111. *Dithiols. Part V. Further Non-vicinal Dithiols.*

By Peter Bladon and L. N. Owen.

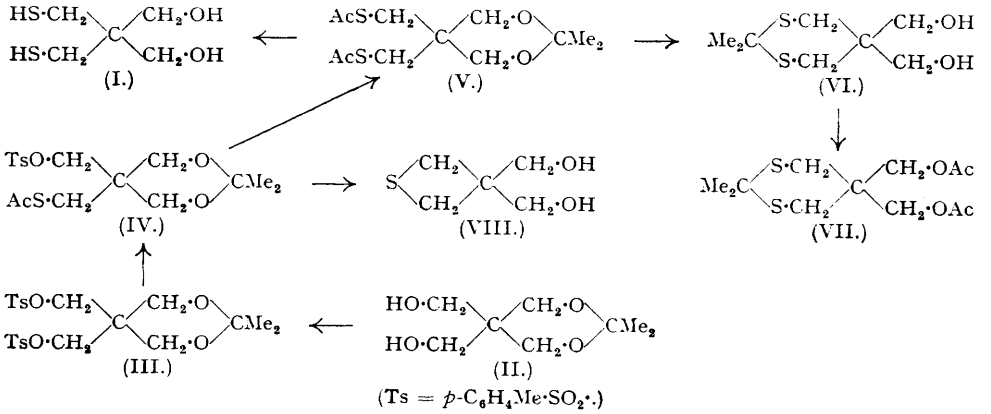
The sulphonyloxy–thiolacetate exchange reaction (Chapman and Owen, preceding paper) has been applied to the preparation of dithiopentaerythritol, 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (*dithio*iso*mannide*), and 1 : 6-*dithiomannitol*. Two unexpected instances of the fission of an *iso*propylidene group have been encountered in some derivatives of pentaerythritol. The formation of a cyclic sulphide, by removal of the toluene-*p*-sulphonyl group from a 1-tosyl-3-acetylthio-compound, is recorded.

Dithiopentaerythritol (I) was first prepared by Backer and Tamsma (*Rec. Trav. chim.*, **1938**, **57**, 1183) by interaction of pentaerythritol dibromohydrin with sodium disulphide, followed by reduction of the intermediate cyclic disulphide with sodium in liquid ammonia. Peppel and Signaigo (U.S.P. 2,402,665) used a similar method, but reduced the disulphide by hydrogenation under pressure over a cobalt polysulphide catalyst.

It was thought that a more convenient laboratory method for the preparation of (I) could be based on the sulphonyloxy–thiolacetate exchange reaction described by Chapman and Owen (Part IV; preceding paper), since suitable starting materials are readily obtained by protection of two of the hydroxyl groups in pentaerythritol by the formation of cyclic acetals, either with aldehydes (Read, *J.*, 1912, **101**, 2090; Schulz and Tollens, *Annalen*, 1896, **289**, 28; Skrabal and Kalpasanoff, *Ber.*, 1928, **61**, 55; Böeseken and Felix, *Ber.*, 1928, **61**, 787; Fairbourne and Woodley, *J.*, 1926, 3240) or with ketones (Böeseken, *Rec. Trav. chim.*, 1922, **41**, 722; Skrabal and Zlatewa, *Z. physikal. Chem.*, 1926, **119**, 305; Böeseken and Hermans, *Ber.*, 1922, **55**, 3760; Böeseken and Felix, *Ber.*, 1929, **62**, 1310; Orthner, *Ber.*, 1928, **61**, 116). It is necessary to remove the protecting groups at a later stage in the synthesis, and since the cyclic acetals with ketones appear to be more readily hydrolysed than those with aldehydes (Skrabal and Zlatewa, *loc. cit.*), the *iso*propylidene derivative (II) was chosen, and was prepared by a modification of Orthner's method (*loc. cit.*).

Treatment of (II) with two moles of toluene-*p*-sulphonyl chloride in pyridine afforded *ditosyl* iso*propylidene pentaerythritol* (III). Similarly, with methanesulphonyl chloride in pyridine, *dimethanesulphonyl* iso*propylidene pentaerythritol* was formed. Throughout this work, Tipson's general method (*J. Org. Chem.*, 1944, **9**, 235) has been followed for the preparation of tosyl and methanesulphonyl compounds; he pointed out that it is essential in many cases to

keep the temperature of the reaction mixture below 5°, and in this connection it is of interest that Rapoport (*J. Amer. Chem. Soc.*, **1946**, **68**, 341; U.S.P. 2,441,595) found that mono*iso*-



(Ts = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}$.)

propylidene pentaerythritol with toluene-*p*-sulphonyl chloride in warm pyridine gave the corresponding dichloro-compound instead of the ditoluene-*p*-sulphonate.

