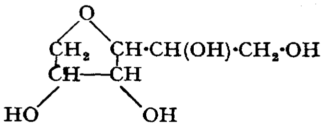
2. *The Anhydrides of Polyhydric Alcohols. Part I. The Constitution of* iso*Mannide.*

By L. F. Wiggins.

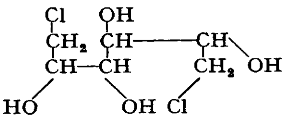
Methods of preparation of *iso*mannide are given, including its production by the dry distillation of 1 : 6-dichloro mannitol. From a study of the products of ring fission with hydrochloric acid and other reactions of *iso*mannide evidence is presented showing it to have the structure of 1 : 4-3 : 6-dianhydromannitol. The 2 : 5-dimethyl dianhydromannitol is described and is prepared by the action of sodium methoxide on 1 : 6-*dichloro* 2 : 5-*dimethyl mannitol.*

It is well known that mannitol readily loses the elements of water on being heated alone or with acids and gives rise to mixtures of several anhydro-derivatives. One of these, named mannitan, has been shown to be 3 : 6-anhydromannitol (I) by its preparation from 3 : 6-anhydromannose (Valentin, *Coll. Czech. Chem. Comm.*, 1936, **8**, 35). When mannitol is heated with formic acid, the mannitan produced is accompanied by a dianhydromannitol which has been named *iso*mannide. The latter is formed in a greater proportion if hydrochloric acid is used instead of formic acid (Fauconnier, *Bull. Soc. chim.*, 1884, **41**, 119; *Compt. rend.*, 1885, **100**, 914). These anhydrides are also formed to a smaller extent when mannitol is subjected to dry distillation (Fauconnier, *Compt. rend.*, 1882, **95**, 991).

More convenient methods of preparation of *iso*mannide have now been developed. It is formed in 35% yield (i) by heating mannitol, suspended in dichloro glycerol, in a stream of hydrogen chloride, or (ii) by boiling mannitol with fuming hydrochloric acid for 3 days. *iso*Mannide also results from the action of heat on 1 : 6-dichloro mannitol (II), which is itself obtained by the action of fuming hydrochloric acid on mannitol (Haworth, Heath, and Wiggins, J., 1944, 155). 1 : 6-Dichloro mannitol, the structure of which has been established by Micheel (*Annalen*, 1932, **496**, 77) and by Haworth and Wiggins (J., 1944, 58), melts with decomposition at 174°, one product being *iso*mannide. When dichloro mannitol is heated under diminished pressure, hydrogen chloride is evolved and *iso*mannide distils in almost quantitative yield.



(I.)



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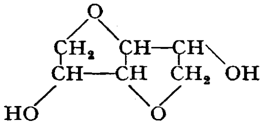


(III.)

The constitution of *iso*mannide has not hitherto been established, although Romburgh and Burg (*Proc. Acad. Sci. Amsterdam*, 1922, **25**, 335) on indirect evidence suggested that it was 1 : 4-3 : 6-dianhydromannitol.

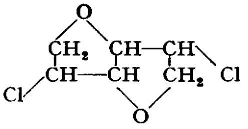
That in fact this is the correct structure is shown in this paper, and *iso*mannide is represented as a dihydroxyhexahydrodifuran (III).

The description of *iso*mannide as 1 : 4-3 : 6-dianhydromannitol is based on the following experimental evidence.

(1) When heated with fuming hydrochloric acid under pressure, *iso*mannide undergoes anhydro ring scission and 1 : 6-dichloro mannitol is obtained. Positions 1 and 6 are therefore involved in the anhydro rings.

(2) Lead tetra-acetate is without action on *iso*mannide, an indication that the two hydroxyl groups are not on adjacent carbon atoms.

(3) Treatment of *iso*mannide with thionyl chloride and pyridine yields a dichloro dianhydrohexitol (m. p. 67°) which is described as 2 : 5-dichloro dianhydromannitol because its treatment with fuming hydrochloric acid under pressure leads to the production of crystalline 1 : 2 : 5 : 6-*tetrachloro mannitol*, which can be reconverted into the original dichloro mannitol by treatment with sodium methoxide. This tetrachloro-compound was shown to possess the configuration of mannitol inasmuch as it was easily convertible into hexachloro mannitol. Moreover, the given allocation of the chlorine atoms was established by the following synthetic procedure.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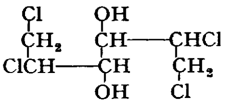
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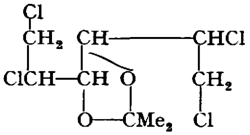
(VI.)

