602. *Ethylidene Derivatives of Mannitol.*

By E. J. Bourne, G. T. Bruce, and L. F. Wiggins.

Triethylidene D-mannitol, which was first reported by Meunier (*Compt. rend.*, 1889, **108**, 408), has now been hydrolysed to a diethylidene and a monoethylidene mannitol, which are proved conclusively to be, respectively, the 1 : 3-4 : 6- and the 1 : 3-derivative; thus the parent triacetal is 1 : 3-2 : 5-4 : 6-triethylidene D-mannitol.

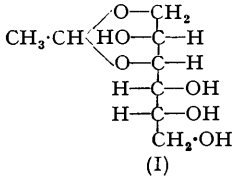
It is now some sixty years since Meunier (*Compt. rend.*, 1889, **108**, 408), and later Delépine (*ibid.*, 1900, **131**, 745), described the preparation of a crystalline triethylidene D-mannitol from D-mannitol and paraldehyde in the presence of a concentrated mineral acid (sulphuric, hydrochloric). In 1948, Bourne and Wiggins (*J.*, 1948, 1933) demonstrated that a crystalline triethylidene hexitol, obtained in small yield from commercial sorbitol and claimed by Appel (*J.*, 1935, 425) to be " triethylidene sorbitol," was in fact identical with Meunier's compound and gave D-mannitol hexa-acetate when hydrolysed and then acetylated. There has been, hitherto, no evidence upon which a structure could be assigned to this triacetal. As a part of our studies on the pattern of condensations between carbonyl compounds and polyhydric alcohols, we have proved that the ethylidene groups span the 1 : 3-, 2 : 5-, and 4 : 6-positions of the mannitol moiety.

Graded acidic hydrolysis of the triacetal afforded, in addition to unchanged starting material and D-mannitol, two new crystalline compounds, *viz.*, a di- and a mono-ethylidene D-mannitol. Treatment of each of these products with the appropriate reagents gave the original triethylidene D-mannitol, so that there was no doubt that they possessed the D-mannitol configuration.

The monoethylidene compound (m. p. 163·5—165°) was not the 3 : 4-ethylidene D-mannitol (m. p. 107—109°) prepared by Wiggins (*J.*, 1946, 384). Moreover, its crystalline tetrabenzoate was different from that produced when the well-characterised 1 : 2 : 5 : 6-tetrabenzoyl D-mannitol was treated with paraldehyde and hydrobromic acid.

The new monoethylidene D-mannitol was characterised almost completely by its behaviour towards glycol-splitting reagents. First, it consumed two molecular proportions of lead tetra-acetate in glacial acetic acid at room temperature, showing that the four free alcohol groups were present, either as two α-glycol groups or as a vicinal triol removed from the fourth hydroxy-group. This observation limited the structure for the acetal to five possibilities, *viz.*, the 1 : 3-, 1 : 4-, 1 : 5-, 2 : 3-, and 3 : 4-compounds; the configuration of mannitol is such that the first four of these are identical with the 4 : 6-, 3 : 6-, 2 : 6-, and 4 : 5-isomers, respectively. Secondly, oxidation with sodium metaperiodate at room temperature afforded one molecular proportion of formic acid and also of formaldehyde, the latter being isolated as its crystalline

dimedone derivative. Such a result was to be expected only from an ethylidene D-mannitol in which the 4 : 5 : 6-positions (the 1 : 2 : 3-positions are identical) were unsubstituted, leaving only the 1 : 3- (I) and the 2 : 3-derivative (II) for further consideration. The deductions thus far made were confirmed by the demonstration that the larger fragment of the oxidative cleavage analysed correctly for an ethylidene tetrose and gave D-erythrosazone on hydrolysis and treatment with phenylhydrazine.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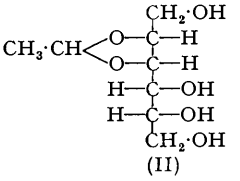
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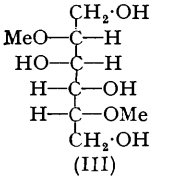
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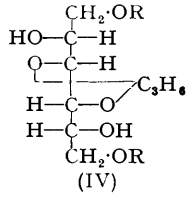
An indication that the ethylidene D-mannitol was in fact the 1 : 3-acetal was obtained when it was shown that its tetratoluene-*p*-sulphonate gave only 0·97 molecular proportions of sodium toluene-*p*-sulphonate when it was heated at 100—110° with sodium iodide in dry acetone. The isomeric ester of the 2 : 3-acetal should have given at least two molecular proportions of the sodium salt under these conditions. Since there is still some dubiety concerning the behaviour of vicinal toluene-*p*-sulphonate groups when submitted to the sodium iodide exchange reaction (for a summary see Bladon and Owen, *J.*, 1950, 598), we do not regard this evidence alone as conclusive. However, as will be shown later, only the 1 : 3-structure offered a satisfactory explanation of the conversion of the above-mentioned diethylidene D-mannitol into the monoacetal.