When the ditosyl compound was refluxed with potassium thiolacetate in acetone for a limited time, only one of the tosyloxy-groups was replaced, and O-*tosyl* S-*acetyl* OO-iso*propylidene monothiopentaerythritol* (IV) was obtained. Prolonged treatment of this product with potassium thiolacetate and acetone gave *di*-S-*acetyl* OO-iso*propylidene dithiopentaerythritol* (V). The same compound was obtained by reaction of the dimethanesulphonate with potassium thiolacetate in boiling ethanol.

An attempt was made to remove simultaneously the acetyl and *iso*propylidene residues in (V) by hydrolysis with hot aqueous methanolic hydrogen chloride. The main product, which separated from the reaction mixture, was a high-melting solid containing no free thiol; furthermore, it showed no selective light absorption in the ultra-violet and was therefore not a thiolacetate. It was identified as *SS-iso*propylidene dithiopentaerythritol (VI), previously prepared by Backer and Tamsma (*loc. cit.*). Evaporation of the mother-liquors gave some dithiopentaerythritol (I). The *iso*propylidene compound (VI) may be formed either by reaction of the dithiol with acetone liberated during the hydrolysis, or by hydrolysis of the acetyl groups in (V), followed by direct migration of the acetone residue (possibly through an intermediate *OS-iso*propylidene compound). The mechanism of this reaction will be investigated further, but it may be pointed out that the migration of *iso*propylidene residues in certain dulcitol derivatives, catalysed by quinoline hydrochloride, has been observed by Hann, Maclay, and Hudson (*J. Amer. Chem. Soc.*, **1939**, **61**, 2432). In accordance with the known stability of the cyclic acetals of dithiols, (VI) was unaffected by acid hydrolysis.

When the bisacetylthio-compound (V) was hydrolysed with methanolic potassium hydroxide, it gave a small yield of *SS-iso*propylidene dithiopentaerythritol (VI), identical with the material obtained by acid hydrolysis. This result was quite unexpected, since *iso*propylidene residues are normally unaffected by alkali.

*SS-iso*Propylidene dithiopentaerythritol (VI) was characterised by acetylation to yield *di*-O-*acetyl* SS-iso*propylidene dithiopentaerythritol* (VII), isomeric with (V), and by reaction with methanesulphonyl chloride in pyridine to yield *di*-O-*methanesulphonyl* SS-iso*propylidene dithiopentaerythritol*, both derivatives being crystalline. Acetylation of dithiopentaerythritol gave a liquid *tetra-acetate*.

Treatment of tosyl *S*-acetyl *iso*propylidene monothiopentaerythritol (IV) with sodium methoxide in methanol–chloroform (the usual conditions for the formation of anhydro-compounds in the carbohydrate field; cf. Peat and Wiggins, *J.*, 1938, 1088) resulted in elimination of sodium toluene-*p*-sulphonate and of the *iso*propylidene residue, with formation of a small amount of 3 : 3-*bishydroxymethylthietan* (VIII). The reaction thus provided another example of the unexpected loss of an *iso*propylidene group; as far as we are aware, it is also the first occasion on which a cyclic sulphide has been prepared by such a method.

During the general investigation of the sulphonyloxy–thiolacetate exchange reaction (Part IV; *loc. cit.*) it was found that secondary groups differed considerably amongst them-

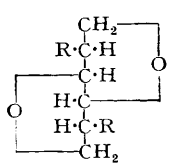
selves in their reactivity. Since, however, it had been shown by Hockett, Fletcher, Sheffield, Goepp, and Soltzberg (*J. Amer. Chem. Soc.*, 1946, **68**, 930) that the two secondary toluene-*p*-sulphonyloxy-groups in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydromannitol were capable of being replaced by iodine when the compound was treated with sodium iodide in acetone at 120°, it appeared probable that an interchange with potassium thiolacetate could be effected; the compound actually used was the 2 : 5-dimethanesulphonate (IX) (Montgomery and Wiggins, *J.*, 1948, 2204), which reacted with potassium thiolacetate in ethanol at 110° to give solid *diacetyl* 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (X), together with much uncrystallisable material. Some deacetylation appeared to occur during the reaction, and the crude product was therefore re-acetylated before being worked up. The thiolacetate (X) was smoothly deacetylated by heating with methanolic hydrogen chloride, and gave 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (XI) as a low-melting solid; it was characterised as the *bis*-2 : 4-*dinitrophenyl* derivative (XII), which showed a remarkably high optical rotation in nitrobenzene solution ($[\alpha]_D^{19}$ −398°).

