267. *The Anhydromethylhexoside formed by the Alkaline Hydrolysis of* 2-p-*Toluenesulphonyl Triacetyl β-Methylglucoside. Characterisation of* 2 : 4 : 6-*Trimethyl Glucose.*

By W. H. G. Lake and S. Peat.

The crystalline dimethyl anhydromethylhexoside prepared by Haworth, Hirst, and Panizzon (J., 1934, 154) from 2-*p*-toluenesulphonyl triacetyl β-methylglucoside is now recognised as dimethyl 2 : 3-anhydro-β-methylmannopyranoside. It is hydrolysed by sodium methoxide to form an equimolecular mixture of 2 : 4 : 6-trimethyl β-methyl-*d*-glucoside and 3 : 4 : 6-*trimethyl* β-*methyl*-d-*altroside*. These products are separated, and the constitution of each is established by classical methods. The glucoside is a

crystalline solid, and it gives on hydrolysis 2 : 4 : 6-trimethyl glucose which is also crystalline. The physical properties of this trimethyl glucose are recorded.

The results of this investigation provide corroboratory evidence of the correctness of the views, already expressed, concerning the course of alkaline hydrolysis of a sugar *p*-toluenesulphonate (Peat and Wiggins, this vol., p. 1088).

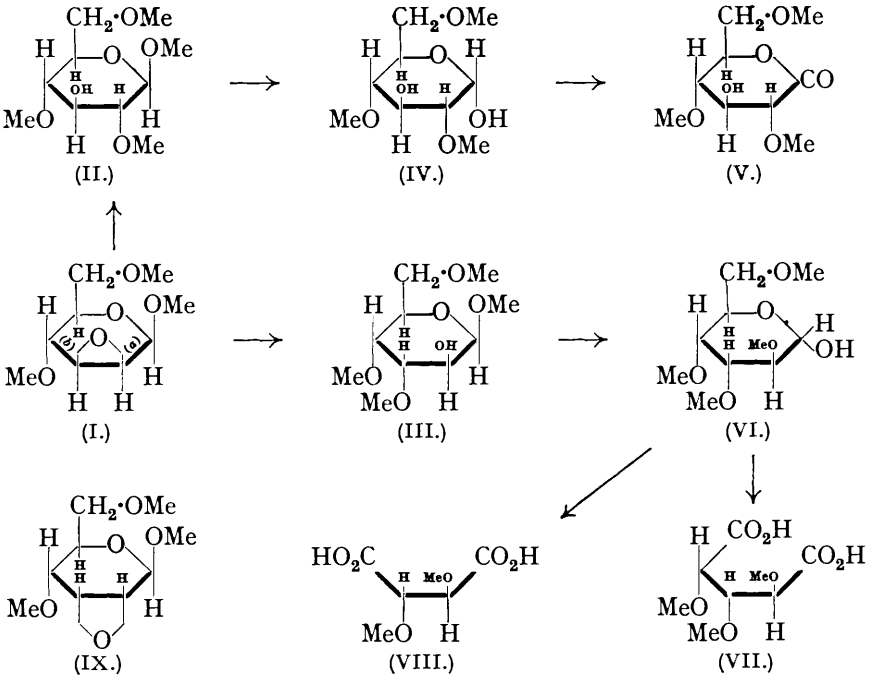
It has been shown by Haworth, Hirst, and Panizzon (J., 1934, 154) that the removal of the *p*-toluenesulphonyl group (by hydrolysis with sodium methoxide) from 2-*p*-toluenesulphonyl 3 : 4 : 6-trimethyl β-methylglucoside is not attended by a Walden inversion, the product being 3 : 4 : 6-trimethyl β-methylglucoside. When, however, the corresponding 2-*p*-toluenesulphonyl triacetyl β-methylglucoside is treated with the same reagent under very mild conditions, all the acyl groups are removed and an anhydromethylhexoside is formed. This product was isolated as a crystalline dimethyl derivative. The view was expressed that the anhydro-ring most probably involved C_2 and C_3, and that its formation was accompanied by Walden inversion on C_2. Evidence is now contributed which confirms this view and establishes the constitution of the crystalline anhydro-compound as being dimethyl 2 : 3-anhydro-β-methylmannopyranoside (I).

