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SOME REACTIONS OF 1,6-DI-*O*-*p*-TOLYLSULPHONYL-D-MANNITOL AND ITS DERIVATIVES*

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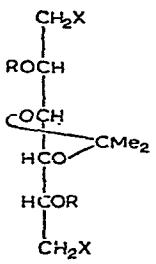
ABSTRACT

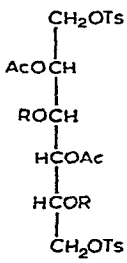
Treatment of 2,4-di-*O*-acetyl-3,5-di-*O*-methanesulphonyl-1,6-di-*O*-*p*-tolylsulphonyl-D-mannitol (**5**) with methanol–hydrochloric acid gave 2,5-anhydro-4-*O*-methanesulphonyl-1,6-di-*O*-*p*-tolylsulphonyl-D-glucitol (**7**, 20%) and 1,4-anhydro-3,5-di-*O*-methanesulphonyl-6-*O*-*p*-tolylsulphonyl-D-mannitol (42%). The corresponding 1,6-dibromide gave >70% of 2,5-anhydride but no 1,4-anhydride. The conversion **5**→**7** involves an acetyl migration. 3,4-*O*-Isopropylidene-1,6-di-*O*-*p*-tolylsulphonyl-D-mannitol was unstable at room temperature and gave a 1,4-anhydro derivative *via* migration of the isopropylidene group and elimination of *p*-tolylsulphonic acid.

INTRODUCTION

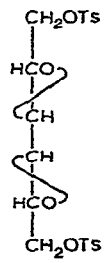
When the isopropylidene group of 2,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol (**1**) was removed under acidic conditions, an acyl migration occurred and the product was 3,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-D-mannitol[1]. The mechanism suggested invoked the electronegativity of the bromine



1 X = Br, R = Ac
2 X = OTs, R = H
3 X = OTs, R = Ac



4 R = H
5 R = Ms



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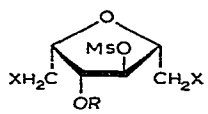
*Dedicated to Dr. Horace S. Isbell, in honour of his 75th birthday.

substituents as the driving force. We now report on the behaviour of the corresponding 1,6-di-*O*-tosyl derivative **3** under similar reaction conditions.

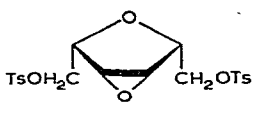
RESULTS AND DISCUSSION

2,5-Di-*O*-acetyl-3,4-*O*-isopropylidene-1,6-di-*O*-tosyl-D-mannitol (**3**) was synthesised first by Wiggins[2], starting from 3,4-*O*-isopropylidene-D-mannitol. Applying the more-selective tosylation procedure of Iqubal and Owen[3], the yield of **3** could be increased from 36 to 62%. When a solution of **3** in acetic acid was treated with conc. hydrochloric acid, the *O*-isopropylidene group was hydrolysed, and the expected migration[1] of one acetyl group occurred, yielding 2,4-di-*O*-acetyl-1,6-di-*O*-tosyl-D-mannitol (**4**). The structure of **4** was proved by converting it into the 3,5-di-*O*-mesyl derivative **5**, which, on treatment with an excess of sodium methoxide, gave the diepoxide **6**. The i.r. and n.m.r. spectra of **6** were very similar to those of 2,3:4,5 dianhydro-1,6-di-*O*-tosyl-D-iditol[4], and the compound showed no optical rotation in accord with the galactitol configuration.

When the dimesyl ester **5** was deacetylated with methanol–conc. hydrochloric acid at elevated temperature, the expected elimination of methanesulphonic acid took place, but the resulting 2,5-anhydro-D-glucitol derivative **7** was isolated in a yield of <20%. The main product of this reaction, which could be isolated by column chromatography as a pure syrup, was 1,4-anhydro-3,5-di-*O*-mesyl-6-*O*-tosyl-D-mannitol (**12**). This observation illustrates the difference in leaving-group character of the bromo and the tosyloxy substituents, since, under similar reaction conditions, the 1,6-dibromo derivative **5** (X = Br) gave >70% of the 2,5-anhydro derivative, and no 1,4-anhydro derivative was obtained[1].



