319. *Methylation of α-Methylglucoside by Thallous Hydroxide and Methyl Iodide.*

By C. C. Barker, E. L. Hirst, and J. K. N. Jones.

It is shown that methylation of α-methylglucoside by the thallous hydroxide–methyl iodide process gives the fully methylated product, in addition to trimethyl α-methylglucoside, if excess of thallous hydroxide is used in the formation of the thallium derivative of the sugar. The trithallium derivative of α-methylglucoside is not homogeneous, but contains all four possible isomers: substitution in positions 2 : 4 : 6 and 2 : 3 : 6 is favoured and the 2 : 3 : 4- and 3 : 4 : 6-trithallium derivatives are present in relatively small amounts. It is concluded that positions 2 and 6 react most readily and that the non-formation of the tetrathallium derivative is due to solubility considerations which result in the precipitation of trithallium derivatives. A method for the preparation of the inaccessible 2 : 4 : 6-trimethyl glucose is given and methods have been devised for the analysis of mixtures of trimethyl glucoses.

It was shown by Fear and Menzies (J., 1926, 929) that α-methylglucoside readily formed a trithallium derivative which reacted with boiling methyl iodide, giving a trimethyl methylglucoside. This method of methylation has been employed also by Purves and Hudson (*J. Amer. Chem. Soc.*, 1937, **59**, 49, 1170) in the case of the simple sugars and it has recently been adapted by two of the present authors for the methylation of polysaccharides (Hirst and Jones, this vol., p. 496). In view of the utility of the reaction we decided to investigate it in greater detail and the present paper is concerned with two main questions, namely, the reason for the formation of a trithallium derivative of α-methylglucoside instead of the expected tetrathallium derivative, and, secondly, the nature of the partly methylated glucose formed from the trithallium compound. It seemed likely that information might be gained in this way concerning the relative reactivities of the four hydroxyl groups and that the way might be opened up for the preparation of partly methylated sugars which are otherwise accessible only with difficulty.

The latter possibility has in fact been realised in that crystalline 2 : 4 : 6-trimethyl glucose can be isolated with ease after hydrolysis of the trimethyl methylglucoside obtained by heating the trithallium derivative of α-methylglucoside with methyl iodide. Nevertheless this trimethyl methylglucoside is not homogeneous, but contains all the four trimethyl derivatives theoretically obtainable from α-methylglucopyranoside. There is a marked predominance of 2 : 4 : 6- and 2 : 3 : 6-trimethyl glucoses, 2 : 3 : 4- and 3 : 4 : 6-trimethyl glucoses being present only in small amount. It appears, therefore, that positions 2 and 6 are favoured in the reaction with thallium hydroxide and that when three thallium atoms have entered the molecule, in any of the four possible ways, the solubilities are such that precipitation of the trithallium derivative occurs.

That there is no special hindrance to complete methylation by this process is revealed by the observation that a considerable yield of tetramethyl α-methylglucoside is obtainable by heating with methyl iodide the above trithallium compounds mixed with an excess of thallous hydroxide. The reaction then becomes analogous to the Purdie method of methylation.

Since no rigid proof of the constitution of 2 : 4 : 6-trimethyl glucose has been given (Oldham's proof, *J. Amer. Chem. Soc.*, 1934, **56**, 1360, although conclusive, being dependent on elimination of other possibilities), this sugar has been further characterised (*a*) by its conversion into the corresponding β-methylglucoside by Oldham's method, (*b*) by its failure to react with cold dilute methyl-alcoholic hydrogen chloride (Haworth and Sedgwick, J., 1926, 283), showing the presence of a methoxyl group at C_4, and (*c*) by its oxidation to a δ-*lactone*, from which the crystalline *amide* of 2 : 4 : 6-trimethyl gluconic acid was obtained. This amide gave a negative Weerman reaction and therefore had a methoxyl group at C_2. The sugar must therefore be either 2 : 3 : 4- or 2 : 4 : 6-trimethyl glucose and its properties definitely rule out the former of these two possibilities. It was identical with the sugar prepared by Haworth and Sedgwick (*loc. cit.*) and tentatively described by them as the 2 : 4 : 6-derivative, proof of this identity being given by *X*-ray crystallographic examination, for which we are indebted to Dr. T. Malkin of this department.

The syrupy mixture of sugars (83% of the total) left after removal of the crystalline 2 : 4 : 6-isomeride (17% of the total) was shown to contain other trimethyl glucoses in the following way. In cold 1% methyl-alcoholic hydrogen chloride partial transformation to a methylglucofuranoside took place, pointing to the presence of 2 : 3 : 6-trimethyl glucose in which the hydroxyl group at C_4 is unmethylated. Each of the other three possible sugars has position 4 methylated and transformation to the furanoside, indicated by initial downward trend of rotation value, cannot take place. By comparison with rotational changes observed with 2 : 3 : 6-trimethyl glucose under similar conditions it was estimated that the syrup contained about 45% of 2 : 3 : 6-trimethyl glucose.