1 : 6-Dichloro mannitol readily forms a monoacetone compound in which the acetone residue was assigned, without proof, to C_3 and C_4 by Micheel (*Annalen*, 1932, **486**, 77). The author has recently confirmed this view (Wiggins, unpublished work). Treatment of 1 : 6-dichloro 3 : 4-monoacetone mannitol with thionyl chloride and pyridine yielded a non-crystalline *tetrachloro monoacetone* derivative in which the chlorine atoms must be located at C_1, C_2, C_5, and C_6. Acetonisation of the tetrachloro mannitol obtained by the ring opening of dichloro *iso*mannide gave a liquid which was identical with the above in respect of refractive index, boiling point and specific rotation. The product of ring fission of dichloro *iso*mannide with hydrochloric acid must therefore be 1 : 2 : 5 : 6-tetrachloro mannitol (V) and the acetone compound must be represented by (VI).

(4) That the hydroxyl groups of *iso*mannide are located at C_2 and C_5 is further shown by the synthesis of dimethyl *iso*mannide from 1 : 6-*dichloro* 3 : 4-*monoacetone* 2 : 5-*dimethyl mannitol*. The latter compound was prepared by the cautious methylation of the known 1 : 6-dichloro 3 : 4-monoacetone mannitol (Micheel, *loc. cit.*). Its hydrolysis led to the isolation of 1 : 6-*dichloro* 2 : 5-*dimethyl mannitol*, which was converted, by treatment with two equivalents of sodium methoxide, into 2 : 5-*dimethyl* iso*mannide*, identical with the product of direct methylation of *iso*mannide.

(5) It is clear, therefore, that the two anhydro rings of *iso*mannide involve positions 1, 3, 4, and 6 and the substance is to be described as either (*a*) 1 : 4-3 : 6-dianhydro-, or (*b*) 1 : 3-4 : 6-dianhydro-mannitol. That the rings are in fact hydrofuranol [*i.e.*, (*a*)] in type is shown by the following facts: (i) The observation of Fauconnier (*loc. cit.*) that *iso*mannide results from the action of formic acid on 3 : 6-anhydromannitol (mannitan) and that mannitan is now found to give *iso*mannide on distillation in the presence of a drop of sulphuric acid, whereas by itself it distils unchanged. (ii) Mannitan is converted into *iso*mannide by the following series of reactions involving only neutral or alkaline reagents. From mannitan (3 : 6-anhydromannitol) is obtained a liquid *tosyl triacetyl* derivative in which the tosyl group is substituting a primary alcoholic group, proved by the fact that sodium toluene-*p*-sulphonate is obtained in 80% yield when it is treated with sodium iodide in acetone solution. This tosyl triacetyl mannitan on treatment with sodium methoxide gives *iso*mannide identical with the substance obtained by the action of hydrochloric acid on mannitol. This view of the constitution of *iso*mannide is supported by the extreme stability of the ring system in the original dianhydro-compound, the dimethyl and dichloro derivatives. Thus *iso*mannide is not affected by heating under pressure with either methyl-alcoholic sodium methoxide or ammonia; furthermore the ring system is stable to oxidising agents such as nitric acid at 100°, since the dimethyl derivative can be recovered unchanged after several hours' treatment with this reagent. This stability is characteristic of the hydrofuranol structure (cf. Peat and Wiggins, J., 1938, 1088) and in no wise agrees with the expected properties of the four-membered ring system postulated under (*b*) above. This anhydro ring type is found in 1 : 2-monoacetone 3 : 5-anhydroxylose, which easily undergoes ring scission with alkaline reagents (Levene and Raymond, *J. Biol. Chem.*, 1933, **102**, 331).

EXPERIMENTAL.

