710. *The Preparation of αω-Di-O-methanesulphonyl Derivatives of Some Sugar Alcohols.*

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Synthetic routes to αω-dimethanesulphonyl derivatives of representative tetritols, pentitols, and hexitols are described. In general, these compounds are unstable in acid and give rise to anhydro-derivatives; some can only be obtained as acetyl derivatives.

Hydroxy-substituted αω-dimethanesulphonyloxyalkanes were required as potentially water-soluble analogues of the cytoactive compound " myleran " (1,4-dimethanesulphonyloxybutane) and its congeners.[1] The sugar alcohols were the starting materials of choice to facilitate correlation of biological activity of the derived sulphonic esters with both chain length and stereochemistry. Some diarenesulphonic esters of free polyols have been prepared,[2,3] but the synthetic methods used in these cases were found to be inapplicable to the preparation of the analogous dialkanesulphonates. Four possible routes to such compounds were available: (*a*) ring opening of terminal dianhydro-derivatives of polyols with methanesulphonic acid (cf. ref. 4); (*b*) preferential methanesulphonation [2] of the primary hydroxyl groups of unsubstituted polyols; (*c*) methanesulphonation of suitably protected polyols,[5] followed by removal of the protecting groups; and (*d*) reaction [2,6] of αω-dideoxy-αω-dihalogenopolyols with silver methanesulphonate.

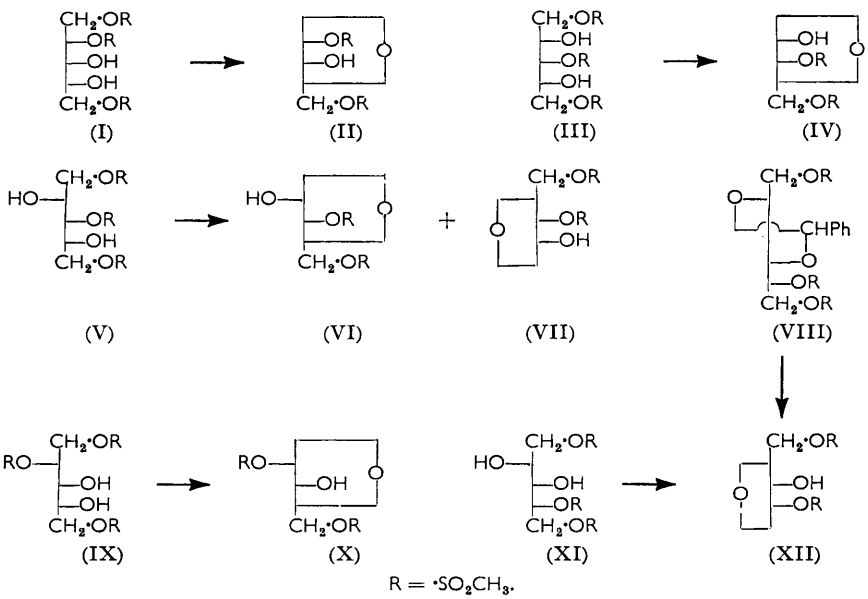
1,2:3,4-Dianhydroerythritol and two mol. of methanesulphonic acid reacted smoothly in ether, but only a poor yield of a crystalline product was isolated. Reaction of erythritol, in pyridine, with two mol. of methanesulphonyl chloride gave a small amount of the tetramethanesulphonyl derivative. However, further treatment of such a reaction mixture with two mol. of acetic anhydride afforded the required 2,3-di-*O*-acetyl-1,4-di-*O*-methanesulphonylerythritol, as did the reaction of 2,3-di-*O*-acetyl-1,4-dibromo-1,4-dideoxyerythritol with silver methanesulphonate in benzene. Crystalline 1,4-di-*O*-methanesulphonylerythritol, which proved to be identical with the material prepared from the diepoxide, was obtained from the diacetyl derivative by treatment with methanolic hydrogen chloride. As an alternative route to the authentic diacetyl derivative, detritylation of 2,3-di-*O*-acetyl-1,4-di-*O*-tritylerythritol was studied. Hydrogenolysis in neutral solution, however, could not be realized, contrary to the opinion of Helferich,[7] whilst the only crystalline product of acid hydrolysis was 1,4-di-*O*-acetylerythritol, formed by double acyl migration such as has been observed in the preparation of α- and β-monoglycerides.[8] It was thus clear that trityl ethers were of no value as blocking groups in the present work.

Ring opening of 1,2:3,4-dianhydro-DL-threitol with methanesulphonic acid gave a syrup, and a heterogeneous solid was obtained by reaction of D-threitol with two mol. of methanesulphonyl chloride and then two of acetic anhydride. Crystalline 2,3-di-*O*-acetyl-1,4-di-*O*-methanesulphonyl-DL-threitol was, however, prepared by reaction of the corresponding diacetoxydibromobutane with silver methanesulphonate; deacetylation gave 1,4-di-*O*-methanesulphonyl-DL-threitol.

Attempts at the " partial " methanesulphonation (*i.e.*, reaction with two mol. of methanesulphonyl chloride) followed by acetylation, of 2-deoxy-D-ribitol, D-arabitol, ribitol,

[1] Timmis, in " Cancer," ed. Raven, Butterworths, London, 1959, Vol. VI, p. 1; Haddow, Timmis, and Brown, *Nature*, 1958, **182**, 1164.
[2] Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 107.
[3] Skinner, Henderson, and Gustafson, *J. Amer. Chem. Soc.*, 1958, **80**, 3788.
[4] Winstein and Henderson, in " Heterocyclic Compounds," ed. Elderfield, Chapman and Hall, London, 1950, Vol. I, p. 1.
[5] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[6] Emmons and Ferris, *J. Amer. Chem. Soc.*, 1953, **75**, 2257.
[7] Helferich, *Adv. Carbohydrate Chem.*, 1948, **3**, 79.
[8] Hartman, *Chem. Rev.*, 1958, **58**, 845; van Lohuizen and Verkade, *Rec. Trav. chim.*, 1960, **79**, 133 and references there cited.

