209. *The Preparation of 2 : 3-Anhydro-, 3 : 4-Anhydro-, and 3 : 6-Anhydro-methylhexosides from 3-p-Toluenesulphonyl Methylglucoside.*

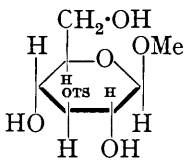
By S. PEAT and L. F. WIGGINS.

The removal by mild alkaline hydrolysis of the *p*-toluenesulphonyl group from 3-*p*-toluenesulphonyl β-methylglucoside yields a mixture of three anhydro-β-methylhexosides, namely, 3 : 6-anhydro-β-methylglucoside, 2 : 3-anhydro-β-methylalloside, and 3 : 4-anhydro-β-methylalloside. The separation and characterisation of derivatives of these substances are described and reasons are adduced for assigning an allose configuration to the last two, the formation of which involves a Walden inversion on C_3. Anhydro-ring formation is not an invariable accompaniment of the alkaline hydrolysis of a sugar *p*-toluenesulphonate, for 3-*p*-toluenesulphonyl glucose monoacetone is hydrolysed by alkali without either anhydro-ring formation or Walden inversion. Walden inversion without anhydro-ring formation has not been observed.

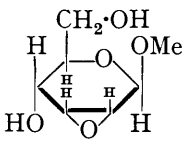
Dimethyl 3 : 4-anhydro-β-methylalloside, when boiled with sodium methoxide solution, gives a mixture of 2 : 3 : 6-trimethyl β-methylglucoside and 2 : 4 : 6-trimethyl β-methylguloside, an indication that the anhydro-ring is opened in both of the possible directions and that in each case Walden inversion occurs. The anhydro-ring is opened also by acid hydrolysis. By the action of hydrochloric acid on dimethyl 2 : 3-anhydro-α-methylalloside and on dimethyl 3 : 4-anhydro-β-methylalloside there are formed dimethyl chlorohexose and dimethyl chloro-β-methylhexoside respectively, the latter being produced in the cold.

The stability of the 3 : 6-anhydro-ring to either acid or alkali is demonstrated and comment is made upon the steric effect of this ring system.

IN an earlier communication (Haworth, Hirst, and Panizzon, J., 1934, 154) it was shown that the alkaline hydrolysis of 2-*p*-toluenesulphonyl β-methylglucoside resulted in the formation of an anhydro-β-methylhexoside, which was isolated as the crystalline dimethyl derivative. It has now been shown that the hydrolysis of 3-*p*-toluenesulphonyl α- or β-methylglucoside by sodium methoxide under mild conditions gives rise to a mixture of three anhydromethylhexosides, which have been separated and [when prepared from the β-glucoside (I)] recognised as 2 : 3-anhydro-β-methylalloside (II), 3 : 4-anhydro-β-methylalloside (III), and 3 : 6-anhydro-β-methylglucoside (IV).



(I.)



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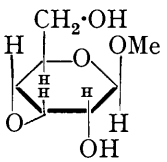

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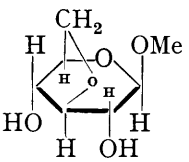


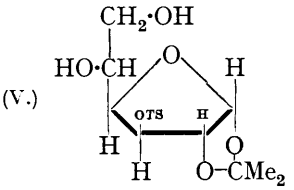
(IV.)

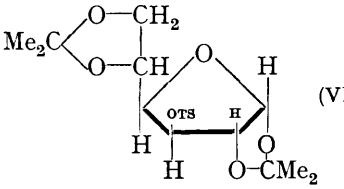
In methylglucoside the only free hydroxyl which is situated in the *cis*-position with respect to the hydroxyl at C_3 is that at C_6 and it is proved that an oxygen bridge is established between these two carbon atoms in 3 : 6-anhydro-β-methylglucoside (IV) when the 3-*p*-toluenesulphonyl β-methylglucoside is hydrolysed. A Walden inversion at C_3, at the instant of removal of the toluenesulphonyl residue, would allow of the formation of two other anhydro-compounds, for the hydroxyl on C_3 would then be in the *cis*-position with respect to the hydroxyl groups at C_2 and C_4. Two such anhydro-compounds (II and III) do in fact accompany the 3 : 6-anhydro-substance (IV).

The isolation of the 3 : 6-anhydromethylglucoside is a clear indication that, in the sugar series, the removal by hydrolysis of a *p*-toluenesulphonyl group is not necessarily accompanied by a Walden inversion. When Walden inversion is observed, however, under these conditions, it is invariably accompanied by anhydro-ring formation. Thus, the *p*-toluenesulphonyl group is removed by alkaline hydrolysis from 3-*p*-toluenesulphonyl diacetone glucose and from 4-*p*-toluenesulphonyl 6-triphenylmethyl 2 : 3-dimethyl α-methylglucoside without Walden inversion (Oldham and Robertson, J., 1935, 685) and in each of these compounds anhydro-ring formation is not possible. We have observed, how-

ever, the interesting fact that the removal of the *p*-toluenesulphonyl group from a derivative of glucose in the furanose form may take place without Walden inversion or anhydro-ring formation even when appropriately placed hydroxyl groups are available for the latter purpose. For example, the treatment of 3-*p*-toluenesulphonyl glucofuranose monoacetone (V, prepared by the method of Ohle and Dickhauser, *Ber.*, 1925, **58**, 2593) or of its diacetyl derivative with cold sodium methoxide solution yields a mixture of compound (V) unchanged and glucofuranose monoacetone (30%).

(V.)