When the dimethyl anhydromethylhexoside of Haworth, Hirst, and Panizzon is boiled with methyl alcohol containing sodium methoxide, the anhydro-ring is opened and a methoxyl group is introduced into the molecule. This product, therefore, has the composition of a trimethyl methylhexoside, and is a mixture, in very nearly equal proportions, of a crystalline trimethyl methylhexoside (A) and an isomeric non-crystalline substance (B). The former (m. p. 71°) was transformed, by methylation with Purdie's reagents, into crystalline tetramethyl β-methylglucopyranoside, the identity of which was established from its constants, a mixed m. p. determination, and from its conversion by hydrolysis into crystalline tetramethyl α-*d*-glucopyranose. It is clear from these observations that substance (A) is a derivative of *d*-glucose and has the pyranose structure. It follows that the original anhydromethylhexoside is also a pyranoside. The disposition of the methyl groups in the trimethyl methylhexoside (A) was determined as follows: Acid hydrolysis of the hexoside gave a crystalline trimethyl hexose (m. p. 115°), from which a non-crystalline *lactone* (V) was prepared by bromine oxidation. The mutarotation of this lactone in aqueous solution showed it to belong to the δ-series, a fact which suggests that a methoxy-group is situated at C_4; were this not so, a γ-lactone would have resulted. Treatment of the lactone with liquid ammonia yielded a crystalline *amide* (m. p. 100°), which, since it gave a negative Weerman test, was not an α-hydroxy-amide. It is evident that a methyl group is substituted at C_2. Furthermore, since anhydro-β-methylmannoside condenses with benzaldehyde (Peat and Wiggins, this vol., p. 1088), it would seem that in the former substance the hydroxyl groups at C_4 and C_6 are not involved in the anhydride linkage, and it is reasonable therefore to suppose that the remaining methoxyl group in substance (A) is located at C_6. The physical constants of substance (A) are identical with those quoted by Oldham (*J. Amer. Chem. Soc.*, 1934, **56**, 1360) for 2 : 4 : 6-trimethyl β-methylglucoside (II).

The syrup (B) was investigated by a similar procedure, and allowance was made for the fact that it contained a small amount of the trimethyl methylglucoside. By methylation of (B) and hydrolysis of the methylated product, a tetramethyl hexose was obtained as a mobile syrup. Oxidation of this hexose with nitric acid gave a mixture of *d*-arabo-trimethoxyglutaric acid (VII) and *l*-dimethoxysuccinic acid (VIII), which were characterised as the methylamides. These acids, occurring together, could have been derived only from *tetramethyl* d-*altropyranose* (VI). A little *i*-xylotrimethoxyglutaric acid was also formed, but this undoubtedly arose from the tetramethyl glucose with which the tetramethyl altrose was contaminated.

Hydrolysis of the hexoside (B) gave a trimethyl hexose from which a further small quantity of trimethyl glucose was separated. The remaining syrup, which was almost pure 3 : 4 : 6-*trimethylaltrose*, gave, on oxidation with bromine, a *lactone* which behaved in aqueous solution as a typical δ-lactone ($[\alpha]_D^{19°}$ — 9·6°, changing to a constant value, + 10·8°, in 24 hrs.). In the trimethyl altrose, therefore, it would appear that the hydroxyl at C_4

is protected by a methyl group. The δ-lactone was converted in the usual way into a non-crystalline *amide*, which gave a positive Weerman test and was therefore an α-hydroxyamide. The conclusion drawn from these observations is that the principal constituent of the syrup (B) is **3 : 4 : 6-*trimethyl* β-*methyl*-d-*altropyranoside*** (III).



From the evidence previously discussed, it is known that in the dimethyl anhydromethylhexoside, C_4 and C_6 carry methoxyl groups, and since the altrose derivative is substituted by methoxyl at C_3 and the glucose derivative at C_2, it is clear that in the dimethyl anhydromethylhexoside from which they originated the anhydro-bridge is formed between C_2 and C_3. In the paper of Peat and Wiggins (*loc. cit.*), a dimethyl 2 : 3-anhydro-β-methylhexoside is described which is not identical with that under discussion and to which a *d*-allose configuration was assigned (IX). If the view therein expressed is correct, it is clear that the product from 2-*p*-toluenesulphonyl β-methylglucoside must be a derivative of *d*-mannose and is represented by (I). The obvious inference is that if, in the formation of an anhydro-sugar by the hydrolysis of a toluenesulphonate, Walden inversion occurs, the carbon atom involved in the inversion is that carrying the toluenesulphonyl group.