and xylitol led to heterogeneous acetyl-methanesulphonyl derivatives which resisted purification. Methanolysis of the crude products from D-arabitol and from ribitol yielded, as the only crystalline materials, traces of sharply melting anhydrodi-*O*-methanesulphonylpentitols. Although anhydro-derivatives of polyols may be formed [2] under sulphonylation conditions it is more likely, in view of the evidence below, that these compounds actually arose by elimination, during the deacetylation step, of one mol. of methanesulphonic acid from trimethanesulphonyl derivatives of the polyols, which were by-products (cf. refs. 9 and 10) of the partial esterification. Ribitol could in this way yield two trimethanesulphonyl derivatives, (I) and (III), and hence two anhydro-compounds, (II) and (IV). Arabitol, however, can give rise to three trimethanesulphonyl derivatives, (V), (IX), and (XI), and hence four anhydro-compounds (VI), (VII), (X), and (XII). Of these, structure (XII) must be ascribed to a second anhydrodi-*O*-methanesulphonylarabitol which was obtained by the partial methanesulphonylation of 2,3-*O*-benzylidene-D-arabitol (VIII; R = H).[9] This reaction gave a syrup, which on spontaneous hydrolysis afforded a crystalline di-*O*-methanesulphonyl-D-arabitol (presumably the 1,5-derivative) but on hydrolysis by strong acid gave an anhydrodi-*O*-methanesulphonyl-D-arabitol different from that obtained directly from arabitol. The structure (XII) for this second anhydro-compound was established because it could also be prepared from the product of the reaction of 2,3-*O*-benzylidene-D-arabitol with 3 mol. of methanesulphonyl chloride; it must be derived from (VIII) and it can, therefore, only have structure (XII). It could not be an artefact of the sulphonylation as benzylidene acetals are known [5] to be stable under the conditions used in this step.



The formation of anhydro-polyols [11] from partially methanesulphonylated polyols, under *acid* conditions, has not previously been reported, but the reaction is not unexpected in view of the lability [12] of polyol phosphates of analogous structure.

[9] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1663.
[10] Hockett and Fletcher, *J. Amer. Chem. Soc.*, 1944, **66**, 469.
[11] Wiggins, *Adv. Carbohydrate Chem.*, 1950, **5**, 191; cf. Baddiley, Buchanan, and Carss, *J.*, 1957, 4138.
[12] Baddiley, Buchanan, and Carss, *J.*, 1957, 4058; Kosolapoff, and Baddiley, in " Phosphoric Esters and Related Compounds," *Chem. Soc. Special Publ.*, No. 8, 1957, p. 127.

Reaction of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol [13] with methanesulphonic acid in ether gave a syrup which underwent spontaneous hydrolysis to a crystalline dimethanesulphonylhexitol, which was shown to be 1,6-di-*O*-methanesulphonyl-D-mannitol by comparison with authentic specimens prepared from 2,3:4,5-di-*O*-benzylidene-D-mannitol [14] by successive methanesulphonation, acetolysis, and methanolysis, and from 2,3,4,5-tetra-*O*-acetyl-1,6-dideoxy-1,6-di-iodo-D-mannitol by reaction with silver methanesulphonate, followed by methanolysis. Partial methanesulphonylation and acetylation of D-mannitol gave an impure specimen of the tetra-acetyldimethanesulphonyl derivative, from which, however, by methanolysis the pure dimethanesulphonylmannitol was readily obtained. From the mother-liquors of the deacetylation an apparently homogeneous trimethanesulphonylmannitol was isolated. Since this compound could be prepared by further methanesulphonylation of 1,6-di-*O*-methanesulphonyl-D-mannitol, and its triacetyl derivative with sodium iodide in acetone [2] gave two mol. of sodium methanesulphonate and only a trace of iodine (cf. ref. 15), its structure is limited, by exclusion, to that of 1,3,6-tri-*O*-methanesulphonyl-D-mannitol.

" Partial " methanesulphonation and acetylation of D-glucitol gave a syrup from which no crystalline material could be obtained by methanolysis. The " partial " methanesulphonylation of 2,4-*O*-benzylidene-D-glucitol,[16] however, gave a dimethanesulphonyl derivative, from which by acetolysis 2,3,4,5-tetra-*O*-acetyl-1,6-di-*O*-methanesulphonyl-D-glucitol was prepared. Its structure was confirmed by the fact that acetolysis of the di-*O*-methanesulphonyl derivative of 2,4:3,5-di-*O*-benzylidene-D-glucitol [17] gave the same compound. Hydrolysis of these benzylidene derivatives, or methanolysis of the tetra-acetyl derivative, did not give crystalline material.

The extreme insolubility of galactitol precluded successful " partial " methanesulphonylation and acetylation. A satisfactory route to 2,3,4,5-tetra-*O*-acetyl-1,6-di-*O*-methanesulphonylgalactitol was found in the reaction of the readily available 2,3,4,5-tetra-*O*-acetyl-1,6-dibromo-1,6-dideoxygalactitol [18] with silver methanesulphonate. The same compound was also prepared by acetolysis of the dimethanesulphonyl derivative of either of the stereoisomeric 2,3,4,5-di-*O*-benzylidenegalactitols,[19] and from tetra-acetylgalactaric acid by Rosenmund reduction to the tetra-acetyl-dialdehyde,[20] followed by catalytic hydrogenation to 2,3,4,5-tetra-*O*-acetylgalactitol and methanesulphonylation. Methanolysis of the tetra-acetyldimethanesulphonylgalactitol could not be achieved, apparently because of its insolubility. As an alternative method of preparing the free 1,6-di-*O*-methanesulphonylgalactitol, the acid hydrolysis of the di-*O*-methanesulphonyl derivative of 2,3:4,5-di-*O*-isopropylidenegalactitol [21] was studied. This reaction, however, gave an anhydrodi-*O*-methanesulphonylgalactitol; circumstantial evidence that this ring closure involved the 3(4)-position, and therefore that the product was racemic 1,4-anhydro-6-*O*-methanesulphonylgalactitol, was provided by the fact that hydrolysis, under the same conditions, of the di-*O*-methanesulphonyl derivative of 2,3:5,6-di-*O*-isopropylidenegalactitol [21] did afford the corresponding di-*O*-methanesulphonylgalactitol. 1,4-Anhydro-D-galactitol is known.[22]

