. The anhydroinositol **2** was recently obtained by deamination of 1L-1-amino-1-deoxy-*chiro*-inositol[5] with nitrous acid.

The second epoxide, 1L-1,2-anhydro-*chiro*-inositol (**6**) was made from 1D-1,2,4,5,6-penta-*O*-benzoyl-*myo*-inositol[2] (**3**). Toluene-*p*-sulphonylation of the latter gave 1L-2,3,4,5,6-penta-*O*-benzoyl-1-*O*-toluene-*p*-sulphonyl-*myo*-inositol (**4**). Catalytic debenzoylation (sodium methoxide in chloroform–methanol) gave 1L-1-*O*-toluene-*p*-sulphonyl-*myo*-inositol (**5**). By using polarimetry to monitor the reaction, **5** was con-

verted by sodium methoxide in methanol–methyl sulphoxide into 1L-1,2-anhydro-*chiro*-inositol (**6**). The structure of **6** was proved by acid hydrolysis which gave *muco*-inositol, together with a trace of *myo*-inositol.



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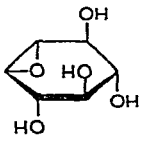

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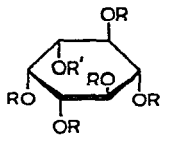
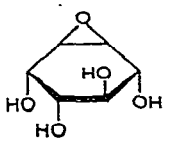


3 R = Bz, R' = H
4 R = Bz, R' = Ts
5 R = H, R' = Ts



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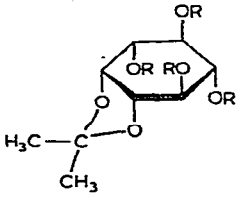
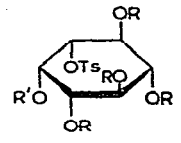


7 R = H
8 R = Bz



9 R = Bz, R' = H

For biological studies, DL-1,2-anhydro-*chiro*-inositol was also required. This epoxide had previously been prepared from DL-1-*O*-toluene-*p*-sulphonyl-*myo*-inositol (**5**) by the use of the carbonate form of a basic ion-exchange resin at 75–80° in aqueous methanol, but this procedure gave several by-products[6]. By the same procedure as for the corresponding 1L compound, DL-(**5**) was converted into the racemic epoxide **6** in 60% yield.

Racemic 1-*O*-toluene-*p*-sulphonyl-*myo*-inositol (**5**) was obtained from the readily available 1,2-*O*-isopropylidene-*myo*-inositol[7] (**7**) by perbenzoylation to give **8**, followed by removal of the isopropylidene group and selective, equatorial toluene-*p*-sulphonylation to give DL-3,4,5,6-tetra-*O*-benzoyl-1-*O*-toluene-*p*-sulphonyl-*myo*-inositol (**9**). Compound **9** was debenzoylated by sodium methoxide to give the known DL-1-*O*-toluene-*p*-sulphonyl-*myo*-inositol (**5**).

The epoxides were tested for biological activity as inhibitors or inactivators of several glycosidases. Unlike the DL-isomer[3], 1L-1,2-anhydro-*myo*-inositol was not an inactivator of almond emulsin β-D-glucopyranosidase, but was a competitive inhibitor of yeast α-D-glucopyranosidase. Both DL- and 1L-1,2-anhydro-*chiro*-inositol slowly and irreversibly inactivated *Helix pomatia* β-D-xylopyranosidase. The nature of this inhibition is under further investigation.

EXPERIMENTAL

Melting points are uncorrected. Rotations were measured on a Perkin–Elmer 141 polarimeter. Preparative chromatography was on Whatman No. 3MM paper with butyl alcohol–ethanol–water (4:1:5, upper layer) as irrigant at a loading of about 1 mg/cm.

