40. *Isolation of a Crystalline Dimethyl Anhydromethylhexoside. Characterisation of* 3 : 4 : 6-*Trimethyl Glucose.*

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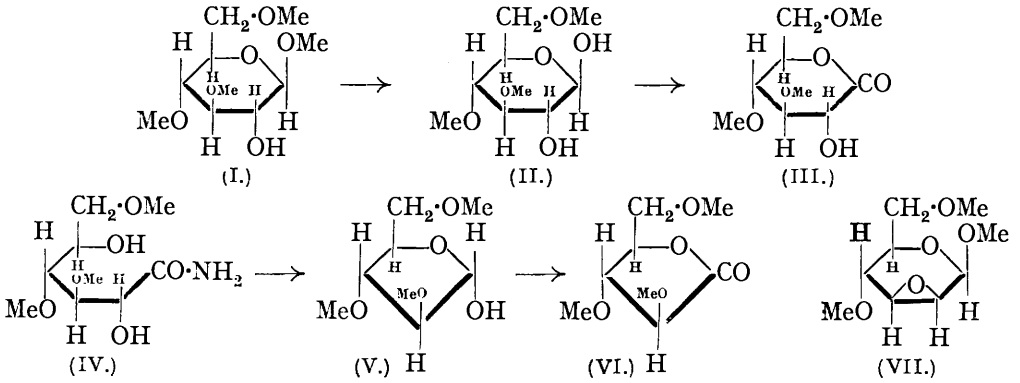
The introduction of methyl groups into 2-*p*-toluenesulphonyl β-methylglucoside proceeds readily with the formation of 2-p-*toluenesulphonyl*-3 : 4 : 6-*trimethyl* β-*methylglucoside*, which is crystalline. The toluenesulphonyl group is resistant to hydrolysis with methyl-alcoholic ammonia or potassium hydroxide and is best removed by sodium methoxide : this leads to the isolation of crystalline 3 : 4 : 6-*trimethyl* β-*methylglucoside* (I). Hydrolysis of the glucosidic group gave rise to 3 : 4 : 6-*trimethyl glucose* (II), and this on oxidation yielded 3 : 4 : 6-*trimethyl gluconolactone* (III), which was found to be a δ-lactone. It gave

a crystalline *phenylhydrazide* and its behaviour on hydrolysis followed very closely that of other δ-lactones in the glucose series.

The amide (IV) of the corresponding acid behaved as an α-hydroxy-amide and gave a positive Weerman reaction. It was degraded by sodium hypochlorite, and the product identified as 2 : 3 : 5-trimethyl *d*-arabofuranose (V). This was converted into the crystalline



2 : 3 : 5-trimethyl *d*-arabonolactone (VI) (Avery, Haworth, and Hirst, J., 1927, 2308). When the α-hydroxy-group is present in a methylated sugar-amide, the Weerman reaction follows its normal course, as indicated by these and our earlier observations, and does not lead to cyclic urethanes (compare Pryde, J., 1931, 1298).

De-acetylation of 2-*p*-toluenesulphonyl 3 : 4 : 6-triacetyl β-methylglucoside in chloroform with sodium methoxide at −10° produces 2-*p*-toluenesulphonyl β-methylglucoside. At 0°, however, the same reagent eliminates the toluenesulphonyl residue and forms an *anhydromethylhexoside*. We were unable to isolate from this the pure form of the parent anhydro-sugar, but methylation of the anhydro-β-methylhexoside gave a crystalline *dimethyl anhydromethylhexoside* which has interesting properties calling for further exhaustive study. If the scission of the toluenesulphonyl residue has involved a Walden inversion, it seems probable that the anhydro-group is situated at position 2 : 3. On the other hand, there are alternative positions possible such as 2 : 6 or 3 : 6. Reviewing the evidence at present available, it would appear that the methylated anhydro-compound is dimethyl 2 : 3-anhydromethylmannoside. The high negative rotation of the hydrolysis product of the unmethylated anhydromethylhexoside suggests that the substance has passed into the altrose series.

Experimental.

2-p-*Toluenesulphonyl* 3 : 4 : 6-*Trimethyl* β-*Methylglucoside*.—2-*p*-Toluenesulphonyl β-methylglucoside (see preceding paper) was dissolved in the minimum volume of methyl alcohol and methylated with methyl iodide and silver oxide in the usual manner. After five such treatments the product was soluble in methyl iodide and after one further methylation gave the fully methylated 2-p-*toluenesulphonyl* 3 : 4 : 6-*trimethyl* β-*methylglucoside*, which after recrystallisation from ethyl acetate (or methyl alcohol) had m. p. 67°, $[\alpha]_D$ − 16° in chloroform (*c*, 1·4) (yield, 70—75% of the theoretical) (Found : C, 52·1; H, 6·8; OMe, 31·1. $C_{17}H_{26}O_8S$ requires C, 52·3; H, 6·7; OMe, 31·8%).