It is clear from these results that there can be no general route to αω-di-*O*-methanesulphonyl esters of the polyols. The ring opening of terminal diepoxides evidently proceeds in more than one sense (cf. ref. 23), and partial methanesulphonation gives

[13] Wiggins, *J.*, 1946, 384.
[14] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1419.
[15] Bladon and Owen, *J.*, 1950, 598.
[16] Vargha, *Ber.*, 1935, **68**, 18, 1381.
[17] Haworth, Gregory, and Wiggins, *J.*, 1946, 488.
[18] Bladon, Overend, Owen, and Wiggins, *J.*, 1950, 3000.
[19] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 136, 137.
[20] Papadakis, *J. Org. Chem.*, 1955, **20**, 630; cf. Smith and Stephen, *Tetrahedron Letters*, 1960, No. 7, 17.
[21] Hann, Maclay, and Hudson, *J. Amér. Chem. Soc.*, 1939, **61**, 2432.
[22] Ness, Fletcher, and Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 3742.
[23] Haggis and Owen, *J.*, 1950, 2250.

complex mixtures of products. The instability of partially methanesulphonylated polyols in acid (as well as alkaline) solution, moreover, restricts the choice of blocking groups which may be used in their synthesis.

Experimental

Unless otherwise specified, suitably purified, anhydrous reagents and solvents were used, and evaporations were carried out *in vacuo* on a rotary evaporator. Analyses were by Mr. P. R. W. Baker, Wellcome Laboratories, Beckenham.

1,4-*Di*-O-*methanesulphonylerythritol*.—(*a*) A stirred, ice-cooled solution of 1,2:3,4-dianhydroerythritol [24] (fractionally distilled; b. p. 139·5—140°/754 mm., n_D^{16} 1·4322) (8·7 g.) in ether (60 ml.) was treated dropwise during 1 hr. with methanesulphonic acid (20 g., 2 mol.). After 1 hr. more, the ether was decanted from the precipitated oil, which was triturated with fresh ether (3 × 60 ml.) and treated with warm methanol (200 ml.). The solution was separated from the insoluble material and evaporated slowly, to leave a gummy solid which was collected and crystallized from ethyl acetate to give 1,4-di-*O*-methanesulphonylerythritol (1·0 g.), m. p. 122—124°. This compound, and its diacetyl and dibenzoyl derivatives, m. p. 178—180° (decomp.) and 186—188°, respectively, did not depress the m. p. of the corresponding compounds described below.

(*b*) A stirred, ice-cooled suspension of powdered erythritol (6·1 g.) in pyridine (20 ml.) was treated dropwise during 1 hr. with methanesulphonyl chloride (12·5 g., 2 mol.). After 1 hr. more, water (80 ml.) was added portionwise. The oily precipitate solidified on trituration with methanol (20 ml.) and crystallized from 2-methoxyethanol, to give 1,2,3,4-*tetra*-O-*methanesulphonylerythritol* (2·1 g.), blades, m. p. 216—217° (Found: C, 22·05; H, 4·2; S, 28·95. $C_8H_{14}O_{12}S_4$ requires C, 22·1; H, 4·2; S, 29·5%), identical with an authentic specimen.

The reaction mixture from such a methanesulphonylation was treated, at 3°, with acetic anhydride (10 g., 2 mol.) in pyridine (20 ml.) and left overnight at room temperature. The precipitate formed on adding the mixture to water was dried, and extracted with boiling dioxan (250 ml.). The filtered solution, on cooling, gave 2,3-*di*-O-*acetyl*-1,4-*di*-O-*methanesulphonylerythritol* (4·0 g.), prisms, m. p. 167—169° (decomp.), raised by recrystallization to 178—180° (decomp.) (Found: C, 33·45; H, 4·9; S, 18·0. $C_{10}H_{18}O_{10}S_2$ requires C, 33·1; H, 5·0; S, 17·7%). This product (16 g.) was boiled under reflux for 3 hr. with 0·58N-methanolic hydrogen chloride (600 ml.). Undissolved material (6·0 g.) was filtered off, and the filtrate evaporated at 20 mm., in a stream of dry air, to a syrup which crystallized largely on desiccation. After trituration with ether (25 ml.), the solid crystallized from ethyl acetate, to give 1,4-*di*-O-*methanesulphonylerythritol* (3·6 g.), tablets, m. p. 119—121°, raised by recrystallization to 123—124° (Found: C, 25·4; H, 4·8; S, 22·85. $C_6H_{14}O_8S_2$ requires C, 25·9; H, 5·1; S, 23·0%). Reacetylation of this product gave the diacetyl derivative m. p. 178—180° (decomp.); benzoylation gave 2,3-*di*-O-*benzoyl*-1,4-*di*-O-*methanesulphonylerythritol*, needles (from dioxan), m. p. 188—190° (Found: C, 49·1; H, 4·7; S, 13·15. $C_{20}H_{22}O_{10}S_2$ requires C, 49·4; H, 4·6; S, 13·2%).

(*c*) 2,3-Di-*O*-acetyl-1,4-dibromo-1,4-dideoxyerythritol [m. p. 140—142° (lit.,[25] m. p. 137°); prepared by acetylation of 1,4-dibromo-1,4-dideoxyerythritol [24]] (2·95 g.) was stirred under reflux for 15 hr. with silver methanesulphonate (3·6 g., 2 mol.) in benzene (50 ml.). The cooled mixture was filtered, and the residue extracted with boiling dioxan (200 ml.) to give the diacetyldimethanesulphonylerythritol (1·4 g.) previously obtained. Methanolysis of this product (2·7 g.) as before, gave recovered material (1·2 g.), and 1,4-di-*O*-methanesulphonylerythritol (0·7 g.), m. p. and mixed m. p. 124—125°.