Another portion of the syrup was converted into the corresponding mixture of lactones and the latter were transformed into the amides. The mixed amides gave a positive Weerman test with sodium hypochlorite and by assuming the usual yield of hydrazodicarbonamide obtainable in this reaction (approximately 40% of the theoretical) it was calculated that the syrup contained some 12% of a sugar (3 : 4 : 6-trimethyl glucose) possessing a hydroxyl group at C_2.

An approximation to the content of 2 : 3 : 4-trimethyl glucose was made by forming the *p*-toluenesulphonates of the mixed methylglucosides and treating the mixture with sodium iodide in acetone. Under these conditions the *p*-toluenesulphonyl group at C_6 is replaced by iodine and a quantitative estimation indicated that about 5% of the syrup consisted of 2 : 3 : 4-trimethyl glucose. The portion of syrup unaccounted for (38%) was presumably 2 : 4 : 6-trimethyl glucose which had failed to crystallise and from these figures it appears that the thallium hydroxide had reacted with α-methylglucoside, giving all the possible trisubstituted derivatives in approximately the following proportions : 2 : 4 : 6-derivative, 50%; 2 : 3 : 6-derivative, 36%; 3 : 4 : 6-derivative, 10%; 2 : 3 : 4-derivative, 4%.

EXPERIMENTAL.

Methylation of α-Methylglucoside.—Formation of the thallium compound of α-methylglucoside by the method of Fear and Menzies (*loc. cit.*), followed by reaction with methyl iodide, gave exclusively trimethyl α-methylglucoside as stated by these authors. When a large excess of thallous hydroxide was used, the product was a thallium derivative of α-methylglucoside admixed with thallium hydroxide and this with boiling methyl iodide gave tetra- in addition to tri-methyl α-methylglucoside. Thallous hydroxide (1·33N, 1200 c.c.) was evaporated to a small volume (400 c.c.) and poured hot into a solution of α-methylglucoside (38 g.) in water (18 c.c.). The precipitate was filtered off and dried (7 days) in a vacuum over phosphoric oxide in the absence of light. The dry powder (243 g.) was boiled with methyl iodide (115 c.c.) for 6 hours, the excess of methyl iodide then distilled off, and the residue extracted with chloroform. The extracts were concentrated to a syrup (31 g.), which gave on fractional distillation : (I) tetramethyl α-methylglucoside (6·15 g.), b. p. 125°/0·01 mm. (bath temp.), $n_D^{17°}$ 1·4450 (Found : OMe, 61·0. Calc. for $C_{11}H_{22}O_6$: OMe, 62·0%). On hydrolysis with 8% hydrochloric acid at 95° this gave nearly quantitatively tetramethyl glucopyranose, m. p. 87°. (II) A mixture of tetramethyl α-methylglucoside and trimethyl α-methylglucoside (4·73 g.), b. p. 135°/0·01 mm. (bath temp.), $n_D^{12·5°}$ 1·4522 (Found : OMe, 55·4%). (III) Trimethyl α-methylglucoside (17·47 g.), b. p. 140—143°/0·01 mm. (bath temp.), $n_D^{18·5°}$ 1·4572 (Found : OMe, 51·9. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The still residue weighed 2·7 g. Fraction III (17·4 g.) was heated with 8% hydrochloric acid on the boiling water-bath for 8 hours. After neutralisation by barium carbonate the filtered solution was concentrated to dryness at 40°/12 mm. The organic material was taken up in chloroform and on removal of the solvent a syrup (14·5 g.) was obtained which partly crystallised. The mixture of syrup and crystals was triturated with ether until the syrup (A) dissolved, leaving crystalline 2 : 4 : 6-trimethyl glucose (2·9 g.), m. p. 123—126° (after recrystallisation from ether). Mixed m. p. with a sample of the sugar prepared by Haworth and Sedgwick (*loc. cit.*) 123—124°. $[\alpha]_D^{20°}$ + 110° ⟶ + 70° (in methyl alcohol; *c*, 1·0). Apart from initial mutarotation to 70° no rotation change was observed during several days when the sugar was dissolved in 1% methyl-alcoholic hydrogen chloride. The sugar (1 g.) was converted into the corresponding β-methylglucoside (0·5 g.), m. p. 69—70°, by the method of Oldham (*J. Amer. Chem. Soc.*, 1934, **56**, 1360) (compare Haworth and Sedgwick, *loc. cit.*) (Found : OMe, 51·8%).

