Dithiols. Part XV. Some Polyhydroxy-derivatives of 3 : 4-Dimercaptobutanol.*

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3 : 4-Dimercaptobutyl β-D-glucoside and D-mannitol 1- and D-glucitol 6-(3 : 4-dimercaptobutyl) ether have been synthesised as their fully acetylated derivatives; there is evidence for partial cyclisation during deacetylation. The secondary ether linkage in the 3-(but-3-en-1-yl) ether of D-mannitol is very readily cleaved by aqueous acid; the isomeric primary 1-ether also undergoes fission, though more slowly.

DURING deacetylation of the acetylated glucoside and hexitol ethers of 2 : 3-dimercaptopropanol (" BAL "), cyclisation between one of the thiol groups and a hydroxy-group in the polyhydroxy-portion may occur to a small extent; the smallest possible ring for such an intramolecular cyclic sulphide would be six-membered (see Harding and Owen, *J.*, 1954, 1536). Interposition of an extra methylene group in an appropriate position would make the smallest possible ring seven-membered, and cyclisation might therefore occur less readily. It was with this possibility in mind that the derivatives of 3 : 4-dimercaptobutanol, described below, were prepared. The methods were essentially similar to those used for the corresponding 2 : 3-dimercaptopropyl compounds (Evans and Owen, *J.*, 1949, 244; Bladon and Owen, *J.*, 1950, 591).

Interaction of acetobromoglucose and but-3-en-1-ol (conveniently prepared by semi-hydrogenation of but-3-yn-1-ol) gave but-3-en-1-yl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (I), which with bromine furnished the 3 : 4-dibromobutyl compound (II); this, on reaction with potassium thiolacetate, gave 3 : 4-bisacetylthiobutyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (III).

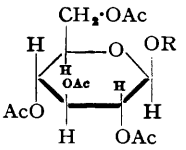
Ring fission of 5 : 6-anhydro-1 : 2-3 : 4-di-*O-iso*propylidene-D-mannitol with but-3-en-1-ol in the presence of its sodium derivative gave the 6-(but-3-en-1-yl) ether (IV). This was hydrolysed to crystalline 1-*O*-(but-3-en-1-yl)-D-mannitol, which was converted into the solid penta-acetate (V). Treatment with bromine then gave a semi-solid product from which a crystalline dibromide (VI) was separated; this was probably one stereochemically pure form of the two possible diastereoisomeric dibromides which arise because of the introduction of a new centre of asymmetry at this stage. The liquid residue on fractional distillation gave some oily dibromide, together with an unexpected crystalline bromine-free product which was identified as hexa-*O*-acetylmannitol; this probably arose by slight fission, at an earlier stage, of the butenyl ether linkage (see below). Reaction of the crystalline dibromide (VI) with potassium thiolacetate gave 1 : 2 : 3 : 4 : 5-penta-*O*-acetyl-6-*O*-(3 : 4-bisacetylthiobutyl)-D-mannitol (VII).

The stereoisomeric sorbitol compound (VIII) was obtained by a similar series of reactions from 5 : 6-anhydro-1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol. In this series no crystalline products were isolated with the exception of a by-product, $C_{24}H_{40}O_{11}$, which accompanied the 6-*O*-(but-3-en-1-yl)-1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol and was probably the intermolecular ether (IX) formed by further reaction between the anhydro-compound and the free 5-hydroxyl group in the main product.

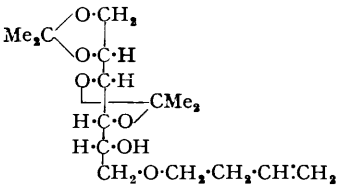
3-*O*-(But-3-en-1-yl)-1 : 2-5 : 6-di-*O-iso*propylidene-D-mannitol was prepared by mono-etherification of 1 : 2-5 : 6-di-*O-iso*propylidene-D-mannitol with but-3-en-1-yl bromide and sodium hydroxide in aqueous dioxan. When this was subjected to acid hydrolysis to remove the *iso*propylidene residues, under conditions similar to those used in the preparation 3-*O*-allyl-D-mannitol (Bladon and Owen, *loc. cit.*), the main product was mannitol, and to obtain the desired 3-*O*-(but-3-en-1-yl)-D-mannitol it was necessary to hydrolyse the di*iso*propylidene compound by much milder treatment; this remarkable sensitivity of the butenyl group is discussed further on p. 1294. When the crystalline 3-butenyl ether was acetylated it gave a liquid penta-acetate which probably contained a small proportion of

* Part XIV, Harding and Owen, *J.*, 1954, 1536.