7 X = OTs, R = H
9 X = OTs, R = Ms
10 2X = SBz and OTs, R = Ms



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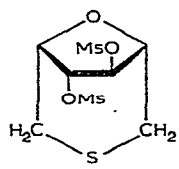

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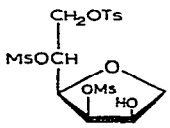

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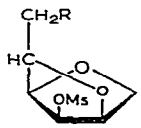
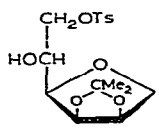


13 R = OTs
14 R = I



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Treatment of **7** with sodium methoxide gave the symmetrical epoxide **8**, and mesylation afforded the di-*O*-mesyl derivative **9**, which was converted *via* the mono-*S*-benzoyl derivatives **10** into the known[5] 2,5-anhydro-3,4-di-*O*-mesyl-1,6-thio-anhydro-D-glucitol (**11**).

It was necessary to establish the structure of the 1,4-anhydro compound **12**, since, theoretically, HO-2 could also be involved in the elimination of *p*-tolylsulphonic acid, yielding a 2,6-anhydro-D-mannitol derivative. When **12** was treated with an excess of sodium methoxide, a second anhydro ring was formed by the elimination of methanesulphonic acid. It is noteworthy that, although the primary tosyloxy group in **12** is sterically in an even more favourable position than the adjacent mesyloxy group for attack by HO-2, no derivative with a 2,6-anhydro ring was formed on treatment with sodium methoxide. The structure of the dianhydride **13** was established on heating with acetone–sodium iodide, when 1,4:2,5-dianhydro-6-deoxy-6-iodo-3-*O*-mesyl-L-gulitol[6] (**14**) was formed as the only product.

3,4-Di-*O*-isopropylidene-1,6-di-*O*-tosyl-D-mannitol (**2**), which was needed for further experiments, had previously been obtained only as an intermediate in solution[3]. The literature method[3] gives a mixture of tosyl derivatives of 3,4-*O*-isopropylidene-D-mannitol, from which **2** could be isolated as an unstable, colourless syrup by column chromatography. After storage of the syrup at room temperature for one month, 35% of crystalline 1,4-anhydro-2,3-*O*-isopropylidene-6-*O*-tosyl-D-mannitol[7] (**15**) could be separated. The formation of **15** was catalysed by *p*-tolylsulphonic acid and involved either an intramolecular migration or an intermolecular transacetalation of the 3,4-*O*-isopropylidene group. The catalytic role of the acid was proved by the fact that **2** remained unchanged in chloroform solution, even during heating, when a small amount of pyridine was present.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with carbon tetrachloride–ethyl acetate (1:1) and detection with 0.1M potassium permanganate–M sulphuric acid (1:1) at 105° and 4-(*p*-nitrobenzyl)pyridine, followed by 2M sodium hydroxide and heating at 105°. Column chromatography was performed on silicic acid, using the same solvent system as for t.l.c. unless stated otherwise. N.m.r. spectra (60 MHz) were recorded at room temperature with a Varian A-60D spectrometer, for solutions in $CDCl_3$ with Me_4Si as internal standard. I.r. spectra were recorded with a Perkin–Elmer 457 spectrometer, using KBr pellets. All evaporations were carried out in a rotary evaporator under diminished pressure, after drying of the organic solutions over sodium sulphate. Light petroleum refers to the fraction b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1).

*3,4-*O*-Isopropylidene-1,6-di-*O*-p-tolylsulphonyl-*D*-mannitol* (**2**). — To a solution of 3,4-*O*-isopropylidene-D-mannitol (44.4 g) in pyridine (300 ml) a solution of *p*-tolylsulphonyl chloride (82 g) in pyridine (200 ml) was added with stirring at −30° during 2 h. The mixture was then stirred at −10° for 2 h and kept overnight at −5°. The slurry was poured into ice, the precipitated oil was extracted with chloroform, and the organic solution was washed in the usual way to give, after evaporation, crude **2** as a yellow syrup (101 g, 94%). A portion (10 g) of this syrup was purified by column chromatography. Evaporation of the fractions containing the component

with R_F 0.55 gave **2** (6.5 g, 61.5%) as a colourless syrup, $[\alpha]_D^{20}$ +21° (Found: S, 11.54. $C_{23}H_{30}O_{10}S_2$ calc.: S, 12.09%). The compound was unstable and decomposed on storage at room temperature.