A second possible route to dithio*iso*mannide was explored. This was based on an observation by Freudenberg and Wolf (*Ber.*, 1927, **60**, 232), who found that the 3-methyl xanthate of di*iso*propylidene glucose, when heated to 300°, underwent a rearrangement and gave a dithiolcarbonate, from which 3-thioglucose was obtained by hydrolysis:

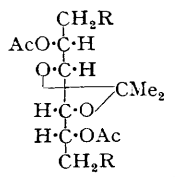
R·O·CS·SMe ⟶ R·S·CO·SMe ⟶ R·SH (R = di*iso*propylidene glucose residue)

Treatment of 1 : 4-3 : 6-dianhydromannitol with sodium in liquid ammonia gave the disodium derivative which, by the action of carbon disulphide, followed by methyl iodide, was converted into the 2 : 5-*di*(*methyl xanthate*) of *iso*mannide (XIII). This, however, failed to undergo any rearrangement on distillation at 170°, since a portion of the product, on hydrolysis, gave *iso*mannide; when it was heated at 290°, extensive decomposition occurred, but the distillate still appeared to consist mainly of unchanged xanthate.

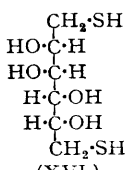
In Part III (Evans, Fraser, and Owen, *J.*, 1949, 248) the preparation of 1 : 6-dithiomannitol was described. Since this compound exhibited some unusual physiological effects, its synthesis by an application of the sulphonyloxy–thiolacetate exchange reaction was devised as a possibly more convenient route. The starting material was 1 : 6-ditosyl 2 : 5-diacetyl 3 : 4-*iso*propylidene mannitol (XIV) (Wiggins, *J.*, 1946, 386). On treatment with potassium thiolacetate in



(IX; R = O·SO$_2$·Me.)
(X; R = SAc.)
(XI; R = SH.)
[XII; R = S·C$_6$H$_3$(NO$_2$)$_2$.]
(XIII; R = O·CS·SMe.)



(XIV; R = OTs.)
(XV; R = SAc.)



(XVI.)

boiling acetone this gave 1 : 2-5 : 6-*tetra-acetyl* 3 : 4-iso*propylidene* 1 : 6-*dithiomannitol* (XV). Removal of the acetyl and *iso*propylidene groups by acid hydrolysis then gave a crude dithiol, which when purified by acetylation afforded crystalline *hexa-acetyl* 1 : 6-*dithiomannitol*. This compound, however, was not identical with the hexa-acetate described by Evans, Fraser, and Owen (*loc. cit.*); furthermore, on deacetylation with methanolic hydrogen chloride it gave pure 1 : 6-*dithiomannitol* (XVI), which differed from the dithiol previously described under this name. This discrepancy led to a reinvestigation of the "dithiomannitol" prepared by the earlier route, and has resulted in the discovery that the original dithiol, its hexa-acetate, and the 1 : 6-dibromide from which it was derived, have the dulcitol configuration (see Bladon, Owen, Overend, and Wiggins, *Nature*, 1949, **164**, 567).

Experimental.

(Light-absorption measurements, in ethanol, were kindly determined by Dr. E. A. Braude.)

iso*Propylidene Derivatives of Pentaerythritol*.—Finely powdered pentaerythritol (180 g.) was stirred vigorously with a mixture of acetone (2 l.), water (670 c.c.), and concentrated hydrochloric acid (80 c.c.) for 15 hours. Unchanged pentaerythritol (81·5 g.) was filtered off and washed with acetone. The filtrate was stirred with potassium carbonate (500 g.), added in small portions, and the lower, aqueous

layer was removed and extracted once with ether–acetone (1 : 1; 500 c.c.). The combined acetone–ether solution was dried by stirring with potassium carbonate (500 g.) for ½ hour, and was then filtered and evaporated. The residue (74 g.), after being dried by distillation with benzene and alcohol under reduced pressure, was powdered and extracted (Soxhlet) with light petroleum (b. p. 40—60°) for ½ hour. Evaporation of this extract gave crude di*iso*propylidene pentaerythritol (4·4 g.), b. p. 160—170° (bath)/30 mm., m. p. 105—111°. The mono*iso*propylidene derivative (58·3 g.) was obtained by exhaustive extraction of the residue with ether in the same apparatus (24 hours); the m. p., 120—125°, was not changed by recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°). A residue (5·1 g.), m. p. >150°, probably unchanged pentaerythritol, remained after the ether extraction.