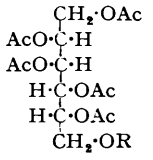
hexa-*O*-acetylmannitol, since it did not take up the theoretical amount of bromine and the crude dibromide on distillation gave some lower-boiling material from which hexa-*O*-acetylmannitol was isolated. It seems likely, therefore, that slight fission of the butenyl ether linkage occurs even during acetylation, though it was not possible to isolate any of the hexa-acetyl compound at that stage owing to an insufficient difference between its boiling point and that of the penta-acetyl ether; after bromination, the difference was enough for some separation to be possible. Owing to the small amount of pure dibromide which was now available, only an impure thiolacetate was obtained in this series.



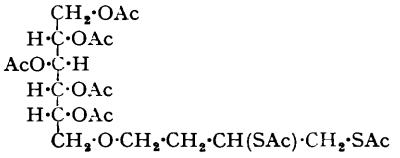
(I; R = $-CH_2\cdot CH_2\cdot CH{:}CH_2$)
(II; R = $-CH_2\cdot CH_2\cdot CHBr\cdot CH_2Br$)
[III; R = $-CH_2\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot SAc$]



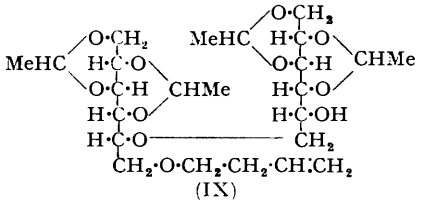
(IV)



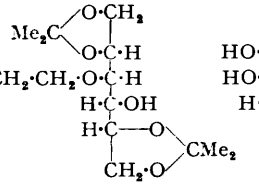
(V; R = $-CH_2\cdot CH_2\cdot CH{:}CH_2$)
(VI; R = $-CH_2\cdot CH_2\cdot CHBr\cdot CH_2Br$)
[VII; R = $-CH_2\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot SAc$]



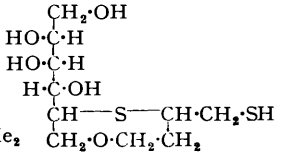
(VIII)



(IX)



(X)



(XI)

Deacetylation of the acetylthio-compounds (III), (VII), and (VIII) was carried out by the usual method with methanolic barium methoxide, which also precipitates the liberated dithiol as the barium salt. Previous experience has shown that owing to their extreme sensitivity towards oxidation, particularly when in contact with solvent, complete purification of these salts is impracticable. The crude material, however, is stable when thoroughly dried, and aqueous solutions for pharmacological tests can conveniently be prepared by precipitation of barium as sulphate and determination of thiol content in the buffered filtrate by titration with iodine. The quality of the salt is most usefully assessed by the ratio of thiol-sulphur to total sulphur, any deficiency from unity being a measure of the amount of cyclisation or of oxidation. The ratio 0·79 for barium salt derived from the glucoside (III) was about the same as that observed in many preparations of its lower homologue, though when the highly purified crystalline hexa-acetyl derivative was used, as a control, the derived barium salt of BAL-glucoside showed a ratio of 0·89. The barium salt from the mannitol ether (VII) was of much better quality (ratio, 0·89) than that (ratio, 0·46) from the stereoisomeric sorbitol compound, probably because the former ether (VII) was prepared from a crystalline dibromide, whereas in the sorbitol series all the intermediates were high-boiling viscous liquids which could not be rigorously purified. Pharmacological tests, kindly carried out by Dr. K. Adam, on the *O*-glucoside of 3 : 4-dimercaptobutanol prepared from the above barium salt showed its therapeutic efficiency against arsenical poisoning to be slightly less than that of BAL-glucoside.

Deacetylation of the ether (VII) was also studied under acid conditions but, although 86% of the theoretical thiol value was attained in boiling methanolic hydrogen chloride, the material obtained on evaporation of the solution contained less than half its total sulphur as free thiol; it afforded a crystalline substance which from the analytical data was probably an anhydro-derivative involving one of the sulphur atoms, such as (XI). Abnormal results of deacetylation under acidic conditions have been encountered before, and were tentatively attributed to the formation of cyclic sulphides (Miles and Owen, *J.*, 1952, 817).

The unexpected fission of the butenyl ether linkage in the hydrolysis of (X) was confirmed by conversion of 3-*O*-(but-3-en-1-yl)-D-mannitol with hot dilute sulphuric acid into mannitol. The other products included butadiene and an unsaturated alcohol which was not but-3-en-1-ol since it gave a strongly positive iodoform test; it was possibly the rearranged product, but-1-en-3-ol, but the quantity available was insufficient for purification. Control experiments showed that but-3-en-1-ol was neither isomerised nor converted into butadiene under the conditions used; the fission therefore does not involve simple hydrolysis. Prolonged treatment of the 6-*O*-(but-3-en-1-yl) ether (IV) with hot aqueous sulphuric acid also gave some mannitol and butadiene, but the primary ether linkage was markedly more stable than the secondary. Fission has also been observed in the simple analogue, 2-hydroxyethyl but-3-en-1-yl ether (unpublished experiments by Mr. M. H. Benn). The lability does not extend to but-3-en-1-yl β-D-glucoside, which underwent acid hydrolysis at a rate not significantly different from that of allyl β-D-glucoside.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°, unless otherwise stated.