3 : 4 : 6-*Trimethyl* β-*Methylglucoside*.—After treatment with 18% methyl-alcoholic ammonia at 120° for 76 hours, the above fully methylated derivative was recovered almost quantitatively; and removal of the toluenesulphonyl group was incomplete after 100 hours' boiling with 5% methyl-alcoholic potassium hydroxide. 2-Toluenesulphonyl 3 : 4 : 6-trimethyl β-methylglucoside (2 g.) was dissolved in a 4% solution of sodium methoxide in methyl alcohol (50 c.c.) and boiled for 8—10 hours, water added to the turbid solution, and the product extracted with chloroform. 3 : 4 : 6-*Trimethyl* β-*methylglucoside*, which crystallised on evaporation of the solvent, was recrystallised from light petroleum (yield, 1·1 g.); m. p. 51°, b. p. 95°/0·04 mm., $[\alpha]_D^{20°}$ − 20° in chloroform (*c*, 1·1) (Found : C, 51·2; H, 8·8; OMe, 52·1. $C_{10}H_{20}O_6$ requires C, 50·9; H, 8·5; OMe, 52·6%).

3 : 4 : 6-*Trimethyl Glucose*.—When 3 : 4 : 6-trimethyl β-methylglucoside was heated at

100° with 5% aqueous hydrochloric acid, the rotation altered steadily from $[\alpha]_D$ — 15° (approx.) to a constant value + 62°, reached in about 2 hours. The solution was neutralised with barium carbonate and evaporated to dryness, and the product extracted with boiling chloroform. Removal of the solvent left 3 : 4 : 6-*trimethyl glucose* as a strongly reducing syrup which had $[\alpha]^{20°}_{5780}$ + 71° in water (*c*, 2·0) (Found : OMe, 38·0. $C_9H_{18}O_6$ requires OMe, 41·9%).

3 : 4 : 6-*Trimethyl Gluconolactone.*—An aqueous solution of 3 : 4 : 6-trimethyl glucose (4·1 g. in 25 c.c.) at 35° was oxidised by bromine (6 c.c.) for 17 hours, the excess of bromine removed by aeration, and the solution extracted several times with chloroform. The united chloroform extracts, dried over magnesium sulphate and freed from chloroform under diminished pressure, left a yellow syrup (2·3 g.), which gave on distillation 3 : 4 : 6-*trimethyl gluconolactone* (2 g.) as a colourless mobile syrup, b. p. 140°/0·1 mm., $n_D^{18°}$ 1·4688, $[\alpha]^{20°}_{5780}$ + 87° in water (*c*, 1·0) (Found : C, 49·2; H, 7·7; OMe, 41·4; *M*, by titration with sodium hydroxide, 223. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%; *M*, 220). When heated on the water-bath with the calculated amount of phenylhydrazine, the lactone gave quantitatively the crystalline *phenylhydrazide* of 3 : 4 : 6-trimethyl gluconic acid, m. p. 126° after recrystallisation from ethyl acetate (Found : C, 54·4; H, 7·6; N, 8·7; OMe, 29·0. $C_{15}H_{24}O_6N_2$ requires C, 54·8; H, 7·4; N, 8·5; OMe, 28·5%).

The rate of hydrolysis of 3 : 4 : 6-trimethyl gluconolactone in water was closely similar to that of other δ-lactones of the glucose series. The hydrolysis was followed polarimetrically : $[\alpha]^{20°}_{5780}$ + 87° (initial value, *c*, 1·0); 75° (30 mins.); 60° (1 hr.); 40° (2 hrs.); 29° (3 hrs.); 23° (4 hrs.); 19° (5 hrs.); 16° (6 hrs.); 15° (7 hrs., constant value).

The calculated amount of sulphuric acid was added to an aqueous solution of sodium 3 : 4 : 6-trimethyl gluconate, and the rotation taken immediately : $[\alpha]^{20°}_{5780}$ + 8° (*c*, 1·0, calc. as lactone; initial value); 9·5° (15 mins.); 11° (30 mins.); 12° (45 mins.); 13° (1 hr.); 14° (1·5 hrs.); 14·5° (2 hrs.); 15° (3 hrs., constant value). From these figures it appears that at equilibrium the lactone and the acid are present in the proportion of 9% and 91% respectively.

