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Note

The reaction of 2,4,6-tri-isopropylbenzenesulphonyl chloride with alditols

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1,6-Di-*O*-sulphonyl and 1,6-dideoxy-1,6-dihalogeno derivatives of certain alditols have been investigated as possible antitumour agents[1–3]. The high biological activities of 1,6-di-*O*-mesyl and 1,6-dibromo-1,6-dideoxy-D-mannitol may be due to the formation, in solution, of the 1,2:5,6-dianhydro derivative, which is a very strong tumour inhibitor[4]. However, the biological activities of the terminal dichlorodideoxy, di-iododideoxy, di-*O*-mesyl, and di-*O*-tosyl derivatives of D-mannitol do not necessarily follow their tendency to form, in solution, the corresponding dianhydro derivatives[5]. In order to extend the work to other alditols, a general method was sought for the preparation of $\alpha\omega$-di-*O*-sulphonyl derivatives of alditols.

In contrast to the relative ease of selective sulphonylation of primary hydroxyl groups in saccharides[6], the difficulty of selective mesylation and tosylation at the primary position of alditols has been clearly demonstrated[7,8], and a bulkier sulphonyl chloride was therefore employed, *viz.*, 2,4,6-tri-isopropylbenzenesulphonyl chloride, in the hope that steric effects would tend to promote reaction at the more-accessible primary positions. Selective monosulphonylation of *vic*-secondary hydroxyl groups on a pyranose ring has been effected with mesitylenesulphonyl chloride[9], although when used for the selective sulphonylation of a primary hydroxyl group in the presence of a secondary one, in the steroid series, this reagent showed no advantage over toluene-*p*-sulphonyl chloride[10].

When 2,4,6-tri-isopropylbenzenesulphonyl chloride was used, the products fell into two classes (behaviour on t.l.c.). Thus, erythritol, L-arabinitol, and D-mannitol formed sulphonic esters (**1**, **3**, and **5**, respectively) with R_F 0.8–0.9 (solvent *B*), whereas the products from ribitol, xylitol, allitol, and D-glucitol (**8**, **10**, **12**, and **13**, respectively) showed R_F 0.4–0.5. The marked difference in R_F values was reflected in the elemental analytical data; the former (high R_F), but not the latter (low R_F), analysed for $\alpha\omega$-disulphonates. Since 1,4-anhydro ring formation can occur under basic conditions[11], it was proposed that the derivatives of low R_F were 1,4-anhydro-ω-sulphonates. The elemental analysis of the sulphonic esters and their acetate

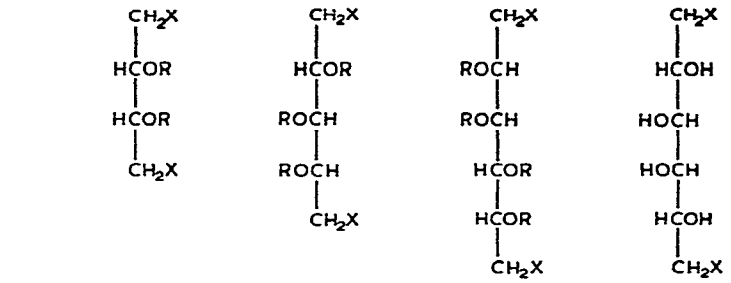
TABLE I

DATA ON 2,4,6-TRI-ISOPROPYLBENZENESULPHONATES

Compound[a]		*Molecular formula*	*Calc.*			*Found*			*M.p. (degrees)*	*Yield (%)*	R_F[b]
			C	*H*	*S*	*C*	*H*	*S*			
1,4-Di-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-erythritol	(1)	$C_{34}H_{54}O_8S_2$	62.4	8.26	9.81	62.2	8.1	9.82	186–187	33	0.80
Diacetate of **1**	(2)	$C_{38}H_{58}O_{10}S_2$	61.8	7.86	8.67	61.7	7.85	8.65	160–162		0.92
1,5-Di-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-L-arabinitol	(3)	$C_{35}H_{56}O_9S_2$	61.4	8.19	9.36	61.2	8.07	9.38	111–112	45	0.76
Triacetate of **3**	(4)	$C_{41}H_{62}O_{12}S_2$	60.7	7.65	7.90	60.7	7.42	8.12	130–132		0.90
1,4-Anhydro-5-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-ribitol	(8)	$C_{20}H_{32}O_6S$	60.0	8.0	8.0	59.7	7.82	8.18	120–121	17	0.55
Diacetate of **8**	(9)	$C_{24}H_{36}O_8S$	59.5	7.44		59.7	7.31		85– 86		0.72
1,4-Anhydro-5-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-xylitol	(10)	$C_{20}H_{32}O_6S$	60.0	8.0	8.0	59.8	7.85	8.20	168–170	45	0.52
1,4-Anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-allitol	(12)	$C_{21}H_{34}O_7S$	58.6	7.86	7.4	58.1	7.61	7.67	180–182	45	0.40
1,6-Di-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-D-mannitol	(5)	$C_{36}H_{58}O_{10}S_2$	60.5	8.11	8.98	60.7	7.84	8.98	145–146	51	0.75
Tetra-acetate of **5**	(6)	$C_{44}H_{66}O_{14}S_2$	59.9	7.48		60.2	7.58		170–171		0.90
1,4-Anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-D-glucitol	(13)	$C_{21}H_{34}O_7S$	58.6	7.86	7.4	58.7	7.77	7.51	140–142	29	0.40
1,6-Di-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-galactitol	(7)	$C_{36}H_{58}O_{10}S_2$	60.5	8.11	8.98	60.3	8.08	8.90	130–131	15	0.83

[a]Periodate uptake (mol/mol) and, in brackets, formic acid released (mol/mol): **1** 0.7; **3** 2.1 (0.7); **8** 1.1; **10** 0.6; **12** 1.2; **5** 3 (1.5); **13** 1.0; **7** 3.6 (1.4). [b]The R_F values of the sulphonates were obtained using solvent *B*, and those of the acetates using solvent *A*.

derivatives supported this proposal, and confirmation was provided by periodate oxidation of the sulphonic esters. The analytical and other data are given in Table I.