But-3-yn-1-ol, b. p. 60—61°, n_D^{21} 1·4403, was prepared by Kreimeier's method (U.S.P. 2,106,182; *Chem. Abstr.*, 1938, **32**, 2547). The 3 : 5-*dinitrobenzoate*, needles from methanol, had m. p. 58° (Found : N, 10·8. $C_{11}H_8O_6N_2$ requires N, 10·6%).

But-3-en-1-ol.—A mixture of but-3-yn-1-ol (249 g.), ethanol (1 l.), and 2·5% palladium–charcoal (20 g.) was shaken in hydrogen at room temperature and pressure. The absorption of hydrogen was regulated occasionally to allow the solution to cool, and was stopped when almost the theoretical quantity (*ca.* 80 l.) had been absorbed (6 hr.). From the filtered solution, most of the ethanol was distilled off through a Lessing column, and the residue was then fractionated through a 30 × 2 cm. Fenske column to give a main fraction (154 g.), b. p. 110—114°. Redistillation gave pure but-3-en-1-ol, b. p. 113—114°, n_D^{21} 1·4206. The 3 : 5-*dinitrobenzoate* formed pale yellow leaflets (from methanol), m. p. 45—47° (Found : C, 49·3; H, 3·8; N, 10·6. $C_{11}H_{10}O_6N_2$ requires C, 49·6; H, 3·8; N, 10·5%). The α-*naphthylurethane*, prepared in boiling ligroin (b. p. 100—120°), crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 78° (Found : C, 75·0; H, 6·5; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

But-3-en-1-yl Bromide.—This was prepared by Linstead and Rydon's method (*J.*, 1934, 1995); redistillation of the fraction, b. p. 97—101°, gave the pure bromide (44 g., 66%), b. p. 99°, n_D^{22} 1·4625. Juvala (*Ber.*, 1930, **63**, 1989) recorded b. p. 98·5—99°, n_D^{20} 1·4621; Birch and McAllan (*J.*, 1951, 2556) give n_D^{20} 1·4575.

But-3-en-1-yl 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside.*—A mixture of acetobromoglucose (82 g.), silver carbonate (35 g.), anhydrous sodium sulphate (25 g.), glass beads (50 g.) and dry benzene (150 c.c.) was vigorously stirred during the addition (15 min.) of but-3-en-1-ol (17·3 g.), and thereafter for 2 hr. at room temperature, 3 hr. at 60°, and 30 min. on the steam-bath under reflux. Salts were then filtered off, and the benzene was removed from the filtrate under reduced pressure to give a syrup, which partly crystallised at 0°. After trituration with ethanol (10 c.c.), the solid was collected and washed with ethanol–light petroleum (1 : 1); a second crop was obtained by the addition of the same mixed solvent to the mother-liquor. The *tetra*-O-*acetyl*-β-*glucoside* (23 g.) crystallised from this solvent in thick prisms, m. p. 80°, $[\alpha]_D^{20}$ −23·4° (*c*, 4·0 in $CHCl_3$) (Found : C, 53·8; H, 6·6. $C_{18}H_{26}O_{20}$ requires C, 53·7; H, 6·5%).

3 : 4-*Dibromobutyl* 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside.*—To the butenyl tetra-acetyl-β-glucoside (13 g.) in carbon tetrachloride (150 c.c.), bromine (5·2 g.) in carbon tetrachloride (50 c.c.) was added during 2 hr.; the pale yellow solution was then evaporated under reduced

pressure and the residual oily *dibromide* (17·5 g.) finally dried at 50°/0·0001 mm. (Found: Br, 28·8. $C_{18}H_{26}O_{10}Br_2$ requires Br, 28·4%).

3 : 4-*Bisacetylthiobutyl* 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside*.—The above dibromide (17·5 g.), potassium thiolacetate (8·2 g.), ethanol (110 c.c.), and thiolacetic acid (0·2 c.c.) were heated and stirred under reflux on the steam-bath under nitrogen for 6 hr. The solution was cooled, filtered from potassium bromide, concentrated to small volume, and then diluted with water (500 c.c.). Extraction with ether gave the *bisthiolacetate* (15·9 g.) as a viscous brown syrup, n_D^{19} 1·4962, $[\alpha]_D^{21}$ −17·2° (*c*, 3·0 in $CHCl_3$) (Found: C, 47·2; H, 6·0; S, 10·9; Ac, 44·2. $C_{22}H_{32}O_{12}S_2$ requires C, 47·8; H, 5·8; S, 11·6; Ac, 46·7%). Light absorption in ethanol: max. 2300 Å (ε 7500).