Attention was next turned to the diethylidene D-mannitol, in which the presence of two hydroxy-groups was confirmed by the isolation of a diacetate, a ditoluene-*p*-sulphonate, and a dimethyl ether, all crystalline. The diacetal did not react with lead tetra-acetate, showing that it was devoid of an α-glycol group, and its ditoluene-*p*-sulphonate was recovered unchanged after being heated at 100—105° with sodium iodide in acetone, indicating that the acetal groups probably engaged both of the primary alcohol groupings. Only the 1 : 3 : 5 : 6- and the 1 : 3 : 4 : 6-structure were consistent with this evidence (N.B. the 1 : 2 : 4 : 6-structure is identical with the former).

Hydrolysis of the dimethyl ether of the diethylidene D-mannitol afforded a syrupy dimethyl D-mannitol, which was purified *via* its crystalline tetra-acetate. The dimethyl mannitol was proved, by two independent routes, to carry its substituents at positions 2 and 5. First, the compound consumed one molecular proportion of sodium metaperiodate, without the concomitant liberation of either formaldehyde or formic acid; of all the possible dimethyl D-mannitols only the 2 : 5-derivative (III) should behave in this way. Secondly, the same crystalline tetra-acetyl dimethyl D-mannitol was synthesised by an alternative method, in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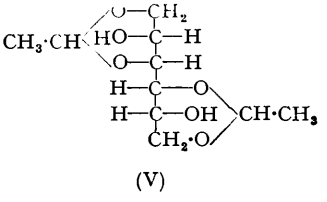
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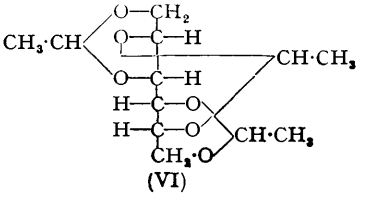
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which the parent compound was the well-known 3 : 4-*iso*propylidene D-mannitol (IV; R = H) (for proof of the structure see Müller, *Ber.*, 1932, **65**, 1055; Brigl and Grüner, *Ber.*, 1933, **66**, 931; Fischer and Appel, *Helv. Chim. Acta*, 1934, **17**, 1574). 3 : 4-*iso*Propylidene D-mannitol, when treated with 2 molecular proportions of triphenylmethyl chloride in pyridine (cf. Müller, *loc. cit.*), readily gave a dityrityl ether (IV; R = CPh_3), very probably the 1 : 6-derivative (cf. Helferich, *Adv. Carbohydrate Chem.*, 1948, **3**, 79). Methylation and subsequent hydrolysis then afforded syrupy 2 : 5-dimethyl D-mannitol (III). The behaviour of this towards sodium metaperiodate was identical with that of the dimethyl D-mannitol obtained from diethylidene mannitol, and its acetylation gave the crystalline tetra-acetyl dimethyl D-mannitol already described.

This evidence allows three possible structures for diethylidene D-mannitol, *viz.*, 1 : 3-4 : 6-, 1 : 4-3 : 6-, and 1 : 6-3 : 4-, of which the first is the most reasonable stereochemically. That

this is indeed the correct structure has been shown by careful hydrolysis of diethylidene mannitol to the monoethylidene mannitol, already proved to be either 1 : 3- or 2 : 3-ethylidene mannitol, probably the former. This transformation, therefore, proves not only that the diethylidene mannitol is 1 : 3-4 : 6-diethylidene D-mannitol (V), but also that the monoethylidene derivative is 1 : 3-ethylidene D-mannitol (I). Since each of these has been obtained by the hydrolysis of triethylidene mannitol, this compound must be 1 : 3-2 : 5-4 : 6-triethylidene D-mannitol (VI). Thus the condensations of mannitol with acetaldehyde and formaldehyde follow the same pattern inasmuch as each leads to the 1 : 3-2 : 5-4 : 6-derivative (cf. Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 2215). It is interesting, however, that, whereas the 2 : 5-ring is the least stable to acidic hydrolysis in the ethylidene compound, it is the most stable to acetolysis in the methylene derivative (cf. Ness, Hann, and Hudson, *loc. cit.*).

Experimental.