*2,5-Di-*O*-acetyl-3,4-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulphonyl-*D*-mannitol* (**3**). — A reaction mixture containing **2** and prepared as described above was treated, after storage for 24 h at −5°, with acetic anhydride (160 ml) and kept for 24 h at room temperature. After the usual work-up, the chloroform solution was evaporated and ethanol was twice evaporated from the residue. The remaining syrup was crystallized from ethanol (300 ml) at −5° to yield **3** (75.3 g, 61.5%), m.p. 110–112°; lit.[2] m.p. 111–113°.

*2,4-Di-*O*-acetyl-1,6-di-*O*-*p*-tolylsulphonyl-*D*-mannitol* (**4**). — Compound **3** (61.4 g) was dissolved by heating in acetic acid (300 ml), the solution was cooled to 30°, and conc. hydrochloric acid (40 ml) was added. The resulting slurry was kept at 40° until complete dissolution occurred and was then stored at 30° for 1 h. Thereafter, it was poured into water, and the slurry was neutralised with solid sodium carbonate and extracted with chloroform. The extract was concentrated and the residue was treated with benzene–light petroleum to yield **4** (35.2 g, 61.2%), m.p. 120–122°, $[\alpha]_D^{20}$ +7°; ν_{max}^{KBr} 3420 (OH), 1720, 1260 (acetyl), 1360, 1190, 1170, 815, 670, 555 cm^{-1} (tosyl). N.m.r. data: δ 2.05 (*s*, 2AcO), 2.45 (*s*, 2 tosyl Me) (Found: C, 50.25; H, 5.41; S, 11.22. $C_{24}H_{30}O_{12}S_2$ calc.: C, 50.16; H, 5.26; S, 11.16%).

*2,4-Di-*O*-acetyl-3,5-di-*O*-methanesulphonyl-1,6-di-*O*-*p*-tolylsulphonyl-*D*-mannitol* (**5**). — A solution of **4** (29 g) in pyridine (200 ml) was treated with methanesulphonyl chloride (12 ml), in the usual manner, to yield a yellow syrup (37.2 g, 102%), which after purification by column chromatography gave **5** (27.6 g, 76%), R_F 0.70, $[\alpha]_D^{20}$ +13°; ν_{max}^{KBr} 1750, 1265 (acetyl), 1360, 1190, 1180, 815, 670, 555 cm^{-1} (mesyl and tosyl). N.m.r. data: δ 2.03, 2.09 (2*s*, 2AcO), 2.46 (*s*, 2 tosyl Me), 3.13 (*s*, 2 mesyl Me) (Found: S, 17.18. $C_{26}H_{34}O_{16}S_4$ calc.: S, 17.55%).

*2,3:4,5-Dianhydro-1,6-di-*O*-*p*-tolylsulphonylgalactitol* (**6**). — A solution of **5** (37 g) in methanol (250 ml) and chloroform (250 ml) was treated at 0° with a solution of 4M methanolic sodium methoxide (35 ml). The mixture was kept at room temperature for 30 min, then neutralised with carbon dioxide, and concentrated. A solution of the residue in chloroform was washed with water, dried, and evaporated. The residue was crystallised from ethyl acetate–carbon tetrachloride to give **6** (5.7 g, 25.2%), m.p. 117–119°, $[\alpha]_D^{20}$ 0°, R_F 0.60; ν_{max}^{KBr} 1365, 1175, 810, 670, 550 (tosyl), 830 cm^{-1} (epoxide). N.m.r. data: δ 2.45 (*s*, 2 tosyl Me), 2.95 (*s*, H-3,4), 3.15 (*t*, H-2,5) (Found: C, 52.92; H, 5.00; S, 14.05. $C_{20}H_{22}O_8S_2$ calc.: C, 52.85; H, 4.88; S, 14.11%).

The residue, obtained after evaporation of the filtrate, gave, on column chromatography, more **6** (0.7 g, 3%) and a colourless syrup (R_F 0.50), which appeared on the basis of n.m.r. data to be a mixture of several isomeric dianhydromesyltosylhexitols.