1L-1,2-Anhydro-myo-*inositol* (2). — A solution of 1L-1-*O*-toluene-*p*-sulphonyl-*chiro*-inositol[2] (1) (480 mg) in 0.13M methanolic sodium methoxide (12 ml) was allowed to stand at room temperature for 2.5 h. Since the solution was then no longer alkaline, a further quantity of sodium methoxide (3 ml) was added and the solution was allowed to stand for a further 1.5 h. The solution was then deionized with methanol-washed Amberlite MB-1 resin, filtered, and evaporated to dryness *in vacuo* to give the product (150 mg, 60%). After recrystallization by dissolving the solid in water (2 drops) and adding hot ethanol (3–4 ml), the product had m.p. 160°, $[\alpha]_D^{24}$ −70° (*c* 0.6, water) (Found: C, 44.2; H, 5.9; O, 44.95. $C_6H_{10}O_5$ calc.: C, 44.4; H, 6.2; O, 49.3%).

Acid hydrolysis of 1L-1,2-anhydro-myo-*inositol.* — A solution of the epoxide (10 mg) in 62.5mM sulphuric acid was refluxed for 2 h. The solution was deionized with Amberlite IR-45 (HO^-) resin and chromatographed on Whatman No. 1 paper by using acetone–water (4:1) as solvent. The major product was *chiro*-inositol, together with a trace of *scyllo*-inositol.

1L-2,3,4,5,6-Penta-O-*benzoyl-1*-O-*toluene*-p-*sulphonyl*-myo-*inositol* (4). — 1D-1,2,4,5,6-Penta-*O*-benzoyl-*myo*-inositol[2] (3) (335 mg) was dissolved in dry pyridine (3 ml) and toluene-*p*-sulphonyl chloride (600 mg) was added. After 2 days at room temperature, the mixture was poured into ice–water, and the crystals were filtered off, dried, and recrystallized from chloroform–methanol to yield 4 (350 mg, 85%), m.p. 210–212°, $[\alpha]_D^{22}$ −11.5° (Found: C, 67.4; H, 4.4; S, 4.2. $C_{48}H_{38}O_{13}S$ calc.: C, 67.5; H, 4.4; S, 3.8%).

1L-1-O-*Toluene*-p-*sulphonyl*-myo-*inositol* (5). — Compound 4 (570 mg) was dissolved in dry chloroform (2 ml) and dry methanol (1 ml). M Methanolic sodium methoxide (0.2 ml) was added and the mixture was stirred rapidly. After 5–10 min, a precipitate appeared which was redissolved by addition of more methanol at intervals to give a final volume of *ca.* 10 ml. The final mixture was an oily suspension. After 1 h, the mixture was poured into water (40 ml) and washed with ether (2 × 25 ml). The aqueous layer was stirred with Amberlite IR-120 (H^+) resin, followed by Amberlite IR-45 (HO^-) resin. The resulting solution was evaporated to dryness, and the residue was recrystallized from 50% aqueous ethanol to give the product (135 mg, 60%), m.p. 202–204° $[\alpha]_D^{22}$ +20.3° (*c* 0.25, methyl sulphoxide) (Found: C, 46.4; H, 5.4; S, 9.4. $C_{13}H_{18}O_8S$ calc.: C, 46.4; H, 5.4; S, 9.6%). 1L-1,2-Anhydro-*chiro*-inositol (6) could be recovered from the mother liquors by preparative, paper chromatography.

1L-1,2-Anhydro-chiro-*inositol* (6). — Compound 1L-5 (88 mg) was dissolved in methyl sulphoxide (2.5 ml), and methanol (3 ml) and M methanolic sodium methoxide (0.3 ml) were added. The rotation was followed at room temperature and became constant after 2 h (α_D +0.430° → −0.395°). The solution was diluted with methanol and deionized with Amberlite MB-1 resin, and the methanol was removed at *ca.* 12 mmHg and methyl sulphoxide at *ca.* 0.1 mmHg. The product (6, 24 mg) was chromatographically homogeneous and had the same R_F value as a sample of DL-1,2-anhydro-*chiro*-inositol prepared by the method previously reported[6]. On standing or

dissolution in water, *muco*-inositol was slowly formed. A sample stored in ethanol for 6 weeks gave crystals, m.p. 140–142°, $[\alpha]_D^{25}$ −47 ±3° (*c* 0.8, water).