1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol from Mannitol.*—Triethylidene D-mannitol was prepared from commercial D-mannitol (200 g.) by Bourne and Wiggins's method (*loc. cit.*). The product (205 g., 71·8%) had m. p. 172°, $[\alpha]_D^{18}$ −72·4° (*c*, 2·37 in chloroform) [Found: C, 55·2; H, 7·8%; *M*, *ca.* 235 (Rast, in camphor). Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·7%; *M*, 260]. Meunier (*loc. cit.*) and Bourne and Wiggins (*loc. cit.*) gave m. p. 174° and 172°, respectively, for this compound. Ettel (*Coll. Czech. Chem. Comm.*, 1930, **2**, 457) recorded $[\alpha]_D^{20}$ −72·7° (*c*, 1·00 in chloroform).

Graded Hydrolysis of 1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol.*—Triethylidene D-mannitol (20·20 g.) was dissolved in a mixture of alcohol (2 l.) and water (100 c.c.) at 70°, cooled to 30° and, after the addition of 5N-hydrochloric acid (210 c.c.), was kept at 30° for 92 hours, before being neutralised with lead carbonate. The lead salts were removed by filtration at 0° and washed with cold 87% alcohol. The combined filtrate and washings were evaporated, leaving a white solid, which was extracted with water (4 × 100 c.c.). The insoluble residue (5·09 g., 25·2%) had m. p. 170—171°, alone and on admixture with the parent triethylidene D-mannitol. Evaporation of the aqueous extracts afforded a white solid (11·90 g.); this was heated under reflux with a mixture of chloroform (20 c.c.) and acetone (20 c.c.), a procedure which was repeated six times. The material which did not dissolve was exhaustively extracted with aqueous acetone (1% water by volume), leaving an insoluble residue from which D-mannitol hexa-acetate (2·10 g., 6·2%) was recovered after acetylation. The solute obtained from the aqueous acetone solution, when crystallised three times from acetone containing a trace of water, gave 1 : 3-*ethylidene* D-*mannitol* (2·09 g., 12·9%), m. p. 163·5—165° (depressed on admixture with D-mannitol), $[\alpha]_D^{19}$ −39·6° (*c*, 0·91 in water) (Found: C, 46·3; H, 7·7. $C_8H_{16}O_6$ requires C, 46·1; H, 7·7%).

The above chloroform–acetone extracts were evaporated and the residual white solid was washed with chloroform (25 c.c.), before being dissolved in acetone (60 c.c.) and introduced into a column of activated alumina, previously saturated with chloroform. After unsuccessful attempts had been made to elute the column with acetone, benzene, and chloroform, severally, eluate fractions showing strong negative rotations were obtained by use of alcohol. These fractions were combined and evaporated to a solid, which, when crystallised twice from absolute alcohol, gave 1 : 3-4 : 6-*diethylidene* D-*mannitol* (2·01 g., 11·1%), m. p. 185—186°, $[\alpha]_D^{14}$ −71·7° (*c*, 2·40 in acetone) (Found: C, 51·6; H, 7·4. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7%). A further quantity (1·8%) of this compound was recovered as its diacetate (m. p. 150—151°, see below) by evaporation of the above chloroform washings and acetylation of the residue.

1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol from* 1 : 3-4 : 6-*Diethylidene* D-*Mannitol.*—Diethylidene D-mannitol (0·050 g.), paraldehyde (0·15 c.c.), and hydrobromic acid (0·05 c.c.; *d* 1·46) were shaken together for 6 hours. A crystalline precipitate separated, and chloroform was added until this dissolved. The solution was washed with water, sodium hydrogen carbonate solution, and again with water. The extract was dried ($MgSO_4$), filtered, and evaporated to dryness. The residual solid was crystallised twice from alcohol, giving needles (0·027 g., 48·6%), $[\alpha]_D^{23}$ −72·8° (*c*, 0·41 in chloroform), m. p. 171—172° alone or on admixture with 1 : 3-2 : 5-4 : 6-triethylidene mannitol prepared directly from mannitol.

1 : 3-2 : 5-4 : 6-*Triethylidene* D-*Mannitol from* 1 : 3-*Ethylidene* D-*Mannitol.*—1 : 3-Ethylidene mannitol (0·082 g.), paraldehyde (1·0 c.c.), and concentrated hydrochloric acid (0·15 c.c.) were shaken together for 24 hours. The solid product was dissolved by addition of chloroform, and the chloroform layer was treated as above. The product (0·075 g., 73·2%) had m. p. 171—172°, alone or on admixture with 1 : 3-2 : 5-4 : 6-triethylidene mannitol prepared directly from mannitol.