The formation in equal quantities of the methylglucoside (II) and the methylaltroside (III) demonstrates that cleavage, under the action of sodium methoxide, of the anhydro-ring of dimethyl 2 : 3-anhydro-β-methylmannoside (I) takes place with equal facility on either side of the oxygen atom. When the break occurs at (*a*), it is accompanied by Walden inversion on C_2, to which the methoxyl group becomes attached, and (II) is formed. A similar change takes place on C_3 when the anhydro-ring opens at (*b*) and the altroside (III) is produced. The same sequence of events is observed when dimethyl 3 : 4-anhydro-β-methylalloside is treated with sodium methoxide (Peat and Wiggins, *loc. cit.*).

Experimental.

4 : 6-*Dimethyl* 2 : 3-*Anhydro*-β-*methylmannoside*.—2-*p*-Toluenesulphonyl 3 : 4 : 6-triacetyl β-methylglucoside was deacetylated, and the resulting anhydromethylhexoside methylated according to the procedure of Haworth, Hirst, and Panizzon (*loc. cit.*). The dimethyl anhydro-β-methylhexoside so prepared was identical with that obtained by these authors; m. p. 69°; $[\alpha]_D^{19°}$ + 24° in water. It separated in long needles from ether–light petroleum.

Alkaline hydrolysis of the dimethyl anhydro-β-methylmannoside. The crystalline material

(2·68 g.) was boiled, under reflux, with a 5% solution of sodium in methyl alcohol (40 c.c.) for 20 hrs. The solution, after cooling, was diluted with water and extracted repeatedly with chloroform. Evaporation of the dried chloroform solution left a syrup which distilled at 95°/0·03 mm.; yield, 2·8 g. On keeping, the distillate partly crystallised. By repeated crystallisation from dry ether–light petroleum, the mixture was separated into a crystalline product (A) (1·13 g.) and a non-crystalline fraction (B) (1·47 g.). Analysis showed both (A) and (B) to be trimethyl methylhexosides. In a second experiment, 3·5 g. of the dimethyl anhydro-β-methylmannoside gave 1·90 g. of (A) and 1·97 g. of (B).

2 : 4 : 6-*Trimethyl* β-*Methylglucopyranoside.*—The crystalline fraction (A) separated from dry ether–light petroleum in long needles, m. p. 71°; $[\alpha]_D^{22°}$ −27·0° in chloroform (*c*, 2·6) (Found: C, 50·9; H, 8·6; OMe, 52·2. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5; OMe, 52·5%).

Methylation. Fraction (A) (0·45 g.) was methylated by three treatments with the Purdie reagents. The product distilled at 75°/0·08 mm. as an oil ($n_D^{19°}$ 1·4400) which crystallised immediately, and was shown to be tetramethyl β-methylglucopyranoside. After recrystallisation from light petroleum, it had m. p. 38—39° (alone or in admixture with an authentic specimen), $[\alpha]_D^{20°}$ −17·1° in water (*c*, 2·4) (Found: OMe, 61·6%).

The fully methylated glucoside (0·25 g.) was hydrolysed by heating in a boiling water-bath with 7% hydrochloric acid (20 c.c.) for 4 hrs. After neutralisation with barium carbonate, the product was extracted with chloroform and shown to be tetramethyl α-*d*-glucopyranose, m. p. 87° (alone or in admixture with an authentic specimen); $[\alpha]_D^{20°}$ +93·0° ⟶ +84·0°, equilibrium value in water (*c*, 1·4) (Found: OMe, 52·3%). Yield, quantitative.

Hydrolysis. The trimethyl methylglucoside (A) (1·65 g.) was hydrolysed by heating with 7% hydrochloric acid for 3 hrs. The trimethyl glucose, isolated in the usual way, separated from ether in colourless needles (1·40 g.), shown below to be 2 : 4 : 6-trimethyl α-glucopyranose, m. p. 115°; $[\alpha]_D^{20°}$ +98·2° ⟶ +74·8°, equilibrium value in water (*c*, 3·38) (Found: C, 48·7; H, 8·2; OMe, 41·8%. Calc. for $C_9H_{18}O_6$: C, 48·7; H, 8·1; OMe, 41·9%).