For the mono- and di-*iso*propylidene derivatives, respectively, Orthner (*loc. cit.*) gives m. p. 128—129° and 117—117·5°; Skrabal and Kalpasanoff (*loc. cit.*) give 135° and 116°; Rapoport (*loc. cit.*) gives 126—127° for the mono-compound.

Ditosyl iso*Propylidene Pentaerythritol* (III).—The mono*iso*propylidene compound (17·6 g.) in dry pyridine (150 c.c.) was treated with toluene-*p*-sulphonyl chloride (42 g., 10% excess), the temperature being kept below 5°. After 12 hours at 0°, water (700 c.c.) was slowly added, and the precipitated solid (m. p. 140—146°) was collected and washed with water. Recrystallisation from acetone gave colourless needles (34·6 g., 71%) of *ditosyl* iso*propylidene pentaerythritol*, m. p. 152—153° (Found: C, 54·4; H, 5·9; S, 13·2. $C_{22}H_{28}O_8S_2$ requires C, 54·2; H, 5·8; S, 13·2%).

Dimethanesulphonyl iso*Propylidene Pentaerythritol*.—The mono*iso*propylidene compound (17·6 g.) was added in small portions to a cooled solution of methanesulphonyl chloride (25·2 g., 10% excess) in dry pyridine (100 c.c.), the temperature being kept below 10°. After being kept overnight at 0°, the mixture was poured into water (400 c.c.). The brown solid was collected, washed with water, and recrystallised from methanol to give *dimethanesulphonyl* iso*propylidene pentaerythritol* (17·9 g.), m. p. 107—110°, raised on further recrystallisation to 110—112° (Found: C, 35·9; H, 6·5; S, 19·35. $C_{10}H_{20}O_8S_2$ requires C, 36·1; H, 6·1; S, 19·3%).

Reaction of Ditosyl iso*Propylidene Pentaerythritol with Potassium Thiolacetate*.—The ditosyl compound (34·5 g., 0·0895 mol.), potassium thiolacetate (20·3 g., 0·178 mol.), and pure acetone (180 c.c.) were heated under reflux for 8 hours, a further quantity of potassium thiolacetate (4 g., 0·035 mol.) being added after 6 hours. The reaction mixture was cooled and filtered, and the salts were well washed with acetone. The filtrate was evaporated, and the residue was treated with water (50 c.c.) and extracted thrice with chloroform (50 c.c. portions). Evaporation of the dried (Na_2SO_4) extracts gave a residue (26·5 g.) which was dissolved in methanol and kept overnight at 0°. The solid (18·7 g.; m. p. 85—92°) was collected and recrystallised from methanol to give O-*tosyl* S-*acetyl* OO-iso*propylidene monothiopentaerythritol* (IV), m. p. 91—93° (Found: C, 52·85; H, 6·4; S, 16·3. $C_{17}H_{24}O_6S_2$ requires C, 52·55; H, 6·2; S, 16·5%). The compound was unstable and underwent extensive decomposition after storage for a few months. Concentration of the methanolic mother-liquors gave further crops of solid, m. p. 55—60°, which probably contained the bisthiolacetate (see below).

Reaction of Tosyl S-*Acetyl* OO-iso*Propylidene Monothiopentaerythritol with Potassium Thiolacetate*.—The above monotosyl compound (7·76 g.), potassium thiolacetate (6·8 g., large excess), and acetone (70 c.c.) were heated under reflux for 30 hours. The precipitated solid was filtered off and well washed with acetone. The filtrates were evaporated to small bulk, the residue was treated with water, and the oil was isolated by chloroform extraction followed by evaporation of the dried (Na_2SO_4) extracts. Crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) failed to give any pure material; apparently the bisthiolacetate and the monotosyl-monothiolacetate form a mixture, m. p. 57—59°, which is not readily separable by crystallisation. Accordingly, the crude product was distilled, b. p. 120° (bath)/0·0001 mm., and the solid distillate (3·95 g., 67·5%) was recrystallised from methanol. *Di*-S-*acetyl* OO-iso*propylidene dithiopentaerythritol* (V) formed colourless tablets, m. p. 63—65° (Found: C, 49·7; H, 7·3; S, 22·15. $C_{12}H_{20}O_4S_2$ requires C, 49·3; H, 6·9; S, 21·9%). Light absorption: max. 2290 A., ε 8500.