2 : 4 : 5 : 6-*Tetrabenzoyl* 1 : 3-*Ethylidene* D-*Mannitol.*—1 : 3-Ethylidene mannitol (0·300 g.) was treated with benzoyl chloride (1·90 c.c.) in pyridine (12 c.c.) at 18° for 48 hours, before being poured into water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from aqueous alcohol. Two recrystallisations gave 2 : 4 : 5 : 6-*tetrabenzoyl* 1 : 3-*ethylidene* D-*mannitol* (0·650 g., 72·2%), m. p. 111—112°, $[\alpha]_D^{20}$ +12·8° (*c*, 0·78 in ethyl alcohol) (Found: C, 69·2; H, 5·3. $C_{36}H_{32}O_{10}$ requires C, 69·2; H, 5·2%).

1 : 2 : 5 : 6-*Tetrabenzoyl* 3 : 4-*Ethylidene* D-*Mannitol.*—1 : 2 : 5 : 6-Tetrabenzoyl D-mannitol (0·050 g.; m. p. 117—119°), prepared by Fischer's method (*Ber.*, 1915, **48**, 266), was shaken with paraldehyde (2·0 c.c.) and hydrobromic acid (0·4 c.c.; *d* 1·46) for 16 hours, before being poured into water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), filtered, and evaporated. The residual syrup, crystallised 3 times from aqueous alcohol, afforded 1 : 2 : 5 : 6-*tetrabenzoyl* 3 : 4-*ethylidene* D-*mannitol* (0·025 g., 47·9%), m. p. 98—99°,

depressed to 88° on admixture with 2 : 4 : 5 : 6-tetrabenzoyl 1 : 3-ethylidene D-mannitol (Found : C, 69·5; H, 5·3. $C_{36}H_{32}O_{10}$ requires C, 69·2; H, 5·2%).

2 : 4 : 5-*Triacetyl* 1 : 3-*Ethylidene* 6-*Toluene*-p-*sulphonyl* D-*Mannitol*.—1 : 3-Ethylidene mannitol (0·460 g.) was treated with toluene-*p*-sulphonyl chloride (0·421 g., 1 mol.) in pyridine (4·3 c.c.) at room temperature for 48 hours. Acetic anhydride (0·75 c.c.) was added, and the solution was kept at room temperature for another 48 hours, before being poured into water and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), filtered, and concentrated to a syrup, which crystallised from aqueous alcohol. After 3 more crystallisations, the *product* (0·392 g., 36·3%) showed m. p. 122·5—124·5°, $[\alpha]_D^{17}$ +9·5° (*c*, 1·37 in chloroform) (Found : C, 51·2; H, 5·9; S, 6·7. $C_{21}H_{28}O_{11}S$ requires C, 51·6; H, 5·8; S, 6·6%).

Reaction of 2 : 4 : 5-*Triacetyl* 1 : 3-*Ethylidene* 6-*Toluene*-p-*sulphonyl* D-*Mannitol with Sodium Iodide in Acetone*.—When the toluene-*p*-sulphonate (0·273 g.) and excess of sodium iodide were heated in dry acetone (10 c.c.), in a sealed tube, at 100° for 3 hours, sodium toluene-*p*-sulphonate (0·104 g., 95·9%) was precipitated.

1 : 3-*Ethylidene* 2 : 4 : 5 : 6-*Tetratoluene*-p-*sulphonyl* D-*Mannitol*.—Toluene-*p*-sulphonyl chloride (0·90 g., 4·3 mols.) was added to a solution of 1 : 3-ethylidene D-mannitol (0·230 g.) in pyridine (6·0 c.c.), and the mixture was kept at 20° for 48 hours. The syrup which formed when the mixture was poured into water was separated by decantation and dissolved in ether. The ethereal solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residual amorphous 1 : 3-*ethylidene* 2 : 4 : 5 : 6-*tetratoluene*-p-*sulphonyl* D-*mannitol* (0·172 g., 18·9%) was dried in a vacuum over phosphoric anhydride (Found : C, 52·7; H, 5·1; S, 15·3. $C_{36}H_{40}O_{14}S_4$ requires C, 52·4; H, 4·9; S, 15·5%). Extraction of the aqueous solution with chloroform afforded a white solid (0·259 g.) which appeared to be mainly tritoluene-*p*-sulphonyl derivatives.

Reaction of 1 : 3-*Ethylidene* 2 : 4 : 5 : 6-*Tetratoluene*-p-*sulphonyl* D-*Mannitol with Sodium Iodide in Acetone*.—The tetratoluene-*p*-sulphonate (0·0558 g.) and sodium iodide (0·205 g.) were heated in dry acetone (15 c.c.) (sealed tube) at 100—110° for 8 hours. The precipitated sodium toluene-*p*-sulphonate (0·0127 g.) represented an exchange of 0·97 ester group per molecule of the mannitol derivative.