Acid hydrolysis of L-*1,2-anhydro*-chiro-*inositol*. — A solution of the crystalline epoxide (1 mg) in M hydrochloric acid (1 ml) was refluxed for 1 h. Chromatography on Whatman No. 1 paper with acetone–water (4:1, v/v) showed the major product to be *muco*-inositol, together with a trace of *myo*-inositol.

DL-*3,4,5,6-Tetra*-O-*benzoyl-1,2*-O-*isopropylidene*-myo-*inositol* (**8**). — A solution of DL-1,2-*O*-isopropylidene-*myo*-inositol[7] (**7**) (4 g) in anhydrous pyridine (100 ml) was treated dropwise, with stirring at 0°, with benzoyl chloride (14 g) during 1.5 h. After standing overnight at 0°, the mixture was poured into a mixture of ice and saturated, aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 100 ml). The extracts were washed with 2M hydrochloric acid and water, dried (Na_2SO_4), and evaporated to give DL-3,4,5,6-tetra-*O*-benzoyl-1,2-*O*-isopropylidene-*myo*-inositol (**8**) which was recrystallized from chloroform–ethanol; yield, 11.2 g (95%); m.p. 232–234° (Found: C, 69.65; H, 4.9. $C_{37}H_{32}O_{10}$ calc.: C, 69.8; H, 5.05%).

DL-*1,4,5,6-Tetra*-O-*benzoyl*-myo-*inositol* (**9**). — A solution of **8** (8 g) in ethanol (360 ml) containing 2M hydrochloric acid (20 ml) was refluxed for 1 h. The solution was evaporated *in vacuo*, the residue was dissolved in ethanol, and the solution was again evaporated. The product was recrystallized twice from methanol to give **9** (6.4 g, 87%), m.p. 204–207° (Found: C, 68.6; H, 4.8. $C_{34}H_{28}O_{10}$ calc.: C, 68.45; H, 4.7%).

DL-*3,4,5,6-Tetra*-O-*benzoyl-1*-O-*toluene*-p-*sulphonyl*-myo-*inositol* (**10**). — Toluene-*p*-sulphonyl chloride (110 mg) was added at 0° with stirring to **9** (3 g) in dry pyridine (30 ml), and the mixture was left at room temperature overnight. It was then poured into ice and saturated, aqueous sodium hydrogen carbonate. The precipitate was washed well with water, dried *in vacuo*, and then recrystallized from chloroform–ethanol (3.4 g, 89%), m.p. 239–241° (Found: C, 65.3; H, 4.8; S, 4.2. $C_{41}H_{34}O_{12}S$ calc.: C, 65.6; H, 4.6; S, 4.3%).

DL-*1*-O-*Toluene*-p-*sulphonyl*-myo-*inositol* (**5**). — Compound **10** (720 mg) was suspended in dry chloroform (4 ml) and dry methanol (4 ml). M Methanolic sodium methoxide (0.4 ml) was added, and the mixture was stirred magnetically. The solution quickly became clear and then an emulsion appeared. Methanol (3 × 1 ml) was added during *ca.* 20 min and, after a further 30 min, the mixture was poured into water (100 ml). The aqueous layer was washed with ether (2 × 25 ml), deionized with Amberlite IR-120 (H^+) and Amberlite IRA-400 (CO_3^{2-}) resins, and evaporated to dryness. The crystalline product (250 mg) was recrystallized from 50% aqueous ethanol to give **5**, m.p. 127–129°; lit.[6] m.p. 124°. The mother liquors contained DL-1,2-anhydro-*chiro*-inositol which could be recovered by paper chromatography.

DL-*1,2-Anhydro*-chiro-*inositol* (**6**). — DL-**5** (170 mg) was dissolved in methyl sulphoxide (4 ml), and methanol (5 ml) and M methanolic sodium methoxide (0.5 ml) were added. The mixture was left at room temperature for 3 h and then deionized by Amberlite MB-1 resin in methanol. The methanol was removed at *ca.* 12 mmHg and methyl sulphoxide at *ca.* 0.1 mmHg/40°. The product (55 mg) was chromatographi-

cally homogeneous. After chromatography, it crystallized on standing; m.p. 115–120°; lit.[6] m.p. 129–130°.

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