*2,5-Anhydro-4-*O*-methanesulphonyl-1,6-di-*O*-*p*-tolylsulphonyl-*D*-glucitol* (**7**) *and 1,4-anhydro-3,5-di-*O*-methanesulphonyl-6-*O*-*p*-tolylsulphonyl-*D*-mannitol* (**12**). — A solution of **5** (37 g) in methanol (700 ml) was treated with conc. hydrochloric acid (175 ml)

at ~95° (steam bath) for 5 h. The cooled solution was neutralised with solid sodium hydrogen carbonate, filtered, and concentrated, and the residue was partitioned between chloroform and water. The washed and dried organic solution was evaporated and the residue was recrystallized from ethanol to give crude **7** (5.5 g, 20%), which was recrystallised from methanol (8 vol.) to give material having m.p. 127–129°, $[\alpha]_D^{20}$ +14°, R_F 0.60; ν_{max}^{KBr} 3440 (OH), 1355, 1190, 1180, 1170, 820, 670, 550 cm^{-1} (mesyl and tosyl). N.m.r. data: δ 2.45 (*s*, 2 tosyl Me), 3.10 (*s*, mesyl Me) (Found: C, 45.65; H, 4.66; S, 17.46. $C_{21}H_{26}O_{11}S_3$ calc.: C, 45.81; H, 4.76; S, 17.47%).

T.l.c. of the material in the mother liquors of the recrystallizations of **7** showed at least 8 spots. Column chromatography of the mixture (15 g), with combination and concentration of the fractions containing the main component of R_F 0.30, gave **12** as a colourless syrup (10 g, 42%), $[\alpha]_D^{20}$ −9°; ν_{max}^{KBr} 3500 (OH), 1350, 1190, 1170, 815, 670, 655, 630 cm^{-1} (mesyl and tosyl). N.m.r. data: δ 2.45 (*s*, tosyl Me), 3.12, 3.23 (2*s*, 2 mesyl Me) (Found: S, 20.06. $C_{15}H_{22}O_{11}S_3$ calc.: S, 20.27%).

2,5:3,4-Dianhydro-1,6-di-O-p-*tolylsulphonylgalactitol* (**8**). — A solution of **7** (0.65 g) in dry chloroform (10 ml) was treated with 4M methanolic sodium methoxide (0.70 ml), and the slurry was kept at room temperature for 30 min. After dilution with chloroform, it was neutralized with carbon dioxide, washed with water, dried, and concentrated. The solid residue was filtered with ether to give **8** (0.47 g, 88%), m.p. 123–124° (unchanged after recrystallization from methanol), $[\alpha]_D^{20}$ 0°, R_F 0.70; ν_{max}^{KBr} 1350, 1190, 1170, 820, 665, 655, 550, 530 cm^{-1} (tosyl). N.m.r. data: δ 2.40 (*s*, 2 tosyl Me), 3.70 (*s*, H-3,4), 4.00 (*s*, H-1,1,2,5,6,6′) (Found: C, 52.75; H, 5.02; S, 14.12. $C_{20}H_{22}O_8S_2$ calc.: C, 52.85; H, 4.88; S, 14.11%).

2,5-Anhydro-3,4-di-O-*methanesulphonyl-1,6-di*-O-p-*tolylsulphonyl*-D-*glucitol* (**9**). — Compound **7** (2.25 g) was mesylated in pyridine, in the usual manner, to give the crude disulphonate (2.2 g, 85%), which, after recrystallization from acetone–light petroleum, afforded **9** (2.0 g, 77.5%), m.p. 118–120°, $[\alpha]_D^{20}$ +17°, R_F 0.70; ν_{max}^{KBr} 1350, 1175, 820, 670, 550, 520 cm^{-1} (mesyl and tosyl). N.m.r. data: δ 2.46 (*s*, 2 tosyl Me), 3.13, 3.7 (2*s*, 2 mesyl Me), 5.20 (*m*, H-3,4) (Found: C, 41.98; H, 4.68; S, 20.18. $C_{22}H_{28}O_{13}S_4$ calc.: C. 42.03; H, 4.49; S, 20.40%).