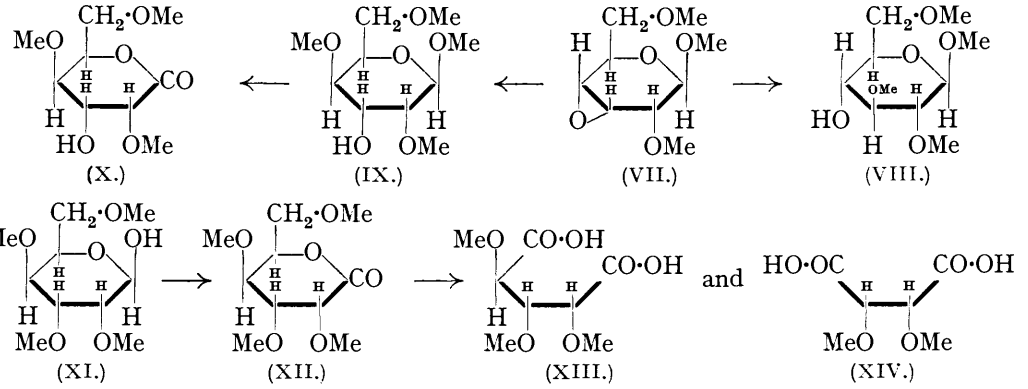
(VI.)

That Walden inversion accompanies the hydrolysis of many *p*-toluenesulphonates of optically active monohydric alcohols is evident from the work of Kenyon, Phillips, and their collaborators (see, for instance, J., 1935, 1072). The method of these authors is not, however, applicable to sugar toluenesulphonates. 3-*p*-Toluenesulphonyl glucose diacetone (VI) was treated with potassium acetate in alcohol under various conditions of temperature and pressure, but in every case the toluenesulphonate was recovered unchanged.

The starting material in this research was 3-*p*-toluenesulphonyl glucose diacetone (VI), which, by boiling with methyl-alcoholic hydrogen chloride, was converted into a syrupy mixture of the α- and the β-form of 3-*p*-toluenesulphonyl methylglucoside. After acetylation of the mixture it was possible to separate by fractional crystallisation the α- and the β-form of the triacetyl derivative. The 3-*p*-toluenesulphonyl triacetyl β-methylglucoside (identical with that of Freudenberg and Ivers, *Ber.*, 1922, **55**, 929) gave, on treatment with cold sodium methoxide, a mixture of anhydro-β-methylhexosides, the separation of which was achieved by the following procedure. The mixture was condensed with benzaldehyde in the presence of phosphoric oxide and crystalline 4 : 6-*benzylidene* 2 : 3-*anhydro*-β-*methylalloside* (XVII) was separated from the product. An aqueous extract of the residue after evaporation to dryness was methylated with methyl iodide and silver oxide to yield a mixture of dimethyl anhydromethylhexosides, from which, after distillation, there crystallised 2 : 6-*dimethyl* 3 : 4-*anhydro*-β-*methylalloside* (m. p. 46°) (VII). The remaining syrup contained *dimethyl* 3 : 6-*anhydro*-β-*methylglucoside*, since it gave dimethyl 3 : 6-anhydroglucose on hydrolysis with cold aqueous acid. The sugar was characterised as the anilide, m. p. 96°, which did not depress the melting point of 2 : 4-dimethyl 3 : 6-anhydroglucose anilide. The latter substance was prepared from 3 : 6-anhydroglucose monoacetone (Haworth and Smith, unpublished result). Further, on oxidation with bromine water the anhydro-sugar gave 2 : 4-*dimethyl* 3 : 6-*anhydrogluconolactone*, characterised as the crystalline *amide* of the corresponding acid, m. p. 91—92°. The gluconolactone in aqueous solution was hydrolysed slowly and incompletely ($[\alpha]_D$ + 90·9° ⟶ + 64·2° in 180 hours) and in this this respect simulated a γ-lactone. Nevertheless, the lactone must belong to the δ-series, since it is prepared from 3-*p*-toluenesulphonyl triacetyl β-methylglucopyranoside (the pyranose structure of this glucoside is established by a method described below) by a series of steps which precludes any possibility of the formation of a five-membered lactone ring or of any ring other than the six-membered ring present in the original glucoside. The appearance in this lactone of properties usually attributed to γ-lactones is to be ascribed to the steric effect of the 3 : 6-oxygen bridge. It is interesting to observe also that dimethyl 3 : 6-anhydro-β-methylglucopyranoside is easily hydrolysed by cold acid, in this respect behaving as a furanoside.

The constitution of 2 : 6-dimethyl 3 : 4-anhydro-β-methylalloside (VII) was established by a study of the products of its hydrolysis by alkali. Treatment of the anhydro-compound (VII) with boiling sodium methoxide solution gave a syrup, from which 2 : 3 : 6-trimethyl β-methylglucoside (VIII) crystallised. It was not found possible to separate completely the trimethyl methylglucoside, and the remaining syrup contained a little of this product.

However, the main constituent of this syrup was a trimethyl β-methylhexoside, which was considered on stereochemical grounds to be 2 : 4 : 6-trimethyl β-methyl-*d*-guloside and this view was confirmed by subsequent reactions.

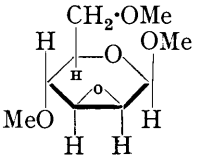


The trimethyl methylguloside (IX) on hydrolysis and oxidation with bromine water yields a lactone (X), which undergoes the rapid hydrolysis in aqueous solution characteristic of δ-lactones. Strong presumptive evidence is thereby provided that a methoxyl group is situated at C_4. Methylation of the trimethyl methylhexoside and hydrolysis of the product yields a tetramethyl hexose (XI), which is oxidised by bromine water to a δ-lactone (XII). This is proved by the evidence of degradative oxidation given below, thus confirming the pyranose structure of the trimethyl methylhexoside and, therefore, of the 3-*p*-toluenesulphonyl triacetyl β-methylglucoside from which it was derived. The tetramethyl δ-hexonolactone (XII) is shown to have the *d*-gulose configuration by the fact that on oxidation with nitric acid there are formed *l*-arabotrimethoxyglutaric acid (XIII) and *i*-dimethoxysuccinic acid (XIV). These acids were isolated and characterised as the methylamides. It has been pointed out that it was not possible to separate completely the trimethyl methylglucoside from the trimethyl methylguloside. Owing to the presence of a small amount of the former in the latter, the acids (XIII) and (XIV) were accompanied by *i*-xylotrimethoxyglutaric acid. The presence of this acid does not, however, invalidate the argument, since the acids (XIII) and (XIV) obtained together could be derived only from a methylated *d*-gulose.