Treatment of Mannitol with Hydrogen Chloride in Dichloro Glycerol.—Mannitol (20 g.) was suspended in dichloro glycerol (70 c.c.), heated at 140—150°, through which hydrogen chloride was passed. After 1½ hours solution was complete and after 3½ hours' heating the solution was evaporated to a syrup, which distilled at 130—140°/0·03 mm., giving a mobile liquid (6·5 g.), $n_D^{18^\circ}$ 1·5010, which crystallised rapidly on cooling. After being recrystallised from ethyl acetate–alcohol it (5·4 g.) had m. p. 87—88° and $[\alpha]_D$ +91·0° in water (*c*, 2·28) and was dianhydromannitol identical with the *iso*mannide of Fauconnier (*loc. cit.*).

Treatment of Mannitol with Concentrated Hydrochloric Acid.—Mannitol (500 g.) was dissolved in fuming hydrochloric acid (3 l.), and the mixture boiled for 72 hours; the acid solution was then evaporated to a syrup, and the last traces of hydrochloric acid removed by evaporation with water. Finally the syrup was distilled on the water-pump at 180—200°. The distillate (140 g.) crystallised completely and was recrystallised from ethyl acetate containing a little alcohol (m. p. 87°). Other volatile products were obtained which are being investigated.

Action of Heat on 1 : 6-*Dichloro Mannitol.*—1 : 6-Dichloro mannitol (2 g.) was heated in a vacuum at 180°. Evolution of hydrogen chloride occurred and the mass became more mobile and eventually distilled completely. The distillate (1·2 g.) crystallised on cooling; recrystallised from ethyl acetate, it formed prismatic crystals (0·95 g.), m. p. 87°, not depressed by authentic 1 : 4-3 : 6-dianhydromannitol.

2 : 5-*Dichloro* 1 : 4-3 : 6-*Dianhydromannitol.*—Dianhydromannitol (4 g.) was dissolved in dry pyridine (5·6 g.), and thionyl chloride (6·4 g.) carefully added at 0°. The mixture was warmed on the water-bath to 90°, sulphur dioxide then being evolved. After being heated for ½ hour at 100°, the mixture was poured into water, the filtered solution extracted with chloroform, and the extract washed with sodium bicarbonate solution and with water and dried over anhydrous magnesium sulphate. On evaporation a crystalline residue (4 g.) was obtained which, recrystallised from ether–petrol, formed long needles (3·3 g.; 70% of the theoretical), m. p. 67°, $[\alpha]_D$ +93·5° in chloroform (*c*, 2·054) (Found : C, 39·4; H, 4·2; Cl, 38·5. $C_6H_8O_2Cl_2$ requires C, 39·2; H, 4·4; Cl, 39·0%). The *substance* was extremely stable, being recovered unchanged by distillation with fused caustic potash.

2 : 5-*Dimethyl* 1 : 4-3 : 6-*Dianhydromannitol.*—Dianhydromannitol (1 g.) was treated four times with methyl iodide and silver oxide at 45°, the product being extracted after each treatment with boiling chloroform. The crystalline *substance* finally obtained, recrystallised from ether–petrol, formed thin leaflets (0·9 g.), m. p. 75—76°, $[\alpha]_D^{18°}$ +175·0° in chloroform (*c*, 2·287) (Found : C, 54·6; H, 8·4; OMe, 34·8. $C_8H_{14}O_4$ requires C, 55·0; H, 8·1; OMe, 35·4%).

Treatment of Dianhydromannitol with Hydrochloric Acid.—Dianhydromannitol (1 g.), dissolved in fuming hydrochloric acid (20 c.c.), was heated for 24 hours in a sealed tube. On evaporation a semi-crystalline mass was obtained; from its solution in a little alcohol–water, crystals of 1 : 6-dichloro mannitol (0·25 g.) separated, m. p. 174° (Bouchardat, *Bull. Soc. chim.*, 1873, **19**, 199, gives m. p. 174°).

Lack of Action of Alkaline Reagents on the Dianhydromannitol.—(a) *Methyl-alcoholic ammonia.* Dianhydromannitol (1 g.) was heated at 120° for 20 hours with methyl alcohol (50 c.c.) saturated with ammonia at 0°. The solution, on evaporation, gave a syrup which crystallised on nucleation with dianhydromannitol. Recrystallisation from ethyl acetate–alcohol gave unchanged dianhydromannitol (0·8 g.), m. p. 87°.

(b) *Sodium methoxide.* Dianhydromannitol (1 g.) was heated at 120° for 20 hours with excess of 10% methyl-alcoholic sodium methoxide. The solution was diluted with water and evaporated to dryness after neutralisation with 5N-sulphuric acid. Extraction of the residue with ethyl acetate gave unchanged dianhydromannitol (0·75 g.), m. p. 87°.