Oxidation of the trimethyl glucose. The crystalline substance (0·7 g.) was oxidised by treatment in aqueous solution (3 c.c.) with bromine (1 c.c.) at room temperature until the reducing power reached a minimum value (36 hrs.). The excess bromine was removed by aeration, the solution neutralised with silver carbonate, silver ions removed with hydrogen sulphide, and the solution evaporated to dryness. After being heated at 100° for 3 hrs. in a vacuum (to complete lactonisation), the residue was extracted with ether. Evaporation of the ether left a syrup (0·58 g.), which was freed from unchanged sugar by treatment with sodium hydroxide solution (1 mol.), evaporation to dryness, and extraction of the residue with chloroform. Thereafter the trimethyl hexonic acid was liberated from the sodium salt by the addition of a slight deficiency of sulphuric acid, evaporation of the aqueous solution, and extraction of the residue (after heating to effect lactonisation) with ether. The extract was a colourless oil which distilled at 140°/0·01 mm. and had $n_D^{20·5°}$ 1·4695 (Found: OMe, 42·0. $C_9H_{16}O_6$ requires 3OMe, 42·3%). In aqueous solution, the product behaved as a δ-lactone, the rotation changing from $[\alpha]_D^{21°}$ +96° to +39·0° (constant value) in 6 hrs. (*c*, 2·2). The trimethyl hexonic acid (generated from the sodium salt by the addition of mineral acid) showed $[\alpha]_D^{21°}$ +37·5° changing to +40·0° (constant value) in 3 hrs. (*c*, 2·0). The lactone is therefore 2 : 4 : 6-*trimethyl* δ-*gluconolactone.*

2 : 4 : 6-*Trimethyl Gluconamide.*—The syrupy lactone (0·18 g.) was dissolved in liquid ammonia (20 c.c.), and the ammonia allowed to evaporate over-night. The *amide* so formed (yield 0·15 g.) crystallised from acetone–light petroleum in needles, m. p. 100°; $[\alpha]_D^{20°}$ +37·0° in chloroform (*c*, 0·7) (Found: C, 45·7; H, 7·9; N, 5·9; OMe, 39·3. $C_9H_{19}O_6N$ requires C, 45·7; H, 8·0; N, 5·9; OMe, 39·3%). It was established that the amide was an α-methoxy-amide by application of the Weerman reaction under the conditions specified by Ault, Haworth, and Hirst (J., 1934, 1722): no hydrazodicarbonamide was formed.

3 : 4 : 6-*Trimethyl* β-*Methylaltropyranoside.*—After separation of the maximum amount of crystalline trimethyl β-methylglucoside, the syrup (B) showed, after distillation, $n_D^{22°}$ 1·4584; $[\alpha]_D^{21°}$ − 25·6° in chloroform (Found: OMe, 52·3%). It probably still contained a little of the trimethyl methylglucoside.

Methylation of fraction (*B*). The syrup (B) (1·90 g.) was methylated by three treatments with the Purdie reagents. The product was a colourless oil; b. p. 86°/0·006 mm., $n_D^{20·5°}$ 1·4468, $[\alpha]_D^{17°}$ − 38·0° in chloroform (*c*, 6·14) (Found: OMe, 61·3. $C_{11}H_{22}O_6$ requires 5OMe, 62·0%); yield, 1·88 g. It is shown later that this product is mainly *tetramethyl* β-*methylaltropyranoside.* Hydrolysis of the methylaltroside (1·80 g.) with 7% hydrochloric acid gave *tetramethyl* d-*altropyranose* as a syrup (1·53 g.); $n_D^{22°}$ 1·4600 (undistilled); $[\alpha]_D^{19°}$ + 63·0° in chloroform (*c*, 4·72) (Found: OMe, 51·7. $C_{10}H_{20}O_6$ requires 4OMe, 52·5%).