6-O-(*But*-3-*en*-1-*yl*)-1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*mannitol*.—Sodium (1·2 g.), in small pieces, was added to but-3-en-1-ol (8 g.) heated on the steam-bath. When the reaction became slow, dry benzene (10 c.c.) was added, and the mixture was boiled under reflux until the metal had disappeared. A hot solution of 5 : 6-anhydro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-mannitol (Bladon and Owen, *J.*, 1950, 591) (11·8 g.) in dry benzene (90 c.c.) was then added, and the boiling was continued for 7 hr. Water (200 c.c.) was added to the cooled reaction mixture, the benzene layer was removed, and the aqueous portion extracted once with benzene. The combined benzene solution was dried and evaporated to an oil, which on distillation gave the 6-*butenyl ether* (9·8 g., 64%) as a colourless oil, b. p. 130—140° (bath)/0·0001 mm., n_D^{19} 1·4580—1·4610. A fraction, n_D^{19} 1·4590, $[\alpha]_D^{23}$ +16° (*c*, 4 in EtOH), was analysed (Found: C, 60·5; H, 9·2. $C_{16}H_{28}O_6$ requires C, 60·75; H, 8·9%).

1-O-(*But*-3-*en*-1-*yl*)-D-*mannitol*.—A solution of the above *O*-butenyldi-*O*-*iso*propylidene-mannitol (8·8 g.) in ethanol (50 c.c.), water (50 c.c.), and sulphuric acid (2 g.) was boiled under reflux for 18 min., and then cooled, diluted with water (150 c.c.), neutralised with barium carbonate (30 g.), filtered, and evaporated to a syrup. This was dissolved in warm ethanol, filtered (charcoal), and again taken down to a syrup, which on dissolution in ethyl acetate deposited a solid (5·3 g.), m. p. 88—92°; recrystallisation from ethanol–ethyl acetate gave 1-O-(*but*-3-*en*-1-*yl*)-D-*mannitol*, m. p. 93—94°, $[\alpha]_D^{20}$ +7·3° (*c*, 3 in H_2O) (Found: C, 50·7; H, 8·7. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(*but*-3-*en*-1-*yl*)-D-*mannitol*.—Acetylation of the 1-*O*-butenylmannitol (12·3 g.) with acetic anhydride (100 c.c.) and fused sodium acetate (6 g.) at 100° for 6 hr. gave the *penta-acetate*, which crystallised from aqueous ethanol in small prisms, m. p. 61—63°, $[\alpha]_D^{21}$ +29·4° (*c*, 7 in EtOH) (Found: C, 53·8; H, 6·9. $C_{20}H_{30}O_{11}$ requires C, 53·8; H, 6·8%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*dibromobutyl*)-D-*mannitol*.—Bromine (7·5 g.) in carbon tetrachloride (70 c.c.) was slowly added (30 min.) to a stirred solution of the above penta-acetate (20 g.) in carbon tetrachloride (130 c.c.), and after a further 30 min. the solution was washed with aqueous sodium sulphite, dried, and evaporated to a syrup (25·5 g.), n_D^{20} 1·4767. This was dissolved in ethanol (40 c.c.), and water was added to slight turbidity; cooling overnight then gave a solid (12 g.), which after 6 recrystallisations from ethanol–light petroleum formed colourless prisms of the *dibromide*, m. p. 87°, $[\alpha]_D^{21}$ +42·2° (*c*, 5 in $CHCl_3$) (Found: C, 39·5; H, 5·3; Br, 26·2. $C_{20}H_{30}O_{11}Br_2$ requires C, 39·6; H, 5·0; Br, 26·4%).

The syrup obtained by evaporation of all mother-liquors was fractionally distilled at 190—220° (bath)/0·0004 mm. to give: (*a*) 2·4 g., n_D^{21} 1·4660; (*b*) 6·6 g., n_D^{21} 1·4741; (*c*) 3·0 g., n_D^{21} 1·4780; (*d*) 0·8 g., n_D^{21} 1·4800. The purity of (*b*), (*c*), and (*d*), from determinations of their bromine content, was 84, 95, and 93% respectively, but no more crystalline dibromide could readily be isolated from them, probably because of the presence of the other stereoisomer. Fraction (*a*) partly crystallised, and the solid material, after several recrystallisations from ethanol–light petroleum and from benzene–light petroleum, was identified as hexa-*O*-acetyl-D-mannitol, m. p. and mixed m. p. 122—124°, $[\alpha]_D^{20}$ +25° (*c*, 1 in $CHCl_3$) (Found: C, 49·8; H, 6·2. Calc. for $C_{18}H_{26}O_{12}$: C, 49·8; H, 6·0%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*bisacetylthiobutyl*)-D-*mannitol*.—The crystalline dibromide (5 g.), potassium thiolacetate (2·4 g.), and ethanol (50 c.c.) were boiled together under nitrogen for 6 hr., and the product was isolated as described for the glucoside. The *bisthiolacetate* was a pale yellow syrup, n_D^{22} 1·4883, $[\alpha]_D^{22}$ +9·2° (*c*, 6 in $CHCl_3$) (Found: C, 48·2; H, 6·3; S, 10·3. $C_{24}H_{36}O_{13}S_2$ requires C, 48·3; H, 6·1; S, 10·7%). It could be distilled in small quantities at 240—250° (bath)/0·0001 mm., without change in refractive index. Light absorption: max. 2300 Å (ε 7600).