Non-oxidation of 2 : 5-*Dimethyl Dianhydromannitol with Nitric Acid.*—The substance (0·5 g.), dissolved in nitric acid (*d* 1·4; 10 c.c.), was heated at 100° for 4 hours without the occurrence of any obvious reaction. Water was added, and the nitric acid removed by evaporation at constant volume. After evaporation to dryness the residual syrup was extracted with chloroform, and the extract filtered and evaporated to a crystalline residue, which, recrystallised from ethyl acetate–light petroleum, had m. p. 75°, not depressed by the original material. Yield, 0·35 g. (Found : OMe, 36·0. Calc. for $C_8H_{14}O_4$: OMe, 35·4%). The product was therefore unchanged 2 : 5-dimethyl dianhydromannitol.

Treatment of Dianhydromannitol with Lead Tetra-acetate.—Dianhydromannitol (2 g.), dissolved in glacial acetic acid (100 c.c.), was shaken with lead tetra-acetate (6·5 g.; 1·1 mols.) for 48 hours, and the solution poured on ice, neutralised with sodium bicarbonate, filtered, and evaporated to dryness. The residue was extracted with ethyl acetate under reflux and on evaporation of the extract a crystalline residue (1·9 g.) was obtained which, recrystallised from ethyl acetate–alcohol, had m. p. 86—87°, not depressed by the original material. Yield, 1·7 g.

1 : 2 : 5 : 6-*Tetrachloro Mannitol.*—2 : 5-Dichloro dianhydromannitol (7·2 g.), suspended in fuming hydrochloric acid (200 c.c.), was heated in a sealed tube for 72 hours at 110°. After evaporation there remained a syrupy residue A (6 g.). The aqueous distillate contained crystals which had distilled with the water vapour and which, after separation and recrystallisation from light petroleum (yield, 1·6 g.), had m. p. 66°, not depressed by authentic 2 : 5-dichloro dianhydromannitol. The syrupy residue A was dissolved in ether, and a little light petroleum added; the crystals that slowly separated were collected in several fractions, but each melted at 69—70°. Total yield, 3·4 g., $[\alpha]_D$ +28·3° in chloroform (*c*, 3·107) (Found : C, 27·7; H, 4·1; Cl, 54·9. $C_6H_{10}O_2Cl_4$ requires C, 28·1; H, 3·9; Cl, 55·5%). The product was 1 : 2 : 5 : 6-*tetrachloro mannitol.*

There was a residual syrup which did not crystallise but distilled at 135°/0·03 mm. (1·6 g.) (Found : Cl, 50·6%).

1 : 2 : 5 : 6-*Tetrachloro* 3 : 4-*Dibenzoyl Mannitol.*—Tetrachloro mannitol (0·14 g.) was dissolved in dry pyridine (2 c.c.), a slight excess of benzoyl chloride (0·2 c.c.) added, and the mixture kept overnight. The solution was poured into water and extracted with chloroform. The extract was washed successively with 5% sulphuric acid, sodium bicarbonate solution, and water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The syrupy residue crystallised on cooling and, recrystallised from ether–light petroleum, formed stout needles (0·15 g.), m. p. 109—110°, $[\alpha]_D^{17°}$ −95·4° in chloroform (*c*, 1·048) (Found : C, 51·9; H, 3·9; Cl, 31·5. $C_{20}H_{18}O_4Cl_4$ requires C, 51·7; H, 3·8; Cl, 30·6%).

Conversion of 1 : 2 : 5 : 6-*Tetrachloro Mannitol into Hexachloro Mannitol.*—1 : 2 : 5 : 6-Tetachloro mannitol (0·4 g.) was heated with phosphorus pentachloride (1 g.) at 130° for 1 hour, hydrogen chloride being evolved. The mixture was diluted with chloroform and poured on ice, and the chloroform layer separated, washed with sodium bicarbonate solution and with water, dried over anhydrous magnesium sulphate, and evaporated. Recrystallisation from light petroleum gave hexachloro mannitol, m. p. 138°, not depressed by an authentic specimen.