Oxidation of 1 : 3-*Ethylidene* D-*Mannitol with Lead Tetra-acetate*.—When 1 : 3-ethylidene D-mannitol ($3·86 \times 10^{-4}$ mole) was oxidised with lead tetra-acetate in glacial acetic acid, according to the method of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667), the number of moles of oxidising agent consumed per mole of the ethylidene compound was 1·14 (30 mins.), 1·58 (60 mins.), 1·84 (120 mins.), and 1·97 (240 mins.).

Periodate Oxidation of 1 : 3-*Ethylidene* D-*Mannitol*.—(a) *Isolation of formaldehyde*. 1 : 3-Ethylidene D-mannitol ($1·01 \times 10^{-4}$ mole), oxidised under the conditions recommended by Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476), gave, per mole, 0·99 mole of formaldehyde, isolated as its dimedone derivative (m. p. 188°).

(b) *Determination of formic acid*. A solution of 1 : 3-ethylidene D-mannitol ($0·85 \times 10^{-4}$ mole) in water (30 c.c.) was treated with 0·25M-sodium metaperiodate (6 c.c.) at 20° (cf. Hirst and Jones, *J.*, 1949, 1659). At intervals, a portion (5 c.c.) of the solution was removed, and treated with excess of ethylene glycol (0·2 c.c.). Titration with 0·009N-sodium hydroxide, with methyl red as indicator, showed that the number of moles of formic acid liberated per mole of ethylidene mannitol was 1·00 (22 minutes), 0·99 (62 minutes), 1·01 (92 minutes), 1·00 (122 minutes), 1·01 (152 minutes), and 1·03 (895 minutes). The oxidation of ethylidene mannitol at 100° gave much higher yields of formic acid, presumably because the acidity produced during the reaction was sufficient, at the higher temperature, to cause hydrolysis of the acetal, so that, in the presence of excess of periodate, further oxidation ensued.

(c) *Isolation of* 2 : 4-*ethylidene* aldehydo-D-*erythrose*. A solution of sodium metaperiodate (0·98 g., 2·4 mols.) in water (13 c.c.) was added dropwise to an aqueous solution (1·5 c.c.) of 1 : 3-ethylidene D-mannitol (0·399 g.). After the mixture had been kept at 20° for 16 hours, it was neutralised with silver carbonate and filtered. The filtrate was treated with an aqueous solution of barium chloride to precipitate barium iodate and barium metaperiodate (cf. Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1663). After 44 hours the solution was filtered, and freeze-dried in the presence of barium carbonate (0·5 g.). The residue was extracted several times with boiling chloroform, and the solution was filtered and concentrated to a syrup, from which the last traces of solvent were removed at 40°/0·05 mm. The *product* (0·22 g., 78·6%), which restored the colour to decolorised magenta, had n_D^{21} 1·4853, $[\alpha]_D^{22}$ −12·8° (*c*, 4·08 in ethyl alcohol) (Found : C, 49·2; H, 7·0. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

(d) *Isolation of* D-*erythrose*. A suspension of 2 : 4-ethylidene *aldehydo*-D-erythrose (0·151 g.) in 0·5N-sulphuric acid (6 c.c.) was kept at 18° for 48 hours and then heated at 70° for 19 hours. The solution was neutralised with barium carbonate and filtered. The filtrate was decolorised with charcoal and evaporated to a syrup (0·102 g., 82·2%), which showed $[\alpha]_D^{15}$ (equilibrium) −17·0° (*c*, 3·39 in water), compared with the value $[\alpha]_D^{14·5}$ (equilibrium) −18·5° (*c*, 3·24 in water) reported for D-erythrose by Overend, Stacey, and Wiggins (*J.*, 1949, 1358). When the syrup (0·092 g.) was treated with phenylhydrazine, under the usual conditions, it gave D-erythrosazone (0·059 g., 25·8%), m. p. 161—163°. Felton and Freudenberg (*J. Amer. Chem. Soc.*, 1935, **57**, 1637) gave m. p. 160—163° for L-erythrosazone. For the D-isomer, Overend, Stacey, and Wiggins (*loc. cit.*) reported m. p. 160—162·5°.