Action of Sodium Hypochlorite on 3 : 4 : 6-*Trimethyl Gluconamide.*—3 : 4 : 6-Trimethyl gluconolactone (1·3 g.) was dissolved in dry methyl alcohol (10 c.c.) saturated with ammonia at 0°. After 45 hours at 15° the solution was evaporated, leaving a pale yellow syrup which failed to crystallise. Its analytical data indicated that it was mainly 3 : 4 : 6-trimethyl gluconamide but contained some of the corresponding ammonium salt (Found : C, 44·7; H, 8·2. $C_9H_{19}O_6N$ requires C, 45·5; H, 8·1%). The syrup responded readily to Weerman's test for α-hydroxy-amides, giving a copious precipitate of hydrazodicarbonamide when semicarbazide hydrochloride was added to a solution of the amide which had been treated with sodium hypochlorite under the conditions prescribed by Weerman. The syrupy amide (1·2 g.) was dissolved in water (15 c.c.) and to it was added a solution of sodium hypochlorite (11 c.c., prepared according to Weerman's directions). The solution was kept at 0° for 30 minutes. Slight evolution of gas was observed (decomposition). Sufficient hydrochloric acid was then added to render the solution slightly acid to Congo-red : evolution of carbon dioxide took place. The solution was heated to 40° and neutralised with barium carbonate, and the product extracted in chloroform. Removal of the solvent left a pale yellow syrup, which on distillation gave 2 : 3 : 5-trimethyl *d*-arabofuranose as a colourless syrup (0·61 g.), b. p. 95°/0·04 mm., n_D^{20} 1·450, $[\alpha]^{20°}_{5780}$ + 45° in water (*c*, 1·0) (Found : OMe, 47·0. Calc. for $C_8H_{16}O_5$: OMe, 48·5%). The identity of this material was confirmed by its conversion (0·46 g.), on oxidation by the method described above, into crystalline 2 : 3 : 5-trimethyl *d*-arabonolactone (0·3 g.), b. p. 95—100°/0·05 mm., $n_D^{22°}$ 1·4422 (superfused solid), m. p. 29° (alone or when mixed with an authentic specimen of the same m. p.), $[\alpha]^{20°}_{5780}$ + 47° in water (*c*, 1·0), initial value, decreasing after about 40 days to the constant value + 27°.

De-acetylation of 2-*Toluenesulphonyl* 3 : 4 : 6-*Triacetyl* β-*Methylglucoside and Preparation of an Anhydro*-β-*methylhexoside.*—When 2-toluenesulphonyl 3 : 4 : 6-triacetyl β-methylglucoside (see preceding paper) is treated in chloroform solution at 0° with sodium methoxide, sodium toluenesulphonate separates and the product is an anhydromethylhexoside. To isolate the latter substance, the filtered chloroform solution is shaken with water and the aqueous extract neutralised with sulphuric acid. The neutral solution is evaporated to dryness (diminished pressure) and mineral impurities are removed by solution of the product in alcohol. The treatment with alcohol is repeated until on evaporation of the solvent an ash-free syrup is obtained. This syrup is non-reducing, contains no sulphur, and consists mainly of *anhydro*-β-*methylhexoside.* $[\alpha]^{20°}_{5780}$ — 25° in water (*c*, 1·0), — 40° in ethyl acetate (*c*, 2·0) (Found : C, 47·0; H, 7·0; OMe, 17·0. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 17·6%).

When heated with 5% aqueous hydrochloric acid at 95°, the anhydro-β-methylhexoside

was transformed into a strongly reducing, hygroscopic syrup, which was isolated after neutralisation of the hydrochloric acid with silver carbonate, and evaporation of the neutral solution to dryness. During the hydrolysis the rotation changed from $[\alpha]^{20°}_{5780}$ — 25° to — 77° (Found : C, 41·4; H, 5·9. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2%). The product was not further purified and may have contained free hexose.

Methylation of the anhydro-β-methylhexoside was readily effected by methyl iodide and silver oxide. Two treatments were sufficient to give the fully methylated *dimethyl anhydromethylhexoside*, which after recrystallisation from ether had m. p. 69°, $[\alpha]^{20°}_{5780}$ + 40° in ethyl acetate (*c*, 1·0), + 24° in water (*c*, 1·0) (Found : C, 52·7; H, 8·2; OMe, 44·1; *M*, by Rast's method, 202. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9; OMe, 45·6%; *M*, 204). The fully methylated derivative was soluble in water, alcohol, ether, and ethyl acetate. It did not reduce Fehling's solution, but on treatment with boiling 5% aqueous hydrochloric acid was converted into the corresponding strongly reducing dimethyl anhydrohexose (?), which, when isolated by the usual procedure, was obtained as a hygroscopic syrup. The amount of material was insufficient for a complete examination and details of its properties will be communicated later. During the hydrolysis the rotation changed smoothly in one hour from $[\alpha]^{20°}_{5780}$ + 21° in dilute hydrochloric acid (*c*, 1·0) to + 67°.

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