Action of Sodium Methoxide on 1 : 2 : 5 : 6-*Tetrachloro Mannitol.*—Tetrachloro mannitol (1 g.) was dissolved in chloroform (10 c.c.), methyl-alcoholic sodium methoxide (containing 0·45 g. of sodium methoxide) added, and the mixture kept for 4 hours at room temperature. After dilution with water the solution was extracted with chloroform, and the extract washed with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue, recrystallised from light petroleum (yield, 0·5 g.), had $[\alpha]_D$ +91·5° in chloroform (*c*, 1·66), m. p. 67—68°, not depressed by authentic 2 : 5-dichloro dianhydromannitol.

Acetonisation of 1 : 2 : 5 : 6-*Tetrachloro Mannitol.*—Tetrachloro mannitol (0·3 g.) was shaken overnight with dry acetone (25 c.c.) containing concentrated sulphuric acid (0·1 c.c.). The acid was neutralised with anhydrous sodium carbonate, and the solution filtered and evaporated to a syrup, which distilled at 115° (bath temp.)/0·05 mm. and was 1 : 2 : 5 : 6-*tetrachloro* 3 : 4-*monoacetone mannitol.* Yield 0·33 g., $n_D^{16°}$ 1·4954, $[\alpha]_D^{20°}$ +56·8° in chloroform (*c*, 2·405) (Found : C, 36·5; H, 4·7. $C_9H_{14}O_2Cl_4$ requires C, 36·5; H, 4·7%).

Chlorination of 1 : 6-*Dichloro* 3 : 4-*Monoacetone Mannitol.*—The material (Micheel, *Annalen*, 1932, **497**, 77) (1 g.) was dissolved in dry pyridine (5 g.), thionyl chloride (4 g.) added at 0°, and the mixture warmed to 100°, evolution of sulphur dioxide then occurring. After being kept thereat for 1 hour, the mixture was poured on ice, the filtered solution extracted with chloroform, and the extract washed successively with sodium bicarbonate solution and water. On evaporation a syrup was obtained, which was purified by extraction with ether, filtration, evaporation, and distillation of the product. The material distilled at 115° (bath temp.)/0·05 mm. and was 1 : 2 : 5 : 6-tetrachloro 3 : 4-monoacetone mannitol (0·4 g.), $n_D^{18°}$ 1·4955, $[\alpha]_D^{18°}$ +57·3° in chloroform (*c*, 1·99) (Found : C, 37·0; H, 4·6; Cl, 47·4. Calc. for $C_9H_{14}O_2Cl_4$: C, 36·5; H, 4·7; Cl, 48·0%).

1 : 6-*Dichloro* 3 : 4-*Monoacetone* 2 : 5-*Dimethyl Mannitol.*—Dry 1 : 6-dichloro 3 : 4-monoacetone mannitol (5 g.) was treated with excess of dry methyl iodide and dry silver oxide at 45° for 9 hours, and after evaporation of the methyl iodide the residue was extracted several times with boiling chloroform. After five such treatments the product distilled at 110° (bath temp.)/0·02 mm. Yield, 3·83 g. The distillate partly crystallised; it was drained on tile, and the product recrystallised from ether–petrol. 1 : 6-*Dichloro* 3 : 4-*monoacetone* 2 : 5-*dimethyl mannitol* had m. p. 56°, $[\alpha]_{\rm D}$ +11·5° in chloroform (*c*, 2·253). Yield, 1·6 g. (Found : C, 45·8; H, 6·7; Cl, 25·0; OMe, 20·6. $C_{11}H_{20}O_4Cl_2$ requires C, 46·0; H, 7·0; Cl, 24·7; OMe, 21·6%).

1 : 6-*Dichloro* 2 : 5-*Dimethyl Mannitol.*—The preceding compound (0·503 g.) was dissolved in 75% alcohol containing 5% sulphuric acid (40 c.c.) and kept at room temperature, and the reaction followed polarimetrically : $[\alpha]_{\rm D}$ +9·5° (initial value); +3·0° (48 hrs.); +1·6° (74 hrs.); −3·2° (95 hrs.); −16·0° (168 hrs.); −25·4° (312 hrs.); −30·2° (383 hrs.); −35·0° (550 hrs.). The solution was thereafter neutralised with barium carbonate, filtered, and evaporated to dryness. The residue was extracted with chloroform, and the extract evaporated to small bulk. The crystals that separated were recrystallised from chloroform, giving 1 : 6-*dichloro* 2 : 5-*dimethyl mannitol* (0·21 g.), m. p. 131° (Found : C, 38·5; H, 6·1; OMe, 24·4. $C_8H_{16}O_4Cl_2$ requires C, 38·9; H, 6·4; Cl, 28·7; OMe, 24·8%).