2 : 5-*Diacetyl* 1 : 3-4 : 6-*Diethylidene* D-*Mannitol*.—Diethylidene mannitol (2·20 g.) was treated with acetic anhydride (8·9 c.c.) in pyridine (35 c.c.) for 48 hours at 18°. The white solid, which separated when the solution was poured into water, was removed by filtration. Recrystallised twice from aqueous alcohol, the *acetate* (1·06 g., 35·5%) had m. p. 150—151°, $[\alpha]_D^{20}$ −87·1° (*c*, 0·62 in acetone) (Found : C, 52·8; H, 6·9; Ac, 26·6. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0; Ac, 27·0%). A further quantity (0·28 g., 9·4%) of the product was recovered from the aqueous filtrate by extraction with chloroform.

1 : 3-4 : 6-*Diethylidene* 2 : 5-*Ditoluene*-p-*sulphonyl* D-*Mannitol*.—Diethylidene mannitol (1·272 g.) was treated with toluene-*p*-sulphonyl chloride (2·277 g., 2·2 mols.) in pyridine (10 c.c.) at 20° for 74 hours, before being poured into ice-water (40 c.c.) and extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$), filtered, and concentrated to a syrup, which crystallised readily from absolute alcohol. After three more crystallisations, the *product* (1·659 g., 56·3%) had m. p. 134—135°, $[\alpha]_D^{22}$ −73·0° (*c*, 0·89 in chloroform) (Found: C, 52·9; H, 5·7; S, 11·7. $C_{24}H_{30}O_{10}S_2$ requires C, 53·1; H, 5·6; S, 11·8%).

Treatment of 1 : 3-4 : 6-*Diethylidene* 2 : 5-*Ditoluene*-p-*sulphonyl* D-*Mannitol with Sodium Iodide in Acetone*.—A solution of the ditoluene-*p*-sulphonate (0·178 g.) and sodium iodide (0·50 g.) in dry acetone was heated in a sealed tube at 100—105° for 6 hours. Sodium toluene-*p*-sulphonate was not deposited. The solution was evaporated, and the residue was extracted with chloroform. The extract was washed with sodium thiosulphate solution and then with water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from absolute alcohol, to give diethylidene ditoluene-*p*-sulphonyl mannitol (0·130 g., 73·0%), m. p. 132—133°, alone and on admixture with the starting material.

Treatment of 1 : 3-4 : 6-*Diethylidene* D-*Mannitol with Lead Tetra-acetate*.—Diethylidene mannitol ($1·09 \times 10^{-4}$ mole), treated according to the procedure of Hockett and McClenahan (*loc. cit.*), consumed no lead tetra-acetate during several hours.

1 : 3-4 : 6-*Diethylidene* 2 : 5-*Dimethyl* D-*Mannitol*.—Diethylidene mannitol (0·775 g.), methyl iodide (5 c.c.), and acetone (5 c.c.) were heated under reflux with silver oxide (3 g.) for 40 hours. The solvents were removed by distillation under diminished pressure and the residue was exhaustively extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and concentrated to a syrup, which was re-treated with methyl iodide (5 c.c.) and silver oxide (3 g.), and the syrupy product isolated as before. Crystallised twice from light petroleum (b. p. 60—80°), it gave prisms of 1 : 3-4 : 6-*diethylidene* 2 : 5-*dimethyl* D-*mannitol* (0·650 g., 74·9%), m. p. 74—75°, $[\alpha]_D^{18}$ −78·3° (*c*, 2·48 in chloroform) (Found: C, 55·0; H, 8·5; OMe, 24·0. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·5; OMe, 23·7%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Dimethyl* D-*Mannitol from* 1 : 3-4 : 6-*Diethylidene* 2 : 5-*Dimethyl* D-*Mannitol*.—Diethylidene dimethyl mannitol (0·453 g.) was stirred at 100° with 1·8N-sulphuric acid until dissolution was complete and a constant optical rotation was achieved. The solution was neutralised with barium carbonate, and the insoluble barium salts were removed by filtration. The filtrate was combined with an acetone extract, obtained by continuous extraction of the barium salts, and the solution was evaporated to a syrup, which was extracted several times with boiling absolute methyl alcohol. Evaporation of the combined extracts, and removal of all residual solvent at 60°/0·05 mm., gave syrupy 2 : 5-*dimethyl* D-*mannitol* (0·355 g., 97·8%) which could not be crystallised.

The syrup (0·350 g.) was dissolved in acetic anhydride (2·55 c.c.), fused sodium acetate (0·34 g.) was added, and the mixture was heated under reflux for 1·75 hours, before being poured into water and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), filtered, and concentrated to a syrup. After being decolorised with charcoal, the syrup was crystallised twice from alcohol, giving 1 : 3 : 4 : 6-*tetra-acetyl* 2 : 5-*dimethyl* D-*mannitol* (0·361 g., 57·3%), m. p. 107—108°, $[\alpha]_D^{23}$ +39·5° (*c*, 2·30 in methyl alcohol) (Found: C, 50·8; H, 6·9; OMe, 16·7; Ac, 45·8. $C_{16}H_{26}O_{10}$ requires C, 50·8; H, 6·9; OMe, 16·4; Ac, 45·5%).