Since the hydrolysis of the dimethyl anhydro-β-methylhexoside (m. p. 46°) with sodium methoxide results in the simultaneous production of a glucose derivative substituted with methoxyl at C_3 and a gulose derivative substituted at C_4, it is clear that the anhydro-bridge is formed between C_3 and C_4 and that the two methoxyl groups are situated at C_2 and C_6. It has been shown that the glucose product is 2 : 3 : 6-trimethyl β-methylglucoside (confirmed by the preparation from it of 2 : 3 : 6-trimethyl glucose, m. p. 114°, of tetramethyl β-methylglucopyranoside, m. p. 40°, and of tetramethyl glucopyranose, m. p. 91°) and it follows that the gulose derivative is 2 : 4 : 6-trimethyl β-methylgulopyranoside. The reaction is most simply explained on the supposition that the anhydro-hexoside has the *d*-allose configuration (VII). It is seen then that the opening of the anhydro-ring takes place in two directions and that each is accompanied by a Walden inversion. This is clearly so inasmuch as a trimethoxyglutaric acid is isolated from the nitric acid oxidation and this is shown to be *l*-arabotrimethoxyglutaric acid in which two methoxyl groups appear on opposite sides to those in *i*-trimethoxyglutaric acid, the normal oxidation product of methylated glucopyranose. It is further to be observed that the methoxyl group of the sodium methoxide becomes attached to the carbon atom in the sugar chain at which Walden inversion occurs. Müller (*Ber.*, 1934, **67**, 421; 1935, **68**, 1094), from a 4-*p*-toluenesulphonyl derivative of glucose, prepared a 2 : 6-dimethyl 3 : 4-anhydro-β-methylhexoside (m. p. 84°) which has different properties from the β-methylalloside described here. It appears very likely, therefore, that Müller's compound has the *d*-galactose configuration.

The fact that one of the anhydro-β-methylhexosides, produced by the mild alkaline hydrolysis of 3-*p*-toluenesulphonyl β-methylglucopyranoside, condenses with benzaldehyde is sufficient indication that in this methylhexopyranoside the hydroxyls at C_4 and C_6 are not involved in the anhydro-ring, which must therefore bridge C_2 and C_3. This view is confirmed in that 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (m. p. 198°) and 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside (m. p. 63°) are prepared by the appropriate treatment of the anhydromethylhexosides formed when the syrupy mixture of the α- and the β-form of 3-*p*-toluenesulphonyl methylglucoside is hydrolysed with sodium methoxide. The former of these compounds is apparently identical with that of Robertson and Griffith (J., 1935, 1197) and the latter with that prepared by Mathers and Robertson (J., 1933, 1076). Again, as the simplest stereochemical expression, the *d*-allose configuration is adopted for the 2 : 3-anhydromethylhexoside. In addition to the two derivatives mentioned, 4 : 6-*ethylidene* 2 : 3-*anhydro-α-methylalloside* (m. p. 128°) was isolated when the anhydromethylhexoside mixture was treated with paraldehyde.

It was found possible to remove the benzaldehyde residue from 4 : 6-benzylidene 2 : 3-anhydro-β-methylalloside, without disturbing the anhydro-bridge, by reduction with hydrogen in the presence of palladium. The product, 2 : 3-*anhydro-β-methylalloside* (m. p. 60—62°), gave 4 : 6-*dimethyl* 2 : 3-*anhydro-β-methylalloside* (m. p. 50°) when treated with Purdie's reagents. The latter compound is not identical with the dimethyl anhydro-β-methylhexoside (m. p. 69°) of Haworth, Hirst, and Panizzon and since the latter substance has been shown to be likewise a 2 : 3-anhydro-derivative (unpublished work), it must necessarily have the *d*-mannose configuration (XV). The non-identity of the two 2 : 3-anhydro-β-methylhexosides was confirmed by a comparison of their benzaldehyde



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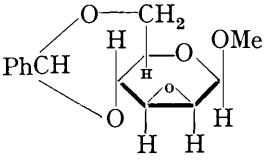
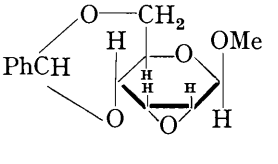


(XVI.)



(XVII.)

derivatives. Treatment of the syrupy 2 : 3-anhydro-β-methylmannoside (prepared by the method of Haworth, Hirst, and Panizzon) with benzaldehyde yielded crystalline 4 : 6-*benzylidene* 2 : 3-*anhydro-β-methylmannoside* (XVI), m. p. 183°. The melting point of this product was depressed by 4 : 6-benzylidene 2 : 3-anhydro-β-methylalloside (XVII).

Some interesting differences were observed in the rates of hydrolysis of the three anhydromethylhexosides prepared, as described above, from 3-*p*-toluenesulphonyl methylglucoside. The 3 : 6-anhydro-ring is not disrupted by either boiling 6% hydrochloric acid or boiling 2·5N-aqueous-alcoholic potassium hydroxide. By the latter reagent, 4 : 6-benzylidene 2 : 3-anhydro-β-methylalloside is hydrolysed with the production of a benzylidene β-methylhexoside (m. p. 188°) which, by analogy, is probably 4 : 6-*benzylidene β-methylaltroside*. No hydrolysis of 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside occurred when it was treated with 5% hydrochloric acid in the cold, but on heating, the glycosidic methyl group was removed and the anhydro-ring opened. The syrupy product analysed as a *dimethyl chlorohexose*. On the other hand, hydrolysis of 2 : 6-dimethyl 3 : 4-anhydro-β-methylalloside proceeds in the cold with the same acid reagent. The anhydro-ring is opened and a chlorine atom is introduced. No hydrolysis of the glycosidic methyl group occurs at this temperature and the product is non-reducing. The *dimethyl chloro-methylhexoside* is not crystalline, nor is the monoacetyl derivative prepared from it. Müller (*loc. cit.*) has shown that the anhydro-ring is opened and chlorine similarly introduced into the molecule when dimethyl 3 : 4-anhydro-β-methylgalactoside is boiled with N-hydrochloric acid. The product, a dimethyl chlorohexose, is crystalline. Robertson and Dunlop (this vol., p. 472) describe the preparation of two α-methylhexoside chlorohydrins by the action of hydrochloric acid in acetone solution on 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside.