1,4-*Di*-O-*acetylerythritol*.—A suspension of erythritol (5·0 g.) and triphenylmethyl chloride (25 g., 2 mol.) in pyridine (45 ml.) was stirred for 2 days and then treated with acetic anhydride (9·0 g., 2 mol.) in pyridine (17 ml.). After 2 days more, ice-water (300 ml.) was added, and the dried precipitate was crystallized by dissolution in hot chloroform and addition of ethanol, to give 2,3-di-*O*-acetyl-1,4-di-*O*-tritylerythritol (15 g.), prisms, m. p. 250—252°, unchanged on recrystallization from xylene (Found: C, 79·0; H, 5·9. Calc. for $C_{46}H_{42}O_6$: C, 80·0; H, 6·1%). The same product was obtained by acetylation of 1,4-di-*O*-tritylerythritol, m. p. 191—193° (lit.,[26] m. p. 182—184°). There was negligible uptake of hydrogen on attempted hydrogenolysis of the product in ethanol or dioxan, over platinum or palladium, under various conditions.

[24] Feit, *Chem. Ber.*, 1960, **83**, 116.
[25] Owen, *J.*, 1949, 241.
[26] Valentin, *Coll. Czech. Chem. Comm.*, 1931, **3**, 499.

The diacetylditritylerythritol (5·0 g.) was boiled under reflux for 30 min. with acetic acid (35 ml.) and water (7·0 ml.). The cooled solution was diluted with water (28 ml.), the precipitated triphenylmethanol (3·5 g., 1·85 mol.) collected, and the filtrate evaporated to an oil which crystallized in part. After 4 months, the solid was triturated with hexane and crystallized from ethyl acetate–hexane, to give 1,4-di-*O*-acetylerythritol (0·7 g.), blades, m. p. 92—94° (lit.,[27] m. p. 93—94°) (Found: C, 46·8; H, 6·9. Calc. for $C_8H_{14}O_6$: C, 46·6; H, 6·8%). Acetylation of this product gave tetra-*O*-acetylerythritol, m. p. and mixed m. p. 87—88°; methanesulphonylation gave 1,4-*di*-O-*acetyl*-2,3-*di*-O-*methanesulphonylerythritol*, rhombs (from ethanol–dioxan), m. p. 140—141° (Found: C, 33·4; H, 5·0; S, 18·4. $C_{10}H_{18}O_{10}S_2$ requires C, 33·1; H, 5·0; S, 17·7%).

2,3-*Di*-O-*acetyl*-1,4-*di*-O-*methanesulphonyl*-DL-*threitol*.—The reaction of 1,2:3,4-dianhydro-DL-threitol[28] (fractionally distilled; b. p. 146—146·5°/763 mm., n_D^{16} 1·4349) with methanesulphonic acid (2 mol.) in ether, as before, gave a syrup, from which no crystalline acetyl or benzoyl derivatives could be prepared. Treatment of D-threitol[29] in pyridine with methanesulphonyl chloride (2 mol.) and acetic anhydride (2 mol.), successively, gave a crystalline, but obviously heterogeneous, solid, m. p. 90—100° (Found: C, 31·8; H, 4·7; S, 19·2%), which could not be purified.

2,3-Di-*O*-acetyl-1,4-dibromo-1,4-dideoxy-DL-threitol [m. p. 98—102° (lit.,[30] m. p.s 96° and 100·5°) obtained by acetylation of the corresponding *threo*-dibromobutanediol, isolated from the mother-liquors of the preparation[24] of the *erythro*-isomer] (5·5 g.) was treated with silver methanesulphonate (2 mol.) in benzene, as before. The reaction mixture was filtered and the filtrate evaporated to an oil which was dissolved in methanol (8 ml.), filtered through charcoal, diluted with ether (25 ml.), and refrigerated, to give 2,3-*di*-O-*acetyl*-1,4-*di*-O-*methanesulphonyl*-DL-*threitol* (1·6 g.), plates, m. p. 85—88°, raised by recrystallization to 88—90° (Found: C, 33·0; H, 4·65; S, 18·1%). Methanolysis of this product gave an oil which, after prolonged desiccation, crystallised to give a 74% yield of 1,4-*di*-O-*methanesulphonyl*-DL-*threitol*, needles (from methanol–ether), m. p. 102—103° (Found: C, 26·0; H, 4·9; S, 22·0%). The *di*-O-*benzoyl* derivative formed needles (from ethanol–hexane), m. p. 114—116° (Found: C, 49·3; H, 5·0; S, 13·4%).

Partial Esterification of the Five-carbon Polyols.—2-Deoxy-D-ribitol, D-arabitol, ribitol, and xylitol were prepared by hydrogenation (Raney nickel in ethanol) of the corresponding aldoses; 2-*deoxy*-D-*ribitol*, reported[31] to be a syrup, formed plates (from acetone–methanol), m. p. 55—57°, $[\alpha]_D^{25}$ −21° (*c* 2 in water) (Found: C, 44·0; H, 9·0. $C_5H_{12}O_4$ requires C, 44·1; H, 8·9%). Treatment of each of these polyols with 2 mol. of methanesulphonyl chloride, and then with the requisite amount of acetic anhydride, gave uncrystallizable syrups in the cases of 2-deoxy-D-ribitol and xylitol, and gummy solids with D-arabitol and ribitol. Persistent recrystallization of these solids from ethyl acetate–hexane or methanol gave needles, melting over wide ranges about 100°, each decomposing slowly to an oil at room temperature (Found, for the products from D-arabitol and ribitol respectively: S, 17·4, 15·8. Calc. for $C_{13}H_{22}O_{12}S_2$: S, 14·8%).