6-O-(*But*-3-*en*-1-*yl*)-1 : 3-2 : 4-*di*-O-*ethylidene*-D-*glucitol*.—To a hot solution of sodium (4·7 g.) in but-3-en-1-ol (40 g.), a solution of 5 : 6-anhydro-1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol (41 g.)

(Bladon and Owen, *J.*, 1950, 591) in dry benzene (250 c.c.) was added. The mixture was boiled under reflux for 7 hr., then diluted with water (200 c.c.) and partly neutralised with acetic acid (10 g.). The benzene layer was removed, and the aqueous portion extracted with benzene (4 × 150 c.c.); evaporation of the dried benzene solutions then gave an oil, which on fractional distillation furnished the 6-*butenyl ether* (32 g., 59%) as a viscous syrup, b. p. 165—175° (bath)/0·0004 mm., n_D^{20} 1·4790, $[\alpha]_D^{20}$ +4·8° (*c*, 4·1 in $CHCl_3$) (Found: C, 57·7; H, 8·7. $C_{14}H_{24}O_6$ requires C, 58·3; H, 8·4%).

The highest-boiling fraction partly crystallised, and recrystallisation of the solid first from benzene–light petroleum and then from ethanol–light petroleum gave prisms, m. p. 158°, of (probably) 6-O-(*but*-3-*en*-1-*yl*)-1 : 3-2 : 4-*di*-O-*ethylidene*-D-*glucitol*-5 1 : 3-2 : 4-*di*-O-*ethylidene*-D-*glucitol*-6 *ether* (IX) (Found: C, 57·6, 57·1; H, 8·2, 8·3. $C_{24}H_{40}O_{11}$ requires C, 57·1; H, 8·0%). The substance was unsaturated, and on microhydrogenation absorbed 0·8 mol. of hydrogen. It was readily soluble in benzene, but sparingly so in cold methanol, ethanol, and carbon tetrachloride. (The foregoing name is used non-commitally pending Anglo-U.S. or I.U.P.A.C. recommendations for this type of compound.)

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(*but*-3-*en*-1-*yl*)-D-*glucitol*.—The 6-*O*-butenyldi-*O*-ethylideneglucitol (29 g.) was heated on the steam-bath for 3·5 hr. with 4% aqueous sulphuric acid (300 c.c.) and ethanol (150 c.c.). The cooled solution was extracted once with benzene to remove oily impurities, and then neutralised with barium carbonate, filtered, and evaporated to a syrup (22 g.). This crude 6-*O*-(but-3-en-1-yl)-D-glucitol (21 g.) was heated at 100° for 10 hr. with acetic anhydride (120 c.c.) and fused sodium acetate (12 g.); the solution was then concentrated under reduced pressure and the residue was stirred with water. Extraction with chloroform gave a brown oil, which on distillation furnished the colourless *penta-acetate* (26 g.), b. p. 190—210° (bath)/0·001 mm., n_D^{21} 1·4545, $[\alpha]_D^{22}$ +4·9° (*c*, 5 in $CHCl_3$) (Found: C, 54·2; H, 7·0. $C_{20}H_{30}O_{11}$ requires C, 53·8; H, 6·8%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*dibromobutyl*)-D-*glucitol*.—Addition of bromine (8·8 g.) in carbon tetrachloride (100 c.c.) to the above penta-acetate (23·5 g.) in carbon tetrachloride (150 c.c.) gave, on distillation of the product, the *dibromide* (21·1 g.), b. p. 210—240° (bath)/0·001 mm., n_D^{20} 1·4842—1·4865. A fraction, n_D^{20} 1·4860, $[\alpha]_D^{18}$ −3·7° (*c*, 5 in $CHCl_3$), was analysed (Found: C, 39·8; H, 5·3; Br, 26·7. $C_{20}H_{30}O_{11}Br_2$ requires C, 39·6; H, 5·0; Br, 26·4%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*bisacetylthiobutyl*)-D-*glucitol*.—The above dibromide (12·9 g.), potassium thiolacetate (6 g.), ethanol (120 c.c.) and thiolacetic acid (0·2 g.) were boiled together under nitrogen for 6 hr., and the mixture was then worked up as already described for the glucoside. The crude bisthiolacetate was a dark red viscous syrup (10 g.), n_D^{20} 1·5027, which had undergone slight deacetylation (Found: C, 46·7; H, 6·1; S, 11·3; Ac, 46·6. Calc. for $C_{24}H_{36}O_{13}S_2$: C, 48·3; H, 6·1; S, 10·7; Ac, 50·5%). Light absorption in ethanol: max. 2290 Å (ε 6000).