Experimental.

Preparation of 3-p-*Toluenesulphonyl Triacetyl* β-*Methylglucoside.*—3-*p*-Toluenesulphonyl diacetone glucose (90 g.; prepared by the method of Freudenberg and Ivers, *Ber.*, 1922, **55**, 929) was boiled with 2% methyl-alcoholic hydrogen chloride until there was no further change in the optical rotation. After neutralisation with silver carbonate, the solution was evaporated under diminished pressure. The residual syrup was freed from colloidal silver and a small amount of silver *p*-toluenesulphonate by repeated solution and filtration, first in methyl alcohol and then in chloroform. There was thus obtained, as a viscid clear syrup, a mixture of the α- and the β-form of 3-*p*-toluenesulphonyl methylglucoside. Yield, 80 g. (90% of the theoretical). The rotation of different batches varied between $[\alpha]_D$ + 30° and + 40° in methyl alcohol.

Acetylation of this product was accomplished by using either (a) acetic anhydride and pyridine at 36° or (b) fused sodium acetate and acetic anhydride at a higher temperature. The second method was usually preferred. The acetylated product from 3-*p*-toluenesulphonyl methylglucoside (34 g.) was a thick syrup which partly crystallised on keeping in contact with ether. By extraction with ether, the acetate was separated into two fractions: a crystalline material (A) and a syrup (B). The substance (A), crystallised repeatedly from methyl alcohol, was 3-*p*-toluenesulphonyl 2 : 4 : 6-triacetyl β-methylglucoside, m. p. 138°, $[\alpha]_D^{19°}$ — 19·5° in chloroform (Freudenberg and Ivers give m. p. 138°, $[\alpha]_D^{25°}$ — 17·0° in acetylene tetrachloride, for the same compound, prepared, however, in a different way) (Found: C, 50·5; H, 5·6. Calc. for $C_{20}H_{26}O_{11}S$: C, 50·6; H, 5·55%). Yield, 8 g. (25% of the theoretical).

The syrup (B) crystallised after being kept in contact with ether for several weeks. It was recrystallised repeatedly from methyl alcohol and proved to be 3-p-*toluenesulphonyl* 2 : 4 : 6-*triacetyl* α-*methylglucoside*, m. p. 97°, $[\alpha]_D^{16°}$ +87·1° in chloroform (Found: C, 50·7; H, 5·6%). Yield, 10 g. (30% of the theoretical).

The Alkaline Hydrolysis of 3-p-*Toluenesulphonyl Triacetyl* β-*Methylglucoside.*—The β-methylglucoside (m. p. 138°, 8·8 g.) was dissolved in chloroform (40 c.c.), mixed with a 5% solution of sodium in methyl alcohol (35 c.c.), and kept for 24 hours at room temperature. After filtration from the precipitated sodium salts, the chloroform–methyl alcohol solution was repeatedly extracted with water. The united aqueous extract, made neutral to phenolphthalein with N-sulphuric acid, was evaporated to dryness at 40° in the presence of a little barium carbonate and the dry residue was extracted with boiling ethyl acetate. Distillation of the ethyl acetate left a colourless viscid syrup, $[\alpha]_D^{20°}$ —82° in ethyl acetate, which later examination showed to be a mixture of anhydro-β-methylhexosides. Yield, 2·76 g. (86% of the theoretical). This anhydro-β-methylhexoside mixture was prepared as required and individual samples showed $[\alpha]_D$ varying between — 80° and — 90°.

*Separation of the Anhydro-*β-*methylhexoside Mixture into its Constituents.*—The anhydro-β-methylhexoside mixture (4·6 g.), dissolved in dry chloroform (40 c.c.), was treated with phosphoric oxide (5 g.) and freshly distilled benzaldehyde (5 c.c.), and the mixture kept overnight at room temperature. The phosphorus residues were then removed by filtration, and the chloroform solution extracted six times with water (total, 6 l.). It was difficult to effect complete separation of the water and chloroform and, in consequence, the former contained a little of the chloroform solution. The aqueous extract was evaporated to dryness in the presence of barium carbonate and the residue was repeatedly extracted with ethyl acetate. This ethyl acetate extract, on evaporation, gave a colourless syrup, referred to as (C). Yield, 2·6 g. $[\alpha]_D^{18°}$ —91·4° in ethyl acetate (Found: OMe, 18·7%).

The chloroform solution, after being dried with anhydrous magnesium sulphate, was also evaporated in the presence of barium carbonate, and the gummy residue submitted to steam-distillation to remove benzaldehyde (a control experiment established that 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside was not hydrolysed when steam-distilled). Thereafter the water was distilled, and the dry residue purified by solution in chloroform, filtration, and removal of the solvent under diminished pressure. The product was a crystalline solid (2·15 g.). After recrystallisation from methyl alcohol it showed m. p. 138° and $[\alpha]_D^{19°}$ —15·6° in chloroform. It was 4 : 6-*benzylidene* 2 : 3-*anhydro*-β-*methylalloside* (Found: C, 63·7; H, 6·1; OMe, 11·8. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1; OMe, 11·8%).

*Methylation of the Non-crystalline Anhydro-*β-*methylhexoside* (*C*).—The syrup (C) (2·6 g.) was given three treatments with methyl iodide and silver oxide, and the product distilled at 92—100° (bath temp.)/0·02 mm. Yield of distillate, 1·43 g.; residue, 0·7 g. (probably benzylidene compound). The distillate, a colourless mobile oil, $n_D^{17°}$ 1·4544, partly crystallised

on keeping at 0°. It was possible by spreading the mixture on a porous tile to separate the crystalline constituent, which formed long needles (0·7 g.) from dry ether–light petroleum. This product had m. p. 46°, $[\alpha]_D^{21°}$ — 144·5° in chloroform, and was shown later to be 2 : 6-*dimethyl* 3 : 4-*anhydro*-β-*methylalloside* (Found : C, 53·0; H, 7·9; OMe, 45·4. $C_9H_{16}O_5$ requires C, 52·9; H, 7·85; OMe, 45·7%). By extraction of the porous tile with chloroform, the syrupy constituent was recovered; it was purified by distillation in a high vacuum (yield, 0·4 g.). This product will be referred to as substance D.