The triacetyldimethanesulphonylarabitol (25 g.) (twice crystallized) was treated with methanolic hydrogen chloride, as above. The product was an oil which crystallized, in part, on long storage; this material was collected and recrystallized from ethyl acetate–hexane to give an *anhydrodi*-O-*methanesulphonyl*-D-*arabitol* (0·4 g.), plates, m. p. 102—103°, $[\alpha]_D^{25}$ +16° (*c* 2 in methanol) (Found: C, 28·95; H, 4·8; S, 21·4. $C_7H_{14}O_8S_2$ requires C, 28·95; H, 4·9; S, 22·1%). Neither the *O*-acetyl nor the *O*-benzoyl derivative of this product was obtained crystalline.

Methanolysis of the triacetyldimethanesulphonylribitol (8·2 g.) (twice crystallized) gave likewise an oil from which a crystalline *anhydrodi*-O-*methanesulphonylribitol* (0·5 g.) was isolated. This formed tablets (from methanol–ethyl acetate), m. p. 107—108° (Found: C, 28·8; H, 4·6; S, 21·6%), and gave an O-*benzoyl derivative*, rhombs (from ethyl acetate–hexane), m. p. 145—147° (Found: C, 42·3; H, 4·5; S, 15·6. $C_{14}H_{18}O_9S_2$ requires C, 42·6; H, 4·6; S, 16·3%).

Partial Methanesulphonation of 2,3-O-*Benzylidene*-D-*arabitol*.—A stirred, ice-cooled solution

[27] Raphael, *J.*, 1952, 401.
[28] Bose, Foster, and Stephens, *J.*, 1959, 3314.
[29] Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351.
[30] Beilstein's "Handbuch der organischen Chemie," Springer, Berlin, 1920, Vol. II, p. 143.
[31] David and Jaymond, *Bull. Soc. chim. France*, 1959, 157.

of 2,3-*O*-benzylidene-D-arabitol [9] (6·8 g.) in pyridine (40 ml.) was treated dropwise during 2 hr. with methanesulphonyl chloride (6·6 g., 2 mol.). After 2 hr. more, water (160 ml.) was added, the precipitated oil was separated by decantation and dissolved in chloroform, and the extract was washed successively with ice-cold water, N-hydrochloric acid, water, N-sodium carbonate, and water, then dried ($MgSO_4$) and evaporated. The residual oil failed to crystallize on prolonged desiccation but did so, slowly, when kept in an open vessel. The product was triturated with 2 : 1 ether–methanol (15 ml.), collected, and recrystallized from methanol–ethyl acetate, to give a *di*-O-*methanesulphonyl*-D-*arabitol* (1·7 g.), blades m. p. 114—116°, $[\alpha]_D^{25}$ +10° (*c* 2 in water) (Found: C, 27·3; H, 5·4; S, 20·6. $C_7H_{16}O_9S_2$ requires C, 27·3; H, 5·2; S, 20·8%), forming a *tri*-O-*acetyl derivative*, needles (from ethyl acetate–hexane), m. p. 95—96°, $[\alpha]_D^{25}$ +23° (*c* 2 in methanol) (Found: C, 36·0; H, 4·9; S, 14·6. $C_{13}H_{22}O_{12}S_2$ requires C, 35·9; H, 5·1; S, 14·8%).

In an effort to improve the yield of the dimethanesulphonylarabitol, a portion (5·0 g.) of the oily precursor was treated at 100° with 9N-acetic acid (30 ml.) and 10N-hydrochloric acid (1·0 ml.) for 30 min. The solution was concentrated to a syrup, which was dried by repeated evaporation with ethanol, followed by desiccation. The gummy solid so formed was triturated with 2 : 1 ether–methanol (15 ml.), collected, and recrystallized from methanol, to yield 2,5-*anhydro*-1,4-*di*-O-*methanesulphonyl*-D-*arabitol* (0·15 g.), blades, m. p. 153—154°, $[\alpha]_D^{25}$ +21° (*c* 2 in pyridine) (Found: C, 29·1; H, 4·9; S, 21·5%), giving an O-*acetyl derivative*, needles, m. p. 75—76° from ethyl acetate–hexane (Found: C, 32·45; H, 4·7; S, 18·95. $C_9H_{16}O_9S_2$ requires C, 32·5; H, 4·85; S, 19·3%).

Evaporation of the mother-liquors from the preparation of the anhydrodimethanesulphonylarabitol above, and acetylation of the residue, gave, as the only water-insoluble product, 2,3-*di*-O-*acetyl*-1,4,5-*tri*-O-*methanesulphonyl*-D-*arabitol* (0·25 g.), needles (from ethanol), m. p. 128—130°, $[\alpha]_D^{30}$ +5° (*c* 2 in pyridine) (Found: C, 30·6; H, 4·8; S, 19·9. $C_{12}H_{22}O_{13}S_3$ requires C, 30·6; H, 4·7; S, 20·4%).

Treatment of 2,3-*O*-benzylidene-D-arabitol (2·0 g.) in pyridine with methanesulphonyl chloride (3 mol.) gave a syrup, from which crystallized slowly the anhydrodi-*O*-methanesulphonyl-D-arabitol (0·3 g.), m. p. 153—154°, previously obtained. Acetylation of the uncrystallizable fraction gave the diacetyltrimethanesulphonyl derivative (2·2 g.), m. p. 128—130°.