Action of Sodium Methoxide on 1 : 6-*Dichloro* 2 : 5-*Dimethyl Mannitol.*—1 : 6-Dichloro 2 : 5-dimethyl mannitol (0·17 g.) was dissolved in chloroform (5 c.c.), methyl alcohol (2 c.c.) containing sodium (0·04 g.) added, and the mixture kept at room temperature overnight; sodium chloride had then separated. The mixture was diluted with water and extracted with chloroform, the extract dried over anhydrous magnesium sulphate and evaporated to dryness, and the crystalline residue recrystallised from ether–light petroleum, giving 2 : 5-dimethyl dianhydromannitol (0·09 g.), m. p. and mixed m. p. 75—76° (Found : OMe, 35·6. Calc. for $C_8H_{14}O_4$: OMe, 35·2%).

Mannitan.—Mannitol (500 g.) was boiled with concentrated hydrochloric acid (2 l.) for 12 hours only. The resulting solution was evaporated, and the syrup obtained dissolved in alcohol and allowed to crystallise. After 3 days the crystals which had separated were collected and recrystallised several times from alcohol–water; m. p. 145—147°, identical with that given by Valentin (*loc. cit.*). Yield, 25·5 g. The filtrates were evaporated, and the residue used to prepare *iso*mannide.

Dry Distillation of Mannitan.—Mannitan (2 g.) was distilled under reduced pressure (10 mm.) over a gauze, practically without decomposition; yield of distillate which crystallised completely, 1·8 g. Recrystallised from alcohol–water, it had m. p. 145—147° and was identical with the original material.

Dry Distillation of Mannitan in the Presence of Acid Catalysts.—Mannitan (2 g.) was melted, 2 drops of concentrated sulphuric acid added, and the mixture distilled over a gauze at 10 mm. Water distilled first, followed by *iso*mannide (1·1 g.), which, recrystallised from ethyl acetate, had m. p. and mixed m. p. 86—87°.

Conversion of Mannitan into iso*Mannide with Alkaline Reagents.*—Mannitan (5 g.) was dissolved in dry pyridine (50 c.c.), and tosyl chloride (6 g.) carefully added at 0°. The mixture was kept at room temperature for 96 hours, acetic anhydride (25 c.c.) being added after the first 48 hours. The solution was poured on ice and extracted with chloroform. The extract was washed successively with 5% sulphuric acid, sodium bicarbonate solution, and water, dried over anhydrous magnesium sulphate, and evaporated. Yield, 10·5 g. The product, however, was a liquid which has, so far, defied attempts at crystallisation. It was 1-*tosyl* 2 : 4 : 5-*triacetyl mannitan* (Found : S, 7·3. $C_{19}H_{24}O_{10}S$ requires S, 7·3%).

Detosylation. The material (10 g.) was dissolved in chloroform (50 c.c.), and methyl alcohol (30 c.c.) containing sodium (2·1 g.) added at 0°. The solution was kept overnight, diluted with chloroform, and extracted with water. The aqueous extracts were combined, neutralised with N-sulphuric acid, and evaporated to dryness in the presence of barium carbonate. The dry residue was extracted with boiling ethyl acetate, the extract evaporated, and the product distilled at 140—160°/0·08 mm. Yield, 1·6 g.; 50% of the theoretical. The distillate crystallised; recrystallised from ethyl acetate, it formed prisms, m. p. 86—87° alone or in admixture with authentic *iso*mannide.

Treatment of 1-*Tosyl* 2 : 4 : 5-*Triacetyl Mannitan with Sodium Iodide in Acetone.*—The liquid monotosyl triacetyl mannitan (5·6 g.) was dissolved in dry acetone (50 c.c.) containing dry sodium iodide (4 g.), and the solution heated at 100° for 12 hours under pressure. The liquid was filtered, and the precipitate of sodium toluene-*p*-sulphonate washed with acetone and dried in a vacuum. Yield, 1·9 g.; 78% of the theoretical.

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