Alkaline Hydrolysis of 2 : 6-*Dimethyl* 3 : 4-*Anhydro*-β-*methylalloside.*—Dimethyl 3 : 4-anhydro-β-methylalloside (1·05 g.) was heated at 95° for 20 hours with methyl alcohol (35 c.c.) containing 5% of sodium. Thereafter, the solution was diluted with water and exhaustively extracted with chloroform. Distillation of the chloroform from the dried extract gave a viscous syrup, which distilled at 110° (bath temp.)/0·01 mm. The distillate (1·05 g.), $n_D^{17°}$ 1·4554, crystallised on keeping at 0° and was recrystallised from dry ether–light petroleum. The crystalline product (0·65 g.) had m. p. 59—60° and $[\alpha]_D^{19°}$ —48·0° in chloroform and $[\alpha]_D^{17°}$ —33·4° in water (*c*, 1·45). Analysis showed it to be a *trimethyl methylglucoside* (Found : C, 51·05; H, 8·7; OMe, 51·4. $C_{10}H_{20}O_6$ requires C, 50·9; H, 8·5; OMe, 52·5%).

From the mother-liquors, after the recrystallisation of the trimethyl β-methylglucoside, was isolated a syrup (0·3 g.), which also was a trimethyl β-methylhexoside (Found : OMe, 52·5%). It is examined below as substance E.

Determination of the Structure of the Crystalline Trimethyl β-*Methylglucoside.—Methylation.* The trimethyl β-methylglucoside (2·33 g.) was methylated by three treatments with Purdie's reagents and the product, isolated in the usual manner, was distilled at 95—100° (bath temp.)/0·035 mm. Yield, 2·32 g. (undistillable residue, 0·06 g.); $n_D^{18°}$ 1·4410. On cooling, the distillate crystallised completely. It separated from dry light petroleum in fine needles, m. p. 38—39°, $[\alpha]_D$ —18·0° in water (*c*, 2·72). In admixture with authentic tetramethyl β-methylglucopyranoside (m. p. 40°, $[\alpha]_D$ — 17·5° in water) there was no depression of m. p.

The tetramethyl β-methylglucopyranoside, m. p. 38—39° (0·73 g.) was heated at 95° with 6% hydrochloric acid until no further change in the rotation occurred ($[\alpha]_D^{18°}$ —24·6 ⟶ +65·2° in 9 hours). The solution was neutralised with lead carbonate and evaporated to dryness; the product, extracted with chloroform, crystallised completely on removal of the solvent. Yield, 0·65 g. (97% of the theoretical). The product separated from dry light petroleum in feathery crystals, m. p. 91° alone and in admixture with authentic tetramethyl α-*d*-glucopyranose; $[\alpha]_D^{18°}$ + 99·0° ⟶ + 83·2° in water (*c*, 1·2).

Hydrolysis. The physical constants of the crystalline trimethyl β-methylglucoside are in agreement with its being 2 : 3 : 6-trimethyl β-methylglucoside. This was confirmed by hydrolysis with hot 6% hydrochloric acid. During the hydrolysis the rotation changed from $[\alpha]_D$ —32·9° to +65·8° (constant value in 7 hours) and 2 : 3 : 6-trimethyl glucose (m. p. 114—115° alone or in admixture with an authentic specimen; $[\alpha]_D^{17°}$ + 86·2 ⟶ + 69·2° in water) was isolated in good yield. Oxidation of the trimethyl glucose with bromine water gave 2 : 3 : 6-trimethyl gluconic acid, which mutarotated in water : $[\alpha]_D$ + 32·5° (15 mins.); + 35·5° (19 hrs.); + 37·7° (61 hrs.); + 38·4° (75 hrs.) constant value. The corresponding 2 : 3 : 6-trimethyl gluconolactone showed $[\alpha]_D^{20°}$ + 54·0° (½ hr.); + 46·5° (21 hrs.); + 45·0° (76 hrs.); + 38·8° (240 hrs.) in water.

Determination of the Structure of the Non-crystalline Trimethyl β-*Methylhexoside* (*E*).—The syrup (E), collected from several preparations, had $n_D^{19°}$ 1·4575 and $[\alpha]_D^{16°}$ — 73·1° in chloroform (*c*, 1·09). It was obvious from its method of preparation that this trimethyl β-methylhexoside would contain at least a little 2 : 3 : 6-trimethyl β-methylglucoside.

Methylation. The syrup (E) (1·16 g.) was methylated by three treatments with methyl iodide and silver oxide. The product, *tetramethyl* β-*methylhexoside*, distilled at 85—90° (bath temp.)/0·01 mm.; it had $n_D^{18°}$ 1·4452 and $[\alpha]_D^{17°}$ — 69·0° in chloroform (*c*, 1·25); yield, 1·08 g. (Found : OMe, 61·6. $C_{11}H_{22}O_6$ requires OMe, 62·0%).

The liquid tetramethyl β-methylhexoside (0·95 g.) was hydrolysed with hot 6% hydrochloric acid, and the tetramethyl hexose isolated in the usual way (yield, 97%). It was non-crystalline and had $n_D^{21°}$ 1·4582 and $[\alpha]_D^{16°}$ + 8·25° in water (*c*, 1·454).

The tetramethyl hexose (0·87 g.) was treated in aqueous solution (3 c.c.) with bromine (1·6 c.c.) and kept at room temperature until the solution was non-reducing to Fehling's solution. Thereafter the solution was aerated and neutralised with lead carbonate, the lead removed with hydrogen sulphide, and the bromine ion with silver carbonate. The solution was evaporated, and the product extracted with chloroform. It was a viscid liquid distilling at 110—115° (bath temp.)/0·015 mm., n_D 1·4628, and was not quite pure *tetramethyl hexonolactone* (Found :

OMe, 51·2. $C_{10}H_{18}O_6$ requires OMe, 53·0%). Attempts to prepare a crystalline phenylhydrazide and a crystalline amide from the lactone were without success. It behaved as a δ-lactone in aqueous solution: $[\alpha]_D^{15°}$ + 64·6° (5 mins.); + 39·5° (5 hrs.); + 25·1° (23 hrs.); + 22·0° (32 hrs.) constant value (*c*, 3·19).