2 : 5-*Diacetyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—3 : 4-*iso*Propylidene D-mannitol (2·50 g.) was treated with triphenylmethyl chloride (6·27 g., 2 mols.) in pyridine (15 c.c.) at 20° for 62 hours. Acetic anhydride (10 c.c.) was added, and the mixture was then kept at the same temperature for 72 hours (cf. Müller, *loc. cit.*), before being poured into water and extracted with chloroform. The extracts were washed with dilute acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$), filtered, and concentrated. The residual syrup, crystallised once from absolute alcohol, and three times from methyl alcohol–acetone, afforded 2 : 5-diacetyl 3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol (4·47 g., 50·2%), m. p. 146—147°, $[\alpha]_D^{18}$ −2·5° (*c*, 6·74 in chloroform) (Found: C, 77·3; H, 6·5; Ac, 11·3. Calc. for $C_{51}H_{50}O_8$: C, 77·4; H, 6·4; Ac, 10·9%). Müller (*loc. cit.*) gave m. p. 143° and stated that the compound was optically inactive.

3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—A solution of diacetyl *iso*propylidene ditrityl mannitol (2·478 g.) in absolute methyl alcohol (250 c.c.) containing a trace of sodium was kept at 20° for 48 hours. The solvent was removed by distillation, and a portion (0·100 g.) of the white residue (2·196 g.) was crystallised twice from absolute alcohol, giving 3 : 4-iso*propylidene* 1 : 6-*dirityl* D-*mannitol* (0·079 g., 78·3%), m. p. 169·5—171°, $[\alpha]_D^{20}$ +15·5° (*c*, 1·03 in chloroform) (Found: C, 79·6; H, 6·3. $C_{47}H_{46}O_6$ requires C, 79·9; H, 6·6%).

2 : 5-*Dimethyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—The residue (2·090 g.) containing 3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol was dissolved in methyl iodide (14 c.c.), and silver oxide (9 g.) was added. The mixture was heated under reflux for 12 hours. Chloroform was added, and the solid was removed by filtration before being extracted several times with boiling chloroform. The filtered extracts were combined, dried ($MgSO_4$), filtered, and evaporated. The residue (2·049 g.) was submitted to two more treatments with the methylating reagents and isolated as before. The product, crystallised twice from chloroform–light petroleum (b. p. 60—80°), gave 2 : 5-*dimethyl* 3 : 4-iso*propylidene* 1 : 6-*dirityl* D-*mannitol* (1·765 g., 81·2%), m. p. 235—236°, $[\alpha]_D^{19}$ +9·5° (*c*, 8·53 in chloroform) (Found: OMe, 8·2. $C_{49}H_{50}O_6$ requires OMe, 8·4%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Dimethyl* D-*Mannitol from* 2 : 5-*Dimethyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* D-*Mannitol*.—2 : 5-Dimethyl 3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol (1·500 g.) was dissolved in a mixture of dioxan (50 c.c.) and alcohol (10 c.c.) and, after the addition of 10N-hydrochloric acid (10 c.c.), the solution was heated on a boiling water-bath for 8 hours, the optical rotation then being constant. The cooled solution was neutralised with silver carbonate (15 g.) and filtered. The insoluble

salts were washed with dioxan, and the combined filtrate and washings were evaporated, leaving a solid residue, which was extracted several times with hot water. The filtered extracts were treated with hydrogen sulphide, concentrated to a small volume (5 c.c.), and filtered to remove traces of coagulated silver sulphide. The solution was freed from ionic material by a method similar to that of Consden, Gordon, and Martin (*Biochem. J.*, 1947, **41**, 590) and evaporated to a syrup (0·176 g., 41·0%), which could not be crystallised.

The syrup (0·170 g.) was heated under reflux with acetic anhydride (1·55 c.c.) and fused sodium acetate (0·21 g.) for 2 hours, before being poured into excess of sodium hydrogen carbonate solution and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from aqueous alcohol. Three more crystallisations gave 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-dimethyl D-mannitol (0·123 g., 40·2%), m. p. 107—108° alone or on admixture with the specimen mentioned above, $[\alpha]_D^{18}$ +39·9° (*c*, 2·86 in methyl alcohol) (Found : C, 50·9; H, 7·2. $C_{16}H_{26}O_{10}$ requires C, 50·8; H, 6·9%).