3-O-(*But*-3-*en*-1-*yl*)-1 : 2-5 : 6-*di*-O-iso*propylidene*-D-*mannitol*.—A hot solution of sodium hydroxide (70 g.) in water (70 c.c.) was gradually added to a vigorously stirred solution of 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol (55·5 g.) (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338) in dioxan (200 c.c.) heated on the steam-bath under reflux. Stirring and heating of the emulsion were maintained for 20 hr., but-3-en-1-yl bromide (18·5 g.) in dioxan (35 c.c.) being added dropwise during the first 4 hr., and more bromide (18·5 g.) in dioxan (25 c.c.) between the 8th and the 12th hour. After completion of the reaction, the mixture was concentrated under reduced pressure to remove dioxan, and then treated with ice (200 g.) and partly neutralised with 20% aqueous sulphuric acid (300 c.c.). Extraction with ether (7 × 200 c.c.), and evaporation of the dried extracts gave an oil, which was dissolved in warm light petroleum (b. p. 60—80°) (250 c.c.) and cooled to 0°; unchanged di*iso*propylidenemannitol (21 g.) crystallised, and was removed, a further crop (2 g.) being obtained on concentration of the filtrate. Evaporation of the residual solution, and distillation of the residue, gave the 3-(*but*-3-*en*-1-*yl*) *ether* (33·3 g., 85% based on di*iso*propylidene compound consumed) as a viscous oil, b. p. 135—145° (bath)/0·0004 mm., n_D^{22} 1·4585, $[\alpha]_D^{21}$ +10·7° (*c*, 3 in EtOH) (Found: C, 60·6; H, 9·2. $C_{16}H_{28}O_6$ requires C, 60·7; H, 8·9%).

Conditions for this reaction are apparently critical, and repetitions of the above experiment gave much poorer yields. Variations in the concentration of alkali, method and time of addition of butenyl bromide, shape and position of stirrer, and the addition of surface-active agents failed to give satisfactory results. A low yield of the butenyl ether was obtained by interaction of the monosodium derivative of 1 : 2-5 : 6-di-*O*-*iso*propylidenemannitol (prepared by evaporation of a solution of the di*iso*propylidenemannitol and 1 atomic proportion of sodium in liquid ammonia) with excess of butenyl bromide in boiling dioxan.

3-O-(*But*-3-*en*-1-*yl*)-D-***mannitol***.—The above butenyl ether (7·7 g.), ethanol (40 c.c.), water (40 c.c.), and sulphuric acid (2 g.) were boiled together under reflux on the steam-bath for 15 min., then rapidly cooled, diluted with water (100 c.c.), and stirred with barium carbonate (25 g.). The neutral solution was filtered and evaporated to a syrup, which was dissolved in ethanol (50 c.c.), shaken with a little charcoal, filtered, and again concentrated; the product was dissolved in ethyl acetate (50 c.c.) and stored at 0° overnight. The crystals so formed were collected (4·7 g.; m. p. 91—93°), and recrystallised from ethanol–ethyl acetate to give prisms of 3-O-(*but*-3-*en*-1-*yl*)-D-*mannitol*, m. p. 93—96°, $[\alpha]_D^{22}$ +16·7° (*c*, 4 in H_2O) (Found: C, 50·4; H, 8·8. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5%).

1 : 2 : 4 : 5 : 6-*Penta*-O-*acetyl*-3-O-(*but*-3-*en*-1-*yl*)-D-*mannitol*.—Acetylation of the preceding butenyl ether (1·8 g.) with acetic anhydride (20 c.c.) and fused sodium acetate (1 g.) for 7 hr. at 100° gave an oil, which on distillation furnished the *penta-acetate* (2·8 g.), b. p. 190—215° (bath)/0·0001 mm., n_D^{16} 1·4534, $[\alpha]_D^{17}$ +32·3° (*c*, 5 in $CHCl_3$) (Found: C, 53·3; H, 7·0. $C_{20}H_{30}O_{11}$ requires C, 53·8; H, 6·8%); this contained a small proportion of hexa-*O*-acetylmannitol (see below).