Oxidation of the Tetramethyl δ-Hexonolactone with Nitric Acid.—The procedure adopted was that described in previous publications from this laboratory. The lactone (0·85 g.) yielded, on treatment with nitric acid (*d* 1·4; 7 c.c.) at 90°, an acid syrup, which was esterified by heating at 80° with 2% methyl-alcoholic hydrogen chloride for 7 hours. The product was a neutral oil (0·52 g.), which was distilled at 110—130° (bath temp.)/0·02 mm. as follows:

Fraction.	Weight (g.).	$n_D^{21°}$.	% OMe.
1	0·15	1·4352—1·4365	61·8
2	0·143	1·4367—1·4383	60·8
3	0·08	1·4395	51·6
Residue	0·11	—	43·0

The fractions were separately dissolved in dry methyl alcohol, mixed with a solution of methylamine in methyl alcohol, and kept at room temperature for 24 hours. Thereafter the solvent was removed from each by evaporation in a vacuum desiccator; the methylamides then crystallised. By a systematic fractional crystallisation from ethyl acetate–ether, there were obtained from fraction 1, *i*-dimethoxysuccinomethylamide (m. p. 208°, alone or in admixture with an authentic specimen; optically inactive) (Found: C, 47·45; H, 8·1; N, 13·9. Calc. for $C_8H_{16}O_4N_2$: C, 47·1; H, 7·8; N, 13·7%) and *l*-trimethoxyaraboglutaromethylamide (m. p. 171°, alone or in admixture with an authentic specimen; $[\alpha]_D^{18°}$ + 57·5°) (Found: C, 48·2; H, 8·1; N, 11·8. Calc. for $C_{10}H_{20}O_5N_2$: C, 48·4; H, 8·1; N, 11·3%). Fraction 2 gave a further quantity of *i*-dimethoxysuccinomethylamide and *i-trimethoxyxyloglutaromethylamide* m. p. 166°; optically inactive (Found: C, 48·4; H, 7·9; N, 11·4; OMe, 37·0%).

A Comparison of 2 : 3 : 6-*Trimethyl* β-*Methylglucoside and the Trimethyl* β-*Methylhexoside* (*E*).—The previous experiments indicate that the syrup E is trimethyl β-methylguloside containing 2 : 3 : 6-trimethyl β-methylglucoside.

Hydrolysis with 6% *hydrochloric acid.*

	$[\alpha]_D^{15°}$. Initial.	$[\alpha]_D^{15°}$. Final.	Time to reach final value.
2 : 3 : 6-Trimethyl β-methylglucoside	− 32·9°	+ 65·8°	7 hrs.
Substance E	− 64·3	+ 3·2	7 ,,

The optical rotations of the trimethyl lactones in water. The sugar obtained by the hydrolysis of substance (E), which showed $[\alpha]_D^{14°}$ + 4·5 in water (*c*, 1·32), was oxidised with bromine water, and the trimethyl lactone isolated in the usual way. It was a syrup, $n_D^{18°}$ 1·4673, and had OMe, 41·4%. A crystalline amide could not be prepared from it.

		$[\alpha]_D$ after						
	c.	½ hr.	24 hrs.	68 hrs.	92 hrs.	165 hrs.	240 hrs.	310 hrs.
2 : 3 : 6-Trimethyl gluconolactone	2·71	+54°	+46·5°	+45·4°	+43·5°	+40·6°	+38·8°	+38·8°
The lactone from substance (E)	2·09	+62·6	+36·3	+32·9	+32·9	—	—	—

It is evident from these figures that the trimethyl lactone from substance (E) is for the greater part a δ-lactone. It is reasonable to assume, therefore, that a methoxy-group is situated at C_4 in the principal constituent of (E), which is thus shown to be 2 : 4 : 6-*trimethyl* β-*methyl*-d-*gulopyranoside*, and (E) is a mixture of this hexoside with a small amount of 2 : 3 : 6-trimethyl β-methylglucoside.

*Examination of the Dimethyl Anhydro-*β-*methylhexoside* (*D*).—The syrup (D) remaining after the separation of crystalline dimethyl 3 : 4-anhydro-β-methylhexoside was given two further treatments with methyl iodide and silver oxide and thereafter distilled at 0·01 mm. The distillate showed $n_D^{17°}$ 1·4558, $[\alpha]_D^{17°}$ − 72·1° in chloroform (*c*, 1·14) (Found: OMe, 46·7%).

Purification. The substance (D) (1·55 g.) was heated at 95° for 100 hours with a 5% solution of sodium in methyl alcohol (20 c.c.), and the product isolated in the usual way. Yield, 1·43 g. The methoxyl content (48·3%) of the product suggests that it is a mixture of trimethyl methylhexoside (OMe, 52·5%) and unchanged dimethyl anhydromethylhexoside (OMe, 45·7%). A partial separation was achieved by fractional distillation from a Widmer flask and a small amount of 2 : 3 : 6-trimethyl β-methylglucoside was removed. The residue was acetylated (with acetic anhydride and sodium acetate), and the product (0·62 g.) again distilled. A residue

(0·1 g.) remained and was presumably trimethyl methylhexoside acetate. The distillate (0·47 g.) had $n_D^{18°}$ 1·4552, $[\alpha]_D^{15°}$ — 1·68° in chloroform (*c*, 2·37). It is shown below that this substance consists in the main of 2 : 4-*dimethyl* 3 : 6-*anhydro*-β-*methylglucoside*.

This anhydro-substance, unlike the methylated 2 : 3- and 3 : 4-anhydrohexosides, was stable to alkali, being recovered unchanged after boiling for 8 hours with 2·5N-potassium hydroxide in aqueous alcohol (75%). The 3 : 6-anhydro-ring, moreover, was stable to boiling 6% methyl-alcoholic hydrogen chloride, although there was an inversion of the glucosidic methoxyl (β to α) with this reagent in the cold.