1,6-*Di*-O-*methanesulphonyl*-D-*mannitol*.—(*a*) Reaction of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol (prepared from 1,6-dichloro-1,6-dideoxy-D-mannitol [13]) (3·7 g.) with methanesulphonic acid (2 mol.) in ether, as above, gave an oil which failed to crystallize on prolonged desiccation but did so rapidly when kept in an open vessel. Trituration with methanol–ether left a solid (1·5 g.; m. p. 127—130°) which, recrystallized from methanol, gave 1,6-*di*-O-*methanesulphonyl*-D-*mannitol*, blades, m. p. 134—135°, $[\alpha]_D^{25}$ +5·5° (*c* 2 in water) (Found: C, 28·3; H, 5·4; S, 19·0. $C_8H_{18}O_{10}S_2$ requires C, 28·4; H, 5·4; S, 18·95%). This product, soluble in 5 parts of water at 25°, consumed 1·96 mol. of 0·03M-sodium metaperiodate within 40 sec. The *tetra*-O-*acetyl derivative* formed prisms (from ethanol–butan-2-one), m. p. 163—164°, $[\alpha]_D^{25}$ +21° (*c* 2 in acetone) (Found: C, 37·75; H, 5·1; S, 12·4. $C_{16}H_{26}O_{14}S_2$ requires C, 37·9; H, 5·2; S, 12·7%), and the *tetra*-O-*benzoyl derivative*, plates (from ethanol–butan-2-one), m. p. 158—159°, $[\alpha]_D^{20}$ +31° (*c* 2 in acetone) (Found: C, 57·25; H, 4·7; S, 8·25. $C_{36}H_{34}O_{14}S_2$ requires C, 57·3; H, 4·55; S, 8·5%). In subsequent experiments, the dimethanesulphonylmannitol was consistently obtained in yields of up to 28% by aspirating moist air over the gummy product. Acetylation of the uncrystallizable residues from these preparations gave only traces of water-insoluble material.

(*b*) Methanesulphonation of 2,3:4,5-di-*O*-benzylidene-D-mannitol [14] gave 2,3:4,5-*di*-O-*benzylidene*-1,6-*di*-O-*methanesulphonyl*-D-*mannitol*, prisms (from ethanol), m. p. 134—135° (Found: C, 51·25; H, 5·25; S, 12·2. $C_{22}H_{26}O_{10}S_2$ requires C, 51·3; H, 5·1; S, 12·5%). This product (6·0 g.) was dissolved in an ice-cold mixture of acetic anhydride (250 ml.), acetic acid (200 ml.), and sulphuric acid (7 ml.), and left overnight at room temperature. The solution was poured into ice-water (1·7 kg.) and stirred at 3° for 3 hr., and the precipitate so formed was recrystallized from ethanol–butan-2-one, to give 2,3,4,5-tetra-*O*-acetyl-1,6-di-*O*-methanesulphonyl-D-mannitol (3·5 g.), identical with the product previously obtained. This compound (15 g.) was treated with methanolic hydrogen chloride as before; evaporation of the solvent left a solid, which was triturated with ethyl acetate, collected, and crystallized from methanol to give 1,6-di-*O*-methanesulphonyl-D-mannitol (6·9 g.). This material, and its tetra-acetyl and -benzoyl derivative, did not depress the m. p. of the corresponding products previously obtained.

(*c*) **2,3,4,5-*Tetra*-O-*acetyl*-1,6-*dideoxy*-1,6-*di-iodo*-D-*mannitol***, cubes (from hexane), m. p. 76—77°, $[\alpha]_D^{20}$ +24° (*c* 2 in methanol) (Found: C, 28·9; H, 3·5; I, 44·5. $C_{14}H_{20}I_2O_8$ requires C, 29·5; H, 3·5; I, 44·5%), was prepared by acetylation of 1,6-dideoxy-1,6-di-iodo-D-mannitol[13] or by the reaction of 1,6-dichloro-1,6-dideoxy-D-mannitol with sodium acetate and sodium iodide in boiling acetic anhydride. It (1·3 g.) was treated with silver methanesulphonate (2 mol.) in benzene, as above. Filtration of the mixture and extraction of the residue with ethyl acetate afforded 2,3,4,5-tetra-*O*-acetyl-1,6-di-*O*-methanesulphonyl-D-mannitol (0·11 g.), identical with the product previously obtained.

(*d*) A stirred suspension of D-mannitol (36 g.) in pyridine (200 ml.) was treated dropwise, at 3° during 2 hr., with methanesulphonyl chloride (48 g., 2·0 mol.). After a further 2 hr., a solution of acetic anhydride (84 g., 4 mol.) in pyridine (150 ml.) was added, as before, after which the mixture was left overnight at room temperature, then cooled once more to 3°. Water (22 g.) was added, the clear solution resulting was poured on ice (1·3 kg.), and the precipitate was crystallized, first from ethanol–butan-2-one, and then from ethyl acetate, to give crude 2,3,4,5-tetra-*O*-acetyl-1,6-di-*O*-methanesulphonyl-D-mannitol (26 g.). The m. p. of this product, 146—148°, {$[\alpha]_D^{25}$ +21° (*c* 2 in acetone) (Found: C, 36·6; H, 5·2; S, 15·4%)} was not raised significantly by further recrystallization. Methanolysis of this material (21 g.), in the usual way, gave a sticky solid which, after trituration with ethyl acetate (50 ml.) and recrystallization from methanol, gave pure 1,6-di-*O*-methanesulphonyl-D-mannitol (4·2 g.). The ethyl acetate washings slowly deposited a bulky water-insoluble solid, which recrystallized from ethanol to give a *tri*-O-*methanesulphonyl*-D-*mannitol* (1·3 g.), rosettes of needles, m. p. 134—136° (decomp.), raised by recrystallization to 143—144° (decomp.) (rapid heating), $[\alpha]_D^{25}$ +14° (*c* 2 in acetone) (Found: C, 26·1; H, 4·8; S, 22·7. $C_9H_{20}O_{12}S_3$ requires C, 25·95; H, 4·85; S, 23·1%). The *tri*-O-*acetyl derivative* formed prisms (from ethanol–butan-2-one), m. p. 147—148°, $[\alpha]_D^{25}$ +19° (*c* 2 in acetone) (Found: C, 33·15; H, 4·5; S, 17·6. $C_{15}H_{26}O_{15}S_3$ requires C, 33·2; H, 4·8; S, 17·7%). The triacetyltrimethanesulphonylmannitol (22 g.) was kept at 100° for 6 hr. with sodium iodide (18·5 g., 2 mol.) in acetone (125 ml.). The cooled mixture was filtered, and the residue washed with acetone and dried, to yield sodium methanesulphonate (8·9 g., 1·85 mol.). The total filtrate was evaporated, and the residue dissolved in chloroform, washed with aqueous thiosulphate to remove a trace of iodine, then with water, and dried ($MgSO_4$). Evaporation left an uncrystallizable syrup.