Reaction of Dimethanesulphonyl iso*Propylidene Pentaerythritol with Potassium Thiolacetate*.—The dimethanesulphonate (17·85 g., 0·054 mol.), potassium thiolacetate (18·5 g., 0·161 mol.), and ethanol (170 c.c.) were heated under reflux for 13 hours. The potassium methanesulphonate (15 g.) was removed and washed with ethanol. The filtrates were concentrated under reduced pressure, then diluted with water and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a syrup (14·9 g., 95%) which crystallised on being stirred with methanol. Recrystallisation from this solvent gave large rectangular tablets of di-S-acetyl *OO-iso*propylidene dithiopentaerythritol (12·0 g., 76%), m. p. 63—65°, undepressed on admixture with the material prepared from the tosyl compound.

Acid Hydrolysis of Di-S-*acetyl* OO-iso*Propylidene Dithiopentaerythritol*.—The compound (10 g.) was heated under reflux for 2 hours with methanol (20 c.c.) and 2N-aqueous hydrochloric acid (20 c.c.) in an atmosphere of nitrogen. Concentration of the solution then gave a solid (4·4 g.), which was collected, washed with water, and recrystallised from dioxan. *SS-iso*Propylidene dithiopentaerythritol (VI) formed flattened needles, m. p. 198—200°, which did not show selective ultra-violet-light absorption or give a thiol reaction (Found: S, 30·7. Calc. for $C_8H_{16}O_4S_2$: S, 30·8%). Backer and Tamsma (*loc. cit.*) give m. p. 199·5—200·5°. Further concentration of the original aqueous solution gave a second crop of crystals (1 g.), m. p. 95—97°, and, on complete evaporation, a final residue (1 g.), m. p. 87—89°. Recrystallisation of these from benzene gave plates, m. p. 95—96°, of dithiopentaerythritol (I) (Found: thiol S, 37·9. Calc. for $C_5H_{12}O_2S_2$: S, 38·1%). Acetylation of dithiopentaerythritol with acetic anhydride and sodium acetate at 100° for 8 hours gave the *tetra-acetate* as a colourless oil, b. p. 100—120° (bath)/0·0001 mm., n_D^{15} 1·5092 (Found: C, 46·55; H, 6·2; S, 19·15. $C_{13}H_{20}O_6S_2$ requires C, 46·5; H, 6·0; S, 19·1%). Light absorption: max. 2310 A., ε 8400.

Alkaline Hydrolysis of Di-S-*acetyl* OO-iso*Propylidene Dithiopentaerythritol*.—The compound (0·93 g.) was kept overnight under nitrogen with potassium hydroxide (1·5 g.) in methanol (15 c.c.). The alkali was then neutralised with carbon dioxide, water added, and the mixture extracted thrice with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a pale yellow oil (0·65 g.) containing free thiol, which on distillation furnished a liquid forerun, b. p. 90—120° (bath)/0·0001 mm., and a semi-solid material

(0·26 g.), b. p. 120—150° (bath)/0·0001 mm. The latter on crystallisation from methanol gave *SS-iso*propylidene dithiopentaerythritol, m. p. and mixed m. p. 197—199°.

*SS-iso*Propylidene dithiopentaerythritol was recovered largely unchanged (64%) after being heated with dioxan–5N-hydrochloric acid (1 : 1) for 4 hours on the steam-bath, followed by dilution with water; the aqueous filtrate gave only a faintly positive thiol test with nitroprusside and alkali.

The *diacetate* (VII), m. p. 71—72° after recrystallisation from methanol, was prepared by heating the compound with acetic anhydride and sodium acetate on the steam-bath for 6 hours (Found: C, 49·6; H, 7·0; S, 21·85. $C_{12}H_{20}O_4S_2$ requires C, 49·3; H, 6·9; S, 21·9%).

The *dimethanesulphonate* was prepared by treatment of *SS-iso*propylidene dithiopentaerythritol with a slight excess of methanesulphonyl chloride in pyridine for 12 hours at 0°; it formed fine needles, m. p. 123—125°, from acetone–methanol (Found: C, 33·2; H, 5·6; S, 35·2. $C_{10}H_{20}O_6S_4$ requires C, 32·9; H, 5·5; S, 35·2%).