2 : 4 : 6-*Trimethyl* δ-*gluconolactone*.* The sugar (1 g.) was dissolved in water (6 c.c.) containing bromine (1 c.c.), and the solution kept at 55° for 4·5 hours until it was non-reducing. Bromine was removed by aeration, the solution neutralised with silver carbonate and filtered, and hydrogen sulphide passed through the filtrate. Silver sulphide was removed by filtration and the aqueous solution was concentrated to a syrup, which gave on distillation 2 : 4 : 6-*trimethyl* δ-*gluconolactone* (0·8 g.), b. p. 150°/0·01 mm. (bath temp.), $n_D^{20°}$ 1·4690, $[\alpha]_D^{20°}$ + 104° (in chloroform, *c*, 5·7). $[\alpha]_D^{20°}$ + 87° (initial value in water, *c*, 1·3); 72° (70 mins.); 65° (100 mins.); 60° (130 mins.); 50° (200 mins.); 40° (350 mins.); 37° (550 mins., constant value) (Found : OMe,

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* After these results had been submitted for publication a paper appeared by Lake and Peat (this vol., p. 1417) in which the lactone and amide of 2 : 4 : 6-trimethyl gluconic acid were described. The constants given in the present paper are in good agreement with those recorded by these authors.

41·1; equiv., by titration, 218. $C_9H_{16}O_6$ requires OMe, 42·3%; equiv., 220). The lactone was dissolved in dry ether, and the solution saturated with dry ammonia. 2 : 4 : 6-*Trimethyl gluconamide* separated as a crystalline solid (yield, quantitative), m. p. (after recrystallisation from acetone–light petroleum) 98°; $[\alpha]_D^{21°}$ + 54° (in methyl alcohol, *c*, 1·1) (Found: C, 45·3; H, 8·2; N, 5·6; OMe, 38·6. $C_9H_{19}O_6N$ requires C, 45·6; H, 8·0; N, 5·9; OMe, 39·2%). A solution of the amide (50 mg.) in water (2 c.c.) was cooled to 0°, a slight excess of cold sodium hypochlorite solution added, and the mixture kept at 0° for 1 hour. Excess of hypochlorite was then removed by addition of sodium thiosulphate, and anhydrous sodium acetate (0·5 g.) and semicarbazide hydrochloride (0·1 g.) added; no precipitate of hydrazodicarbonamide formed during several hours.

Estimation of 2 : 3 : 6-*Trimethyl Glucose in the Syrup A*.—The syrup A (see above) was recovered from its solution in ether, and a portion of it dissolved in 1% methyl-alcoholic hydrogen chloride (*c*, of sugar, 3·32). $[\alpha]_D^{20°}$ + 73° (initial value); 63° (45 mins.); 57° (1·5 hrs.); 50° (2·5 hrs.); 26° (10 hrs., minimum value, followed by very slow change). Under similar conditions 2 : 3 : 6-trimethyl glucose (*c*, 1·0) showed the following rotational changes: $[\alpha]_D^{20°}$ + 73° (value on completion of mutarotation); + 50° (1 hr.); + 30° (2 hrs.); + 15° (3 hrs.); − 4° (4 hrs.); − 17° (5 hrs.); − 23° (6 hrs.); − 29° (7 hrs.); − 31° (8 hrs.) (minimum value). From the magnitude of the rotational changes between the initial and the minimum values given above it is possible to calculate the approximate content (45%) of 2 : 3 : 6-trimethyl glucose in the syrup, since only the latter sugar displays rotational change under these conditions.

Detection and Estimation of 3 : 4 : 6-*Trimethyl Glucose in Syrup A*.—The syrup was oxidised with bromine water in the usual way and the product was heated to convert the acids into lactones (yield, 80%). The mixed lactones had b. p. 150°/0·01 mm. (bath temp.), $n_D^{17°}$ 1·4642, and $[\alpha]_D^{20°}$ + 70° (initial value in water, *c*, 1·4), falling rapidly (6 hrs.) to + 42°, followed by slow downward change (these figures are in agreement with the view that 2 : 3 : 6-trimethyl glucose is present to the extent of 40—45%) (Found: OMe, 40·4%; equiv., 219).

The mixed amides were prepared by dissolving the lactones in liquid ammonia (method of Jellinek and Upson, *J. Amer. Chem. Soc.*, 1938, **60**, 356). The syrupy amide mixture was treated with sodium hypochlorite as described above. Yield of hydrazodicarbonamide, m. p. and mixed m. p. 256°, 5% of the theoretical. Since arabonamide and amides of other sugar acids having a free hydroxyl group at C_2 give hydrazodicarbonamide in about 40% yield under these conditions, it is inferred that the mixed amides contained some 12% of 3 : 4 : 6-trimethyl gluconamide.

Estimation of 2 : 3 : 4-*Trimethyl Glucose in Syrup