Oxidation of Tetramethyl Altrose with Nitric Acid.—The tetramethyl hexose (0·8 g.) was dissolved in nitric acid (*d* 1·42; 8 c.c.), and the oxidation and subsequent isolation of the products were conducted in the usual manner (see, *e.g.*, Hirst, J., 1926, 350). Esterification of the mixed acids was completed by treatment with 2% methyl-alcoholic hydrogen chloride; yield, 0·71 g. The esters were distilled at 115°/0·05 mm., and the mixture had $n_D^{20°}$ 1·4369, $[\alpha]_D^{20°}$ − 16·5° in methyl alcohol (*c*, 2·24) (Found: OMe, 59·4%). The esters were converted into the corresponding methylamides by treatment of the mixture (0·65 g.) with a saturated solution of methylamine in dry methyl alcohol (8 c.c.). After 24 hrs. at 0°, the solvent was removed, and the residue fractionally crystallised from warm ethyl acetate. Six fractions were separated which had the following properties.

Fraction	1	2	3	4	5 *	6
Weight, mg.	53	35	12	15	5	9
M. p.	172°	172°	172°	172°	167°	206°
$[\alpha]_D^{20°}$ in water	−60·3°	−61·0°	−60·0°	−60·5°	0·0°	−131·0°

* The constants given for Fraction 5 are those after two recrystallisations. Fraction 6 was obtained after the residual syrup had been treated for a second time with methylamine.

Fraction 1 is *d*-arabo-trimethoxyglutarmethylamide (Found: C, 48·5; H, 8·2; N, 11·3; OMe, 37·4. Calc. for $C_{10}H_{20}O_5N_2$: C, 48·4; H, 8·1; N, 11·3; OMe, 37·5%); no depression of m. p. was observed in admixture with authentic material prepared from *d*-arabinose. Fraction 6 is *l*-dimethoxysuccinmethylamide (Found: C, 47·0; H, 7·9; N, 13·7; OMe, 30·2. Calc. for $C_8H_{16}O_4N_2$: C, 47·0; H, 7·8; N, 13·7; OMe, 30·4%) for which Haworth and Jones (J., 1927, 2349) give m. p. 205°, $[\alpha]_D$ −131·8° in water. The production of these two substances together establishes the constitution of the sugar as tetramethyl *d*-altropyranose.

Fraction 5 is *i*-xylotrimethoxyglutarmethylamide (Haworth and Jones, *loc. cit.*, give m. p. 167—168°), arising from the small amount of tetramethyl glucopyranose accompanying the tetramethyl altrose.

Hydrolysis of the Trimethyl β-*Methylaltroside* (B).—Fraction (B) (1·25 g.) was hydrolysed with 7% hydrochloric acid and yielded a trimethyl hexose as a viscous syrup (1·05 g.). By treatment of this syrup with ether–light petroleum, a crystalline fraction (0·15 g.) was separated. This proved to be 2 : 4 : 6-trimethyl glucose. The remaining syrup failed to crystallise and was probably almost pure 3 : 4 : 6-*trimethyl altrose*. After drying, it showed $n_D^{20°}$ 1·4738; $[\alpha]_D^{20°}$ + 53·0° in water (*c*, 2·11) (Found: OMe, 41·0. $C_9H_{18}O_6$ requires 3OMe, 41·9%).

3 : 4 : 6-*Trimethyl* δ-*altronolactone*. Trimethyl altrose (0·55 g.) was oxidised with bromine water, and the acid purified in the usual way by formation of the sodium salt. The *lactone* (0·36 g.) distilled as a colourless oil at 150°/0·02 mm., and showed $n_D^{21·5°}$ 1·4785 (Found: OMe, 41·7. $C_9H_{16}O_6$ requires 3OMe, 42·3%). In aqueous solution (*c*, 1·75) it behaved as a δ-lactone: $[\alpha]_D^{19°}$ − 9·6°, changing to a constant value, + 10·8°, in 24 hrs.

The amide, prepared by solution of the lactone in liquid ammonia, could not be obtained crystalline. The Weerman reaction was applied as follows. The amide (0·1 g.) was treated at 0° in aqueous solution (3 c.c.) with a slight excess of standard sodium hypochlorite solution. After ½ hr. the excess hypochlorite was removed with thiosulphate, and the solution treated with sodium acetate and semicarbazide hydrochloride. Hydrazodicarbonamide (m. p. and mixed m. p. 254°) was formed; yield, 11 mg. (*i.e.*, 22% of theory). The amide is therefore an α-hydroxy-amide. Taken in conjunction with the fact that the lactone belongs to the δ-series, this shows that the three methoxyl groups must be situated on positions 3, 4, and 6 in trimethyl altrose.

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