Reaction of Tosyl S-*Acetyl* OO-iso*Propylidene Monothiopentaerythritol with Sodium Methoxide.*—The tosyl compound (1·94 g.) in chloroform (5 c.c.) was treated at 0° with sodium (0·14 g.) in dry methanol (3 c.c.). Sodium toluene-*p*-sulphonate rapidly separated, at first as a gel, and subsequently in crystalline form. The mixture was kept for an hour at room temperature, and at 0° overnight. Water (15 c.c.) was then added, and the chloroform layer was separated; the aqueous solution was extracted thrice more with chloroform. The dried (Na_2SO_4) extracts were evaporated and the residue was brought to crystallisation by evaporation several times with light petroleum (b. p. 40—60°). Crystallisation from methanol gave a small amount (0·19 g.) of ditosyl *iso*propylidene pentaerythritol, m. p. and mixed m. p. 152—154°, presumably present as impurity in the starting material. The mother-liquors were evaporated, and the residue was heated under reduced pressure; 3 : 3-*bishydroxymethylthietan* (VIII) (54 mg.), m. p. 72—74°, sublimed at 90—120° (bath temp.)/0·01 mm. (Found: C, 44·8; H, 7·5; S, 24·1. $C_5H_{10}O_2S$ requires C, 44·8; H, 7·5; S, 23·9%). A considerable amount of viscid non-volatile material probably consisted of polymer.

1 : 4-3 : 6-*Dianhydromannitol* (cf. Hockett *et al.*, *loc. cit.*; Montgomery and Wiggins, *J.*, 1947, 433).—Mannitol (50 g.) and toluene-*p*-sulphonic acid (5 g.) were thoroughly mixed by shaking in a 400-c.c. Claisen flask, fitted with the usual capillary leak and thermometer, and connected to a cooled receiver. The pressure was reduced to 50 mm., and the mixture was heated to 160—180° till molten. The bath temperature was then reduced to 140—150° and kept thereat for 1 hour whilst water was collected in the receiver. The pressure was then reduced to 2 mm., and as much material as possible was distilled into a clean receiver at a bath temperature of 160—200°, care being taken, particularly towards the end of the distillation, to keep the frothing under control. The pale yellow distillate, b. p. 120—130°/2 mm. (12·9 g.), crystallised on being seeded with *iso*mannide, and after recrystallisation from the minimum amount of ethyl acetate it formed prisms (10·5 g., 26%), m. p. 85—86°. The preparation was successfully carried out on twice this scale.

Diacetyl 2 : 5-*Dithio*-1 : 4-3 : 6-*dianhydromannitol* (X).—2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (Montgomery and Wiggins, *J.*, 1948, 2204) (6·0 g.), potassium thiolacetate (6·9 g.; excess), and thiolacetic acid (0·2 c.c.) in ethanol (30 c.c.) were heated in a sealed tube at 110—115° for 12 hours. The precipitated potassium methanesulphonate (5·5 g.; calc., 5·4 g.) was removed, and the alcoholic filtrates were evaporated to dryness. The residue was acetylated by heating with acetic anhydride (20 c.c.) and fused sodium acetate (2 g.) for 2 hours on the steam-bath, in order to counteract any deacetylation which might have occurred during the initial reaction. The resulting mixture was stirred with water to decompose the excess of acetic anhydride, and the oil was isolated by 4 extractions with chloroform (35 c.c.; 3 × 15 c.c.). The extracts were washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to a red oil (6·3 g.) which was fractionally distilled in nitrogen. After removal of some low-boiling material, the main product was collected at 135—140°/0·1 mm. (bath temp. 190—200°), n_D^{17} 1·558—1·552; on storage, it solidified. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave prisms, m. p. 35—37°; yield 3·25 g. (62%). Further recrystallisation from the same solvents gave colourless crystals, m. p. 36—37·5°, $[\alpha]_D^{17}$ +19·2° (*c*, 2·2 in chloroform), of *diacetyl* 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (Found: C, 46·1; H, 5·65; S, 24·55. $C_{10}H_{14}O_4S_2$ requires C, 45·8; H, 5·4; S, 24·45%). Light absorption: max. 2310 A., ε 8400.

2 : 5-*Dithio*-1 : 4-3 : 6-*dianhydromannitol* (XI).—The above diacetyl compound (3·12 g.) was heated under reflux with 2·5% hydrogen chloride in methanol (50 c.c.) for 4 hours. The solvent was removed by distillation under reduced pressure and the residual oil (2·12 g., 100%) was kept under reduced pressure over potassium hydroxide, whereupon it partly solidified. Distillation furnished 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* as a pale yellow oil, m. p. 15—16°, b. p. 60—80° (bath)/0·0001 mm., n_D^{17} 1·5692, $[\alpha]_D^{18}$ +85° (*c*, 2·5 in chloroform), $[\alpha]_D^{19}$ +120° (*c*, 1·4 in 0·2N-aqueous sodium hydroxide) (Found: C, 40·6; H, 5·75; S, 36·1; thiol S, 36·4. $C_6H_{10}O_2S_2$ requires C, 40·4; H, 5·65; S, 36·0%). The dithiol was readily soluble in all the common organic solvents.