2 : 5-*Dimethyl* D-*Mannitol from* 1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Dimethyl* D-*Mannitol*.—1 : 3 : 4 : 6-Tetra-acetyl 2 : 5-dimethyl mannitol (0·062 g.), derived from 2 : 5-dimethyl 3 : 4-*iso*propylidene 1 : 6-ditrityl D-mannitol, was deacetylated, with a trace of sodium in absolute methyl alcohol (5 c.c.), at 18° for 38 hours, and the solution was evaporated. The residual syrup was dissolved in water, and, after the solution had been " desalted " by the method previously described (cf. Consden, Gordon, and Martin, *loc. cit.*), it was evaporated to a syrup (0·034 g., 98·7%), showing $[\alpha]_D^{17}$ −16·2° (*c*, 0·68 in water) (sample A).

In the same way the other specimen of 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-dimethyl D-mannitol (0·231 g.), prepared from 1 : 3-4 : 6-diethylidene 2 : 5-dimethyl D-mannitol, was converted into syrupy 2 : 5-dimethyl D-mannitol (0·123 g., 95·9%), having $[\alpha]_D^{20}$ −15·9° (*c*, 1·39 in water) (sample B).

Periodate Oxidation of 2 : 5-*Dimethyl* D-*Mannitol*.—(a) *Quantity of oxidising agent consumed.* 2 : 5-Dimethyl mannitol (sample A, $1·24 \times 10^{-4}$ mole) was dissolved in water (5 c.c.) and 0·30M-sodium metaperiodate (5 c.c.) was added. The solution was diluted to 50 c.c. and kept at 18°. At intervals, portions (2 c.c.) of the solution were removed, and the residual periodate was estimated by adding solutions of sodium hydrogen carbonate and excess of potassium iodide and titrating the liberated iodine with 0·005N-arsenious oxide, starch being used as the indicator (cf. Jackson, *Organic Reactions*, 1944, **2**, 358, 360; Müller and Friedberger, *Ber.*, 1902, **35**, 2652). The number of moles of oxidising agent consumed by each mole of the mannitol derivative was 1·08 (10 mins.), 1·07 (30 mins.), 1·06 (120 mins.), and 1·10 (960 mins.).

In the same way, it was shown that the number of moles of periodate consumed by the other sample (B) of 2 : 5-dimethyl D-mannitol was 0·92 (15 mins.), 0·94 (30 mins.), 1·01 (120 mins.), and 1·14 (540 mins.).

(b) *Production of formaldehyde.* Each of the samples (A and B) of 2 : 5-dimethyl D-mannitol was oxidised with periodic acid and treated with dimedone, under the conditions recommended by Reeves (*loc. cit.*); in neither case could formaldehyde be detected.

(c) *Production of formic acid.* To 2 : 5-dimethyl D-mannitol (sample A; $6·33 \times 10^{-5}$ mole) in water (31 c.c.), 0·30M-sodium metaperiodate (5 c.c.) was added and the mixture was kept at 20° (cf. Hirst and Jones, *loc. cit.*). At intervals, portions (5 c.c.) of the solution were removed, mixed with ethylene glycol (0·2 c.c.), and titrated with 0·010N-sodium hydroxide, methyl-red being used as the indicator. No formic acid was produced for, even after 21 hours, the slightly acid solution required the same quantity of alkali for neutralisation as did a control containing the same components except the mannitol derivative.

A similar result was obtained with the other sample (B) of dimethyl D-mannitol.

1 : 3-*Ethylidene* D-*Mannitol from* 1 : 3-4 : 6-*Diethylidene* D-*Mannitol*.—Diethylidene mannitol (0·472 g.) was dissolved in a mixture of alcohol (38 c.c.) and water (2 c.c.) at 70°. The solution was cooled, and, after 5N-hydrochloric acid (5·5 c.c.) had been added, it was heated at 65° for 35 minutes. The acid was neutralised with lead carbonate; the lead salts were removed by filtration at 0° and washed with cold aqueous alcohol. The filtrate and washings were combined, and evaporated to a white solid, which was heated under reflux with a mixture of chloroform (3 c.c.) and acetone (3 c.c.) for 1 hour. After the extraction had been repeated twice, the filtered extracts were combined and evaporated. The solid residue was heated with boiling chloroform (5 c.c.) for 3 hours; the undissolved material was removed by filtration, and crystallised from absolute alcohol. Recrystallisation from absolute alcohol gave 1 : 3-ethylidene D-mannitol (0·050 g., 11·9%), m. p. 161—162° not depressed on admixture with the monoethylidene mannitol mentioned above.

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