Hydrolysis with aqueous acid. The 3 : 6-anhydro-ring was also stable to the action of boiling 6% hydrochloric acid, but the glycosidic methyl group was removed by cold aqueous acid. The purified dimethyl anhydro-β-methylglucoside was dissolved in 6% hydrochloric acid (*c*, 1·81), and the rotation changes observed : $[\alpha]_D^{18°}$ — 1·1° ⟶ + 61·9° in 300 hours. The product, a viscid reducing syrup, was *dimethyl anhydroglucose* (Found : OMe, 31·4. $C_8H_{14}O_5$ requires OMe, 31·0%).

2 : 4-*Dimethyl* 3 : 6-*Anhydroglucose Anilide*.—Dimethyl anhydrohexose (0·13 g.) in ethyl alcohol (1·0 c.c.) was heated at 95° for 2 hours with aniline (0·07 g., a slight excess) in alcohol (1·0 c.c.). Removal of the solvent left a red syrup, which crystallised on nucleation. After recrystallisation the product, 2 : 4-dimethyl 3 : 6-anhydroglucose anilide melted at 96°, alone or in admixture with an authentic specimen. Yield, 0·1 g.

2 : 4-*Dimethyl* 3 : 6-*anhydrogluconolactone* was prepared by the oxidation of the dimethyl anhydroglucose with bromine water in the cold. The product, isolated in the usual way, distilled at 105—115° (bath temp.)/0·015 mm. as a syrup, non-reducing, $n_D^{17°}$ 1·4669, $[\alpha]_D$ in water (*c*, 1·50) + 90·9 ⟶ + 64·2° in 180 hours (Found : OMe, 32·8. $C_8H_{12}O_5$ requires OMe, 33·0%).

2 : 4-*Dimethyl* 3 : 6-*Anhydrogluconamide*.—The lactone (0·16 g.) was dissolved in liquid ammonia (20 c.c.), and the solution kept in a Dewar flask for 8 hours. Thereafter the solution was poured out, and the ammonia allowed to evaporate. The residue, recrystallised from ether–light petroleum, had m. p. 91—92° (Found : C, 47·0; H, 7·2; N, 7·2; OMe, 31·3. $C_8H_{15}O_5N$ requires C, 46·8; H, 7·3; N, 6·8; OMe, 30·3%).

4 : 6-*Dimethyl* 2 : 3-*Anhydro*-α-*methylalloside*.—3-*p*-Toluenesulphonyl (α and β)-methylglucoside (6 g.) was treated in chloroform (40 c.c.) with a slight excess of 5% sodium methoxide solution, and the mixture kept at room temperature for 3 days. The product, anhydro-(α and β)-methylhexoside, was isolated in the usual way. By two treatments with Purdie's reagents the anhydromethylhexoside was converted into dimethyl anhydro-(α and β)-methylhexoside, which, after distillation, showed $n_D^{18°}$ 1·4552 and $[\alpha]_D^{18°}$ + 52·8° in chloroform (Found : OMe, 45·5%).

When kept at 0° for 2 days, the product partly crystallised. The crystalline material was separated on porous tile and recrystallised from petrol. It had m. p. 63° and $[\alpha]_D^{18°}$ + 187° and was apparently identical with the 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside of Mathers and Robertson (*loc. cit.*) (Found : C, 52·6; H, 7·8; OMe, 45·7. Calc. for $C_9H_{16}O_5$: C, 52·9; H, 7·8; OMe, 45·7%).

4 : 6-*Ethylidene* 2 : 3-*Anhydro*-α-*methylalloside*.—Anhydro-(α and β)-methylhexoside (0·33 g.), dissolved in paraldehyde (5 c.c.), was treated at 10° with 1 drop of concentrated sulphuric acid. After 12 hours the solution was diluted with chloroform and extracted with water. Evaporation of the chloroform solution left a syrup, which crystallised. The product separated from light petroleum in large feathery crystals, m. p. 128°, $[\alpha]_D^{18°}$ + 100° in chloroform.

4 : 6-*Benzylidene* 2 : 3-*Anhydro*-α-*methylalloside*.—Anhydro-(α and β)-methylhexoside (0·5 g.) was mixed in chloroform (10 c.c.) with phosphoric oxide (1 g.) and freshly distilled benzaldehyde (1 c.c.). After the mixture had been kept at room temperature for 2 hours, the liquid was filtered and concentrated to quarter bulk, and light petroleum added until a turbidity was produced. On keeping at 0°, crystals separated. This product, after recrystallisation from methyl alcohol, showed m. p. 198° and $[\alpha]_D^{20°}$ + 161° and would seem to be identical with the 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside prepared by Robertson and Griffiths (*loc. cit.*).

2 : 3-*Anhydro*-β-*methylalloside*.—4 : 6-Benzylidene 2 : 3-anhydro-β-methylalloside (0·78 g.) in ethyl alcohol–acetone (40 c.c.) was hydrogenated in the presence of a palladium–charcoal catalyst (for details, see Tausz and Putnoky, *Ber.*, 1919, **52**, 1573) at 1½ atms. pressure and room temperature until hydrogen ceased to be absorbed (uptake, 120 c.c.). Evaporation of the solution yielded a syrup (0·48 g.), which crystallised on keeping. After recrystallisation from ethyl acetate–ether–petrol, the *anhydromethylhexoside* showed m. p. 60—62° and $[\alpha]_D^{17°}$ — 6·1° in ethyl acetate (*c*, 1·31) (Found : C, 48·0; H, 6·8; OMe, 17·0. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8; OMe, 17·6%). The product was hygroscopic, but could be preserved under petrol.

4:6-*Dimethyl* 2:3-*Anydro*-β-*methylalloside*.—The anhydromethylhexoside (0·09 g.) was converted by two treatments with methyl iodide and silver oxide into 4:6-*dimethyl* 2:3-*anhydro*-β-*methylalloside*, which crystallised in short needles, m. p. 50—51°, $[\alpha]_D^{19°}$ + 35·3° in chloroform (*c*, 1·51) (Found: C, 53·0; H, 7·9; OMe, 45·0%).