Bis-2 : 4-*dinitrophenyl Derivative* (XII).—The dithiol (0·26 g.) was heated under reflux with 2 : 4-dinitrochlorobenzene (0·6 g.) and potassium hydroxide (0·17 g.) in ethanol (10 c.c.) for 1 hour. A copious precipitate of potassium chloride was produced. On pouring the solution into water, an emulsion was obtained, but this was broken on acidification with dilute sulphuric acid. The brown precipitate was collected, washed with water, and dried; yield, 0·73 g. (98%); m. p. 145—150°. One recrystallisation from aqueous acetic acid, and three from acetone gave the *derivative* as yellow needles, m. p. 187—188°, $[\alpha]_D^{19}$ −398° (*c*, 1 in nitrobenzene) (Found: C, 41·9; H, 3·0; N, 11·1. $C_{18}H_{14}O_{10}N_4S_2$ requires C, 42·35; H, 2·8; N, 11·0%). The substance was difficultly soluble in most common solvents, but dissolved readily in hot acetic acid or acetone.

1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di*(*methyl Xanthate*) (XIII).—1 : 4-3 : 6-Dianhydromannitol (7·3 g.) in liquid ammonia (300 c.c.) was treated with finely divided sodium (2·3 g.). After a few minutes, during which the blue colour had not entirely disappeared, the ammonia was allowed to evaporate, and the last traces were removed from the residue by heating under reduced pressure on the steam-bath. The fine white powder was heated under reflux with carbon disulphide (80 c.c.) for 22 hours. Methyl iodide (43 g.) was then added, and the heating continued for a further 16 hours. The mixture was

shaken with water (100 c.c.), and the lower aqueous layer was separated and extracted thrice with ether (100-c.c. portions). The combined carbon disulphide and ethereal solutions were dried (Na_2SO_4) and evaporated. The deep-red residue (12·2 g.) on distillation from a wide-necked retort under high vacuum gave some very volatile material (possibly dimethyl *iso*mannide) which condensed in the liquid-air trap. The second fraction (0·43 g.), b. p. <120° (bath)/0·0001 mm., n_D^{26} 1·6387, $[\alpha]_D^{21}$ +159° (*c*, 2·3 in chloroform), probably consisted mainly of monomethyl *iso*mannide mono(methyl xanthate). After the collection of some intermediate fractions (2·8 g.), the main bulk (6·2 g.) distilled at 170° (bath)/0·0001 mm. Redistillation gave the *di(methyl xanthate)* as a viscous orange liquid, n_D^{20} 1·6318, $[\alpha]_D^{21}$ +266° (*c*, 2·8 in chloroform) (Found: C, 36·6; H, 4·5; S, 39·3. $C_{10}H_{14}O_4S_4$ requires C, 36·8; H, 4·3; S, 39·3%). Light absorption: max. 2280, 2800 A.; ε 10,100 and 14,000, respectively. After being kept for several weeks, the syrup crystallised. Two recrystallisations from ethyl acetate–methanol afforded pale yellow plates, m. p. 58—60°, $[\alpha]_D^{18}$ +274° (*c*, 2·0 in chloroform) (Found: C, 37·0; H, 4·5; S, 39·3%). Light absorption: max. 2270, 2800 A.; ε 14,500 and 17,500; infl. 2730 A.; ε 15,000.

Reaction of 1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di(methyl Xanthate) with Sodium Methoxide.*—The above compound (1 g.; a syrup) was heated under reflux for 4 hours with sodium methoxide (1 g.) in methanol (15 c.c.). The alkali was then neutralised with carbon dioxide, the solution was filtered, and the filtrate and washings were evaporated to dryness. The crystalline residue was extracted overnight in a Soxhlet apparatus with chloroform; evaporation of these extracts gave *iso*mannide (0·43 g.), which was characterised by conversion into the dimethanesulphonyl derivative, m. p. and mixed m. p. 101—102°, $[\alpha]_D^{19}$ +134° (*c*, 1 in chloroform).

Pyrolysis of 1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di(methyl Xanthate).*—A portion of the syrup (1·2 g.) was heated at 290° at atmospheric pressure in a small retort held vertically in a metal-bath. Under these conditions, the compound refluxed gently, and slowly evolved a small amount of volatile material which collected in a liquid-air trap attached to the end of the retort. The temperature was allowed to fall to 250° during one hour, and the retort was then rearranged for distillation in the usual way. A small quantity (0·06 g.) of an oil was collected at 120—125° (bath)/0·0001 mm., which probably consisted of unchanged xanthate; light absorption: max. 2260, 2810 A., $E_{1\,cm.}^{1\%}$ 240, 220; infl. 2870 A., $E_{1\,cm.}^{1\%}$ 160. A considerable amount of dark viscous material remained in the retort.