1 : 2 : 4 : 5 : 6-*Penta*-O-*acetyl*-3-O-(3 : 4-*dibromobutyl*)-D-*mannitol*.—The above penta-acetate (2·5 g.) in carbon tetrachloride (30 c.c.) was gradually treated with bromine (1 g.) in carbon tetrachloride (15 c.c.). The reaction appeared to cease after about three-quarters of the bromine solution was added, and after being set aside overnight the mixture was still deeply coloured; it was therefore washed successively with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and water, and finally dried and evaporated to an oil (2·6 g.). This was distilled from a small retort, the following fractions being collected at 215—235° (bath)/0·0004 mm.: (*a*) 0·8 g., n_D^{19} 1·4600; (*b*) 0·5 g., n_D^{19} 1·4673; (*c*) 0·8 g., n_D^{19} 1·4793; (*d*) 0·4 g., n_D^{19} 1·4833. The first two fractions were cloudy, and when (*a*) was treated with ethanol–light petroleum (b. p. 60—80°) it gave hexa-*O*-acetylmannitol, m. p. and mixed m. p. 124°. Fraction (*d*) was the required *dibromide* (Found: C, 40·0; H, 5·3; Br, 26·9. $C_{20}H_{30}O_{11}Br_2$ requires C, 39·6; H, 5·0; Br, 26·4%).

Deacetylation of Thiolacetates.—(i) To a stirred solution of 3 : 4-bisacetylthiobutyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (9·3 g.) in dry methanol (100 c.c.), kept at about −17°, under nitrogen, 1·5N-methanolic barium methoxide (40 c.c.) was added. The temperature was allowed to rise to 0° (2 hr.) (the barium salt began to separate after 25 min.) and the mixture was then warmed to 25° for 15 min., stirring being maintained throughout; a further quantity of barium salt was suddenly precipitated at the higher temperature. The solid was filtered off under nitrogen, and was washed with dry methanol and with dry ether, and dried in a vacuum over phosphoric oxide. The barium salt (5·1 g.) was a fine yellow hygroscopic powder, $[\alpha]_D^{22}$ −16° (*c*, 4 in 1% aqueous HCl) (Found: C, 24·8; H, 4·6; S, 11·7; thiol-S, 9·25; Ba, 29·9. Calc. for $C_{10}H_{18}O_6S_2Ba$: C, 27·6; H, 4·2; S, 14·7; Ba, 31·5%).

(ii) (With P. S. Fitt.) Similar treatment of crystalline 2 : 3-bisacetylthiopropyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (Evans and Owen, *loc. cit.*) gave the barium salt of 2 : 3-dimercaptopropyl β-D-glucoside (Found: C, 26·7; H, 3·7; S, 13·25; thiol-S, 11·7; Ba, 27·9. Calc. for $C_9H_{16}O_6S_2Ba$: C, 25·6; H, 3·8; S, 15·2; Ba, 32·6%).

(iii) Similar treatment of penta-*O*-acetyl-6-*O*-(3 : 4-bisacetylthiobutyl)-D-mannitol gave a barium salt, $[\alpha]_D^{18}$ −7·7° (*c*, 4 in 2N-HCl) (Found: C, 29·3; H, 6·1; S, 12·1; thiol-S, 10·8; Ba, 27·3. Calc. for $C_{10}H_{20}O_6S_2Ba$: C, 27·4; H, 4·6; S, 14·6; Ba, 31·4%).

The same hepta-acetyl compound (0·97 g.) was boiled under reflux with methanol (30 c.c.) and concentrated hydrochloric acid (3 c.c.) for 2 hr. in nitrogen. The solution was then concentrated under reduced pressure, and the residue repeatedly evaporated under reduced pressure with dry methanol (4 × 10 c.c.) to give a yellow glass (Found: C, 37·0; H, 7·7; S, 17·1; thiol-S, 8·4%). This was dissolved in warm ethanol (1·5 c.c.) and cooled to 0° to give a colourless solid (0·2 g.), which was readily soluble in water; it sintered at 57—60° and became waxy at 85—95° (Found: C, 41·1; H, 7·1; S, 23·9; thiol-S, 11·2. Calc. for $C_{10}H_{20}O_5S_2$: C, 42·3; H, 7·1; S, 22·6; thiol-S, 11·3%).

(iv) Penta-*O*-acetyl-6-*O*-(3 : 4-bisacetylthiobutyl)-D-glucitol with methanolic barium methoxide gave a salt of poor quality (Found: C, 33·7; H, 6·1; S, 15·2; thiol-S, 7·1; Ba, 19·5. Calc. for $C_{10}H_{20}O_6S_2Ba$: C, 27·4; H, 4·6; S, 14·6; Ba, 31·4%).