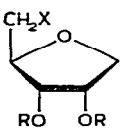


1 R = H
2 R = Ac

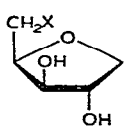
3 R = H
4 R = Ac

5 R = H
6 R = Ac

7



8 R = H
9 R = Ac



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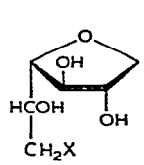

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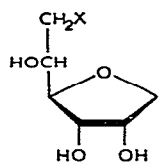

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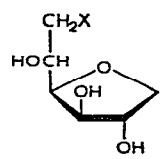
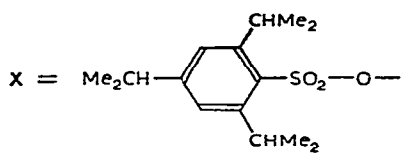


13

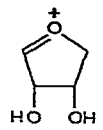


The relative rates of 1,4-anhydro ring formation for the alditols follows the sequences[12,13] ribitol > xylitol > arabinitol, and allitol > talitol > iditol > glucitol > altritol > galactitol > gulitol > mannitol. A similar trend was found in the present investigation. Reaction of D-glucitol with 2,4,6-tri-isopropylbenzenesulphonyl chloride could give rise to derivatives of 1,4-anhydro-D-glucitol and 1,4-anhydro-L-gulitol, although the former should preponderate on conformational grounds; 1,4-anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-D-glucitol (**13**) was the product isolated. Reaction of 1,4-anhydro-D-glucitol[14] with 2,4,6-tri-isopropylbenzenesulphonyl chloride also gave **13**.

The reaction of galactitol with 2,4,6-tri-isopropylbenzenesulphonyl chloride gave 1,6-di-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)galactitol (**7**) and 1,4-anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-galactitol (**11**). The structures were assigned on the basis of t.l.c. (solvent *B*), elemental analytical, and periodate-oxidation data.

Mass spectrometry provided further evidence for the 1,4-anhydro-type structures. Precise mass measurement of the molecular ions for the 1,4-anhydro-sul-

phonates (**12** and **11**) of allitol and galactitol were 430.2032 and 430.2045, respectively (calc. for $C_{21}H_{34}O_7S$: 430.2026). Molecular ions could not be detected for **5** and **7**. The fragmentation patterns did not provide conclusive evidence for the presence of a 1,4-anhydro ring; a peak at *m/e* 103 corresponding to the oxycarbonium ion **14** was observed for 1,4-anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-allitol (**12**) and 1,4-anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-galactitol (**11**), but it was also detected, though at a lower relative intensity, in the disulphonates (**5** and **7**) of D-mannitol and galactitol.



m/e = 103

14

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. I.r. spectra were measured as Nujol mulls on a Perkin–Elmer Model 237 spectrometer, and were calibrated against the 1603 cm^{-1} band of a polystyrene film. T.l.c. was performed on Kieselgel HF_{254} (Merck), using ethyl acetate–light petroleum (b.p. 40–60°) mixtures: *A* 1:2; *B* 3:2; detection was effected with u.v. light, and by spraying with 5% ethanolic sulphuric acid followed by charring. Solutions were concentrated under reduced pressure below 40°. Standard procedures were used for the quantitative determination of periodate[15] and formic acid[16]. 2,4,6-Tri-isopropylbenzenesulphonyl chloride was prepared by the method of Newton[17]. Pyridine was dried by refluxing over, followed by distillation from, barium oxide. Mass spectra were recorded by P.C.M.U. Harwell, using an A.E.I. MS-902 instrument operating at 70 eV with a direct-insertion system.

For the preparation of the 2,4,6-tri-isopropylbenzenesulphonates, to an ice-cold solution (~10%) of the alditol (1 mol) in dry pyridine was added dropwise a solution (~40%) of 2,4,6-tri-isopropylbenzenesulphonyl chloride (2.1 mol) in dry pyridine with stirring, and the resulting solution was stored at 5° for 1 week. On pouring into excess ice–water with stirring, the solid formed was collected, washed with water, and recrystallised from methanol. The physical properties of the compounds so obtained are given in Table I.

*1,4-Anhydro-6-*O*-(2,4,6-tri-isopropylbenzenesulphonyl)-DL-galactitol* (**11**). — To the mother liquors from the recrystallisation of **7** (see general method of preparation), water was added dropwise to give a white precipitate, which was recrystallised from benzene–light petroleum (b.p. 60–80°) to give **11** (25%), m.p. 138–139°, R_F 0.50 (solvent *B*), which consumed 1.0 mol of periodate/mol.

Anal. Calc. for $C_{21}H_{34}O_7S$: C, 58.5; H, 7.86; S, 7.4. Found: C, 58.5; H, 7.89; S, 7.6.

1,4-Anhydro-6-O-(2,4,6-tri-isopropylbenzenesulphonyl)-D-glucitol (**13**). — 1,4-Anhydro-D-glucitol (0.23 g) was dissolved in pyridine (5 ml), and a solution of 2,4,6-tri-isopropylbenzenesulphonyl chloride (0.43 g) in pyridine (5 ml) was added dropwise at 0°. After two weeks, the reaction mixture was poured into ice–water, giving a solid which, on recrystallisation, was identical with **13** (R_F, m.p., mixture m.p., and i.r. spectrum).

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