1 : 2-5 : 6-*Tetra-acetyl* 3 : 4-iso*Propylidene* 1 : 6-*Dithiomannitol* (XV).—1 : 6-Ditosyl 2 : 5-diacetyl 3 : 4-*iso*propylidene mannitol, m. p. 111—113°, $[\alpha]_D^{20}$ +22·9° (*c*, 1·7 in chloroform) was prepared by Wiggins's method (*J.*, 1946, 384). This substance (8 g.), potassium thiolacetate (4·5 g.), and dry acetone (30 c.c.) were heated under reflux for 4 hours. Precipitated potassium toluene-*p*-sulphonate was removed (6·7 g., 102%) and washed with acetone, and the filtrates were concentrated and then diluted with water (30 c.c.). The oily layer was taken up in chloroform, and the aqueous portion was extracted thrice with chloroform. Removal of solvent from the dried (Na_2SO_4) extracts gave the *tetra-acetyl* derivative as a dark viscid oil, which could be distilled only in small quantities, b. p. 120° (bath)/0·0001 mm., n_D^{18} 1·4950, $[\alpha]_D^{20}$ +114° (*c*, 1·4 in chloroform) (Found: C, 47·6; H, 6·4; S, 14·9. $C_{17}H_{26}O_8S_2$ requires C, 48·35; H, 6·2; S, 15·2%). Light absorption: max. 2280 A., ε 8000.

1 : 6-*Dithiomannitol* (XVI).—The above bisthiolacetate (5·6 g.; not distilled) was heated under reflux for 8 hours with 2% methanolic hydrogen chloride in an atmosphere of nitrogen. The solvent was then removed under reduced pressure, but the residual glass could not be induced to crystallise, and possibly contained some partly hydrolysed material. It was therefore heated for a further 8 hours with 2N-hydrochloric acid (7 c.c.) at 100°, under nitrogen. Freeze-drying of the solution at *ca.* 0° under reduced pressure then gave the crude dithiol (2·7 g.) as a powder, m. p. 120—135°, $[\alpha]_D^{18}$ +18° (*c*, 1·2 in water) (Found: thiol S, 24·4. $C_6H_{14}O_4S_2$ requires S, 29·9%), which was acetylated by being heated on the steam-bath for 5 hours with acetic anhydride (12 c.c.) and fused sodium acetate (1 g.). The reaction mixture was then stirred with water and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue from methanol gave needles (0·6 g.) of *hexa-acetyl* 1 : 6-*dithiomannitol*, m. p. 107—109°, $[\alpha]_D^{17}$ +81·8° (*c*, 1 in chloroform), raised on further recrystallisation from methanol to m. p. 109—111°, $[\alpha]_D^{18}$ +85° (*c*, 1 in chloroform) (Found: C, 46·5; H, 5·9; S, 13·65. $C_{18}H_{26}O_{10}S_2$ requires C, 46·3; H, 5·6; S, 13·7%). Light absorption: max. 2300 A., ε 8200.

Deacetylation of the hexa-acetate (0·59 g.) by heating under reflux with 2% methanolic hydrogen chloride for 5 hours, followed by evaporation to dryness under reduced pressure, gave a solid (0·3 g.), which was freed from traces of acid by being kept under reduced pressure for several hours over potassium hydroxide. Recrystallisation from methanol gave 1 : 6-*dithiomannitol*, m. p. 155—157°, $[\alpha]_D^{20}$ +1·86° (*c*, 0·6 in water), $[\alpha]_D^{20}$ +15° (*c*, 0·6 in 2·9% aqueous borax) (Found: C, 34·3; H, 6·85; S, 29·4; thiol S, 28·7. $C_6H_{14}O_4S_2$ requires C, 33·6; H, 6·6; S, 29·9%). The dithiol is hygroscopic, and recrystallisation is attended with some difficulty. Unlike 1 : 6-dithiodulcitol (the former "1 : 6-dithiomannitol"), it is readily soluble in water.

1 : 2-3 : 4-*Di*iso*propylidene* 1 : 4-*Dithioerythritol.*—In Part III (Evans, Fraser, and Owen, *loc. cit.*) the m. p. of this substance was erroneously given as 145°; it has m. p. 105°.

Acknowledgment is made to the Department of Scientific and Industrial Research for a maintenance grant (to P. B.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

[*Received, November 3rd,* 1949.]