Fission of Butenyl Ethers of Mannitol with Aqueous Acid.—(A) *Formation of mannitol*. (i) 3-*O*-(But-3-en-1-yl)-1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol (35 g.) was heated on the steam-bath with N-sulphuric acid (125 c.c.) for 3·5 hr. (the mixture became homogeneous after 20 min.). The cooled solution was neutralised with barium carbonate, filtered, and evaporated to a semi-solid residue (22 g.), which was dissolved in hot water (20 c.c.) and ethanol (150 c.c.),

and cooled to 0° to give mannitol (11·5 g.), m. p. and mixed m. p. 166°. Evaporation of the filtrate gave material which on fractional crystallisation from 90% ethanol and from ethanol–ether gave more mannitol (1·4 g.) and crude 3-*O*-butenylmannitol (4 g.), m. p. 82—86°, raised after several recrystallisations from ethanol–ethyl acetate to m. p. and mixed m. p. 93—96°.

(ii) 3-*O*-(But-3-en-1-yl)-D-mannitol (0·5 g.) was boiled under reflux with water (10 c.c.) and sulphuric acid (1 g.). The reaction, followed polarimetrically, was complete in 1 hr.: $[\alpha]_D^{20}$ (initial) +16·5°, (final) +4°. After 3 hr. the solution was neutralised with barium carbonate and worked up as described above to give mannitol (0·1 g.), m. p. and mixed m. p. 166°.

(B) *Volatile products.* (i) 3-*O*-Butenylmannitol (2 g.) and 2N-sulphuric acid (20 c.c.) were boiled under reflux for 70 min. The cooled solution was neutralised with sodium carbonate and continuously extracted with ether for several hours. The dried (K_2CO_3) extract was fractionated to remove ether, and the residue on distillation gave 80 mg., boiling up to 135° (bath), which were unsaturated and gave a strong iodoform reaction; this product gave a 3 : 5-dinitrobenzoate, m. p. 29—39°, insufficient for purification. The 3 : 5-*dinitrobenzoate* of authentic but-1-en-3-ol, prepared in pyridine, crystallised from methanol in soft flattened needles, m. p. 58° (Found: N, 10·7. $C_{11}H_{10}O_6N_2$ requires N, 10·5%).

(ii) The above experiment was repeated, a slow stream of nitrogen being passed through the reaction mixture and then *via* a drying tube ($CaCl_2$) into a solution of bromine in carbon tetrachloride. Concentration of the latter solution gave an oil which on trituration with cold ethanol furnished butadiene tetrabromide, m. p. and mixed m. p. 115—118° (sealed tube). No tetrabromide was obtained when mannitol (1 g.), but-3-en-1-ol (0·4 g.), and 2N-sulphuric acid (10 c.c.) were similarly treated.

(iii) 6-*O*-(But-3-en-1-yl)-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-mannitol (5 g.) was heated on the steam-bath for 3 hr. with N-sulphuric acid (50 c.c.), in a stream of nitrogen; the butadiene in the exit gases was detected colorimetrically with diazotised 2 : 4-dinitroaniline (Terent'ev and Demidova, *Chem. Abs.*, **1943**, **37**, 2682) and with alkaline methanolic sodium nitroprusside (cf. Scagliarini and Lucchi, *ibid.*, 1940, **34**, 2287). Fractional crystallisation of the product isolated from the reaction solution gave mannitol (0·5 g.), m. p. and mixed m. p. 163—166°, and 6-*O*-butenylmannitol (1·25 g.), m. p. and mixed m. p. 91—93°.

Rates of Hydrolysis of Glucosides.—A solution of allyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (0·194 g.) in methanolic sodium methoxide (from 20 mg. of sodium in 10 c.c. of methanol) was boiled under reflux for 15 min. and then evaporated to dryness under reduced pressure. The residual allyl β-D-glucoside was dissolved in 0·28N-sulphuric acid (10 c.c.), and the filtered solution was heated on the steam-bath, the hydrolysis being followed polarimetrically. A similar experiment was carried out with an equivalent quantity (0·201 g.) of but-3-en-1-yl tetra-*O*-acetyl-β-D-glucoside. The following values of α_D^{20} (1-dm. tube) were observed:

Time (hr.)	0	0·5	3	8	14	36
Allyl glucoside	−0·44°	−0·40°	−0·25°	+0·01°	+0·24°	+0·46° (const.)
Butenyl ,, ...	−0·38°	−0·34°	−0·22°	+0·02°	+0·23°	+0·45° (const.)

The half-life for each glucoside is *ca.* 8·5 hr. The initial values correspond to $[\alpha]_D^{20}$ −40° and −33° for the two glucosides respectively; Fischer (*Z. physiol. Chem.*, 1920, **108**, 3) gives $[\alpha]_D^{17}$ −40·5° for allyl β-D-glucoside in water. The final constant rotations, calculated for glucose, correspond to $[\alpha]_D^{20}$ +51° and +50° respectively; the equilibrium value for D-glucose is +52·7° in water.

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