4:6-*Benzylidene* β-*Methylaltroside*.—4:6-Benzylidene 2:3-anhydro-β-methylalloside (2 g.) was heated at 90° with 2·5N-alcoholic potassium hydroxide solution (150 c.c.) until no crystals separated on cooling (14 hrs.). The solution was diluted with water and extracted repeatedly with chloroform. Evaporation of the solvent from the chloroform extract left a crystalline residue, which, recrystallised from methyl alcohol–ether–petrol, showed m. p. 188° and $[\alpha]_D$ — 62·9° in acetone (*c*, 1·08).

4:6-*Benzylidene* 2:3-*Anhydro*-β-*methylmannoside*.—2-*p*-Toluenesulphonyl 3:4:6-triacetyl β-methylglucoside (2·7 g., prepared by Mr. W. O. Cutler of this laboratory) was converted by treatment with sodium methoxide into 2:3-anhydro-β-methylmannoside (Haworth, Hirst, and Panizzon) in 70% yield. The non-crystalline product ($[\alpha]_D^{19°}$ — 28·8°) was treated in the usual way with benzaldehyde and 4:6-benzylidene 2:3-anhydro-β-methylmannoside was isolated. After recrystallisation from methyl alcohol, it showed m. p. 183° and $[\alpha]_D^{18°}$ — 30·7° in chloroform (*c*, 0·82).

Aqueous Acid Hydrolysis of Anhydromethylhexosides.—(a) *Of* 4:6-*dimethyl* 2:3-*anhydro*-α-*methylalloside*. The substance (0·13 g.), dissolved in 5% hydrochloric acid (5·5 c.c.), showed $[\alpha]_D^{20°}$ + 181·7°. There was no change in rotation at room temperature during 2 hours, but hydrolysis occurred when the solution was heated at 95°, the rotation falling to a constant value, $[\alpha]_D^{20°}$ + 67·5° in 17 hours. The product isolated after neutralisation of the acid with silver carbonate was a viscous syrup, which was strongly reducing and contained chlorine. Analysis showed it to be a *dimethyl chlorohexose* (Found: C, 42·0; H, 6·9; Cl, 15·5; OMe, 27·0. $C_8H_{15}O_5Cl$ requires C, 42·4; H, 6·6; Cl, 15·7; OMe, 27·4%).

(b) *Of* 2:6-*dimethyl* 3:4-*anhydro*-β-*methylalloside*. The substance (0·19 g.) was dissolved in 5% hydrochloric acid (3 c.c.). Hydrolysis occurred in the cold, the following polarimetric readings being observed: $[\alpha]_D^{20°}$ (calculated on original material) — 139·7° (4 mins.); —136·7° (8 mins.); — 121·1° (32 mins.); — 109·6° (1 hr.); — 97·4° (2 hrs.); — 90·3° (3 hrs.); — 76·6° (15 hrs., constant value). The product was non-reducing and contained non-ionised chlorine. An attempt was made to obtain a crystalline derivative by acetylation of the product. The dimethyl monoacetyl chloromethylhexoside, which was not crystalline, had $[\alpha]_D^{20°}$ — 41·4° in chloroform (Found: OMe, 32·0%)

The Alkaline Hydrolysis of 3-p-*Toluenesulphonyl* 1:2-*Monoacetone* 5:6-*Diacetyl Glucofuranose*.—The substance (2 g., prepared by the method of Ohle and Erlbach, *Ber.*, 1928, **61**, 1870) in chloroform (10 c.c.) was treated with sodium methoxide (1 mol.) in methyl alcohol at 0° for 2 hours and thereafter the solution was kept at room temperature for 12 hours. The precipitate (sodium *p*-toluenesulphonate and sodium acetate) was removed, and the filtrate extracted three times with water. The aqueous extract, after neutralisation with N-acetic acid, was evaporated in the presence of barium carbonate, and the dry residue extracted with boiling ether. Evaporation of the ether left a solid which, on recrystallisation from ethyl acetate, showed m. p. 155° and $[\alpha]_D^{20°}$ — 11·25° in water. There was no depression of m. p. in admixture with authentic monoacetone glucose (m. p. 158°; $[\alpha]_D^{20°}$ — 11·8° in water). A further quantity of monoacetone glucose was obtained by extraction of the residue with ethyl acetate. Yield, 0·1 g. (10%).

The chloroform solution after the aqueous extraction was evaporated, and the residue acetylated (acetic acid and pyridine at 36° for 3 days). The product was a solid which, after recrystallisation from methyl alcohol, had m. p. 76° and $[\alpha]_D^{20°}$ — 19° in chloroform. It was 3-*p*-toluenesulphonyl monoacetone diacetyl glucofuranose. Yield, 40%.

3-*p*-Toluenesulphonyl monoacetone glucose (0·35 g.), when submitted to the same treatment, also yielded monoacetone glucose, in 30% yield.

Attempted Replacement of the p-*Toluenesulphonyl Group by the Acetyl Group*.—The conditions employed were varied as follows: (a) *p*-Toluenesulphonyl diacetone glucofuranose (2 g.) and fused sodium acetate (2 g.) in glacial acetic acid solution were heated on the water-bath for 2 hours; (b) the same in alcoholic solution were heated on the water-bath for 24 hours; (c) 3-*p*-toluenesulphonyl glucose (1 g.) and fused potassium acetate (1 g.) in alcohol (25 c.c.) were heated in a sealed tube at 115° for 8 hours; (d) the same at 120° for 14 hours; (e) the same with acetone instead of alcohol as the solvent; (f) the same as in (d), heated at 220° for 14 hours; (g) 3-*p*-toluenesulphonyl triacetyl β-methylglucoside (0·5 g.) and potassium acetate in alcohol (50 c.c.) were heated on the water-bath for 4 hours; (h) the same, heated in a sealed

tube at 130° for 10 hours. In all cases the original *p*-toluenesulphonate was recovered unchanged.

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