1,6-Di-*O*-methanesulphonyl-D-mannitol (5·0 g.) in pyridine (20 ml.) was treated at 3° with methanesulphonyl chloride (1·3 g., 0·8 mol.). After 4 hr. the mixture was poured into ice-water (150 ml.), but no trimethanesulphonylmannitol was precipitated, even on seeding and refrigeration. The solution was evaporated to a gum, which was freed from an excess of pyridine by further evaporation with water, and then taken up in ethyl acetate. The solution was washed with water, dried ($MgSO_4$), and evaporated to a syrup which crystallized in part on desiccation. Trituration with ethyl acetate, followed by recrystallization from ethanol, gave the trimethanesulphonylmannitol (0·16 g.) previously obtained.

1,6-Di-*O*-methanesulphonyl-L-mannitol, prepared as in (*d*) above from L-mannitol[32] (14% overall yield), had m. p. 133—134°, $[\alpha]_D^{25}$ −5·5° (*c* 2 in water). The racemic mixture of the D- and the L-derivative had m. p. 121—122°.

2,3,4,5-*Tetra*-O-*acetyl*-1,6-*di*-O-*methanesulphonyl*-D-*glucitol*.—2,4-*O*-Benzylidene-D-glucitol[16] (27 g.) in pyridine (100 ml.) was treated dropwise at 3° with methanesulphonyl chloride (23 g., 2 mol.) during 30 min. After a further 2 hr., ice-water (300 ml.) was added, and the precipitate so formed was collected, washed, dried, and recrystallized from ethanol–acetone, to give 2,4-O-*benzylidene*-1,6-*di*-O-*methanesulphonyl*-D-*glucitol* (19 g.), needles, m. p. 150—151°, $[\alpha]_D^{25}$ +16° (*c* 2 in acetone) (Found: C, 41·7; H, 5·2; S, 14·7. $C_{15}H_{22}O_{10}S_2$ requires C, 42·2; H, 5·2; S, 15·0%). The *di*-O-*acetyl derivative* formed rhombs (from ethanol–2-methoxyethanol), m. p. 142—143°, $[\alpha]_D^{25}$ −13° (*c* 2 in acetone) (Found: C, 45·15; H, 5·15; S, 12·3. $C_{19}H_{26}O_{12}S_2$ requires C, 44·7; H, 5·1; S, 12·6%).

An ice-cooled suspension of 2,4-*O*-benzylidene-1,6-di-*O*-methanesulphonyl-D-glucitol (36 g.) in acetic anhydride (550 ml.) and acetic acid (240 ml.) was treated dropwise during 45 min. with sulphuric acid (16 ml.). The clear solution so formed was kept at 3° for 1 hr. more, concentrated to half-volume (40 min. at 50°), cooled, and poured into ice-water (400 ml.). The stirred solution was kept at 3° for 15 hr. and the precipitate was recrystallized from methanol–ether, to give 2,3,4,5-*tetra*-O-*acetyl*-1,6-*di*-O-*methanesulphonyl*-D-*glucitol* (74 g.), needles, m. p.

[32] Kuhn and Klesse, *Chem. Ber.*, 1958, **91**, 1989.

99—100°, $[\alpha]_D^{25}$ +16° (*c* 2 in methanol) (Found: C, 38·3; H, 5·3; S, 12·2%). This compound decomposed slowly at room temperature, with loss of acetic acid.

Acetolysis, similarly, of the *di*-O-*methanesulphonyl derivative* of 2,4:3,5-di-*O*-benzylidene-D-glucitol [17] [felted needles from acetone, m. p. 174—175° (Found: C, 51·5; H, 5·55; S, 12·4%)] (11 g.) gave the same tetra-acetyldimethanesulphonylglucitol (6·7 g.). When the reaction mixture from such a run was added directly to water, without prior concentration to half-volume, the precipitated solid (1·5 g.) proved to be the diacetylbenzylidenedimethanesulphonylglucitol previously prepared from 2,4-*O*-benzylidene-D-glucitol. The tetra-acetyldimethanesulphonylglucitol was, however, isolated from the aqueous mother-liquor by neutralization with sodium hydrogen carbonate and ether-extraction.

2,3,4,5-*Tetra*-O-*acetyl*-1,6-*di*-O-*methanesulphonylgalactitol*.—The only identifiable product of the reaction of galactitol (36 g.) with methanesulphonyl chloride (2 mol.) and acetic anhydride (4 mol.), in the usual way, was hexa-*O*-acetylgalactitol (5·5 g.). Reaction of galactitol (11 g.) with methanesulphonyl chloride (2 mol.) gave unchanged galactitol (4 g.), and a *penta*-O-*methanesulphonyl*-DL-*galactitol* (1·6 g.), needles (from 2-methoxyethanol), m. p. 185—187° (decomp.) (Found: C, 22·9; H, 4·3; S, 27·5. $C_{11}H_{24}O_{16}S_5$ requires C, 23·05; H, 4·2; S, 28·0%). The use of tertiary bases other than pyridine in these reactions was equally unsuccessful. The required dimethanesulphonyltetra-acetylgalactitol was, however, prepared by the following methods:

(*a*) 2,3,4,5-Tetra-*O*-acetyl-1,6-dibromo-1,6-dideoxygalactitol (obtained [18] from hexa-*O*-acetyl-D-glucitol) (4·7 g.) was treated with silver methanesulphonate (2 mol.) in benzene, as above. Filtration of the mixture and extraction of the residue with boiling dioxan (200 ml.) afforded 2,3,4,5-*tetra*-O-*acetyl*-1,6-*di*-O-*methanesulphonylgalactitol* (1·2 g.), rhombs, m. p. 168—171° (decomp.) raised by recrystallization to 173—175° (decomp.) (Found: C, 38·1; H, 5·2; S, 12·6%).