2,5-Anhydro-1(6)-S-*benzoyl-3,4-di*-O-*methanesulphonyl-1(6)-thio-6(1)*-O-p-*tolylsulphonyl*-D-*glucitol* (**10**). — A solution of **9** (0.63 g) and potassium thiolbenzoate (0.18 g) in dry acetone (10 ml) was kept at room temperature overnight. The resulting slurry was boiled until the yellow colour disappeared (30 min) and then concentrated. The residue was partitioned between chloroform and water, and the organic solution was washed, dried, and concentrated to give the crude product as a syrup (0.4 g, 67.2%). Column chromatography afforded **10** (0.28 g, 52%) as a colourless syrup, $[\alpha]_D^{20}$ 0°, R_F 0.75. N.m.r. data: δ 2.41 (*s*, tosyl Me), 3.17 (*s*, 2 mesyl Me), 5.2 (*m*, H-3,4) (Found: S, 21.15. $C_{22}H_{26}O_{11}S_4$ calc. : S, 21.58%).

2,5-Anhydro-3,4-di-O-*methanesulphonyl-1,6-thioanhydro*-D-*glucitol* (**11**). — A solution of **10** (0.2 g) in dry chloroform (5 ml) was treated with 4M methanolic sodium methoxide (0.1 ml). After 30 min at room temperature, the reaction mixture was washed with water, dried, and concentrated. The residue, on recrystallization from

benzene, gave **11** (41 mg, 40%), m.p. 139–140° alone and in admixture with authentic material[5].

1,4:2,5-Dianhydro-3-O-methanesulphonyl-6-O-p-tolylsulphonyl-L-gulitol (**13**). — A solution of **12** (2 g) in chloroform (20 ml) and methanol (2 ml) was treated with 4M methanolic sodium methoxide (1.5 ml) at room temperature overnight. The slurry was diluted with chloroform, saturated with carbon dioxide, and washed with water. Concentration of the dried solution and trituration of the residue with methanol gave **13** (0.70 g, 43%), m.p. 93–94° (unchanged on recrystallization from methanol), $[\alpha]_D^{20}$ +40.5°, R_F 0.40, ν_{max}^{KBr} 1350, 1190, 1175, 820, 810, 670, 650, 620 cm^{-1} (mesyl and tosyl). N.m.r. data: δ 2.45 (*s*, tosyl Me), 3.12 (*s*, mesyl Me), 5.05 (*m*, H-3) (Found: C, 44.21; H, 4.75; S, 16.91. $C_{14}H_{18}O_8S_2$ calc.: 44.44; H, 4.79; S, 16.95%).

1,4:2,5-Dianhydro-6-deoxy-6-iodo-3-O-methanesulphonyl-L-gulitol (**14**). — A solution of **13** (0.2 g) and sodium iodide (0.5 g) in acetone (5 ml) was heated in a sealed tube at 100° for 8 h. The reaction mixture was cooled and filtered, and heating of the filtrate was repeated in the presence of more sodium iodide (0.5 g). The mixture was concentrated, and a solution of the residue in chloroform was washed with water and 5% aqueous sodium thiosulphate. Concentration of the dried organic solution and recrystallisation of the residue from methanol afforded **14** (0.14 g, 79.5%), m.p. 113–114° alone or in admixture with authentic material[6].

1,4-Anhydro-2,3-O-isopropylidene-6-O-p-tolylsulphonyl-D-mannitol (**15**). — Syrupy disulphonate **2** (obtained from 11.1 g of 3,4-*O*-isopropylidene-D-mannitol) was stored at room temperature for one month. The semisolid material was treated with methanol, and the crystals were collected and washed with methanol, 5% aqueous sodium hydrogen carbonate, and water. The crude anhydro derivative (6.6 g, (37%), m.p. 128–130°, on recrystallization from methanol, gave **15** (5.85 g, 33%), m.p. 133–134°, $[\alpha]_D^{20}$ −25°, R_F 0.55; ν_{max}^{KBr} 3480 (OH), 2960, 2860, 1390, 1380 (isopropylidene), 1355, 1190, 1175, 820, 670, 550, 515 cm^{-1} (tosyl). N.m.r. data: δ 1.32, 1.44 (2*s*, $CMe)_2$, 2.45 (*s*, tosyl Me), 2.95 (*s*, OH, disappears on addition of D_2O), 4.80 (m, H-2,3); lit.[7] m.p. 133–134°, $[\alpha]_D^{20}$ −21.8°.

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