(*b*) Condensation [19] of 1,6-di-*O*-benzoylgalactitol with benzaldehyde in the presence of hydrogen chloride or zinc chloride gave mixtures of the stereoisomeric dibenzoyldibenzylidenegalactitols, which were separated by fractional crystallization. From these, by successive debenzoylation and methanesulphonation, were prepared the stereoisomeric 2,3,4,5-*di*-O-*benzylidene*-1,6-*di*-O-*methanesulphonylgalactitols* [" Series I," needles (from ethanol), m. p. 144—145° (Found: C, 51·3; H, 5·05; S, 12·1. $C_{22}H_{26}O_{10}S_2$ requires C, 51·3; H, 5·1; S, 12·5%); " Series II," needles (from ethanol–dioxan), m. p. 152—153° (Found: C, 51·4; H, 5·0; S, 12·4%)]. Acetolysis of either of these compounds, as described for 2,3:4,5-di-*O*-benzylidene-1,6-di-*O*-methanesulphonyl-D-mannitol, gave almost quantitative yields of the tetra-acetyldimethanesulphonylgalactitol previously obtained.

(*c*) Tetra-*O*-acetylgalactaric acid (55 g.) was boiled under reflux for 4 hr. with thionyl chloride (290 g.) and pyridine (0·5 ml.). The solid which crystallized on cooling was collected, washed with ether, and dried, to give the acid chloride (50 g.), further purification of which was unnecessary. This product (16 g.) was added to a stirred suspension of 5% palladium–charcoal (4·0 g.) in boiling xylene (160 ml.). Hydrogen was passed over the surface of the mixture, and the effluent gas titrated with alkali, until, after 35 min., 2 mol. of hydrogen chloride had been liberated. The cooled mixture was filtered and the residue extracted with boiling ethyl acetate, to yield tetra-*O*-acetylgalactodiose (9·5 g.), plates, m. p. 175—177° (decomp.) (lit.,[20] m. p. 189°) (Found: C, 48·6; H, 5·3. Calc. for $C_{14}H_{18}O_{10}$: C, 48·6; H, 5·2%), giving a *bis*-2,4-*dinitrophenylhydrazone*, yellow needles (from dimethylformamide–ethanol), charring *ca.* 220° (Found: C, 44·5; H, 4·1; N, 15·9. $C_{26}H_{26}N_8O_{16}$ requires C, 44·2; H, 3·7; N, 15·9%).

The dialdehyde (25 g.) in ethanol (100 ml.) containing Raney nickel (7 g.) was hydrogenated at 45°/75 atm. during 15 hr. The mixture was treated with boiling ethanol (700 ml.) and filtered, and the solution refrigerated, to yield 2,3,4,5-*tetra*-O-*acetylgalactitol* (21 g.), plates, m. p. 169—170°, decomposing slowly at room temperature (Found: C, 48·2; H, 6·4. $C_{14}H_{22}O_{10}$ requires C, 48·0; H, 6·3%). Methanesulphonation of this product gave a quantitative yield of the tetra-acetyldimethanesulphonylgalactitol previously obtained.

The tetra-acetyldimethanesulphonylgalactitol was insoluble in methanolic or ethanolic hydrogen chloride, and was recovered unchanged after prolonged boiling. Dissolution could be effected, however, in mixtures containing dioxan but, then, the only product of the reaction was a dark oil.

Hydrolysis of the Di-isopropylidenedimethanesulphonylgalactitols.—The *di*-O-*methanesulphonyl derivative* of 2,3:4,5-di-*O*-isopropylidenegalactitol [21] [rhombs from ethanol–butan-2-one,

m. p. 153—154° (Found: C, 40·2; H, 6·1; S, 15·2. $C_{14}H_{26}O_{10}S_2$ requires C, 40·2; H, 6·1; S, 15·3%)] (14 g.) was heated at 100° with 80% acetic acid (400 ml.) till dissolution was complete (40 min.). The solution was concentrated to a syrup (30 min. at 45°) from which water (3 × 30 ml.) was further evaporated. The residue, after desiccation, solidified on trituration with ether, and was collected and crystallized from ethanol, to give a water-soluble product (5·0 g.), m. p. 125—128°. Recrystallization afforded an *anhydro*-O-*methanesulphonyl*-DL-*galactitol*, needles, m. p. 136—137° (Found: C, 34·8; H, 5·8; S, 12·9. $C_7H_{14}O_7S$ requires C, 34·7; H, 5·8; S, 13·2%), giving a *tri*-O-*benzoyl derivative*, needles (from ethanol–butan-2-one), m. p. 134—135° (Found: C, 60·5; H, 4·8; S, 5·4. $C_{28}H_{26}O_{10}S$ requires C, 60·6; H, 4·7; S, 5·8%).

Hydrolysis, likewise, of the *di*-O-*methanesulphonyl derivative* of 2,3:5,6-di-*O*-isopropylidene-DL-galactitol [21] [needles (from ethanol), m. p. 148—149° (Found: C, 39·8; H, 6·2; S, 14·9%)], gave 1,4-*di*-O-*methanesulphonyl*-DL-*galactitol* (3·3 g.), needles (from methanol–ether), m. p. 105—110° raised by recrystallization to 116—118° (Found: C, 28·6; H, 5·15; S, 18·7%). The *tetra*-O-*acetyl* derivative formed plates (from ethanol), m. p. 128—129° (Found: C, 37·8; H, 5·1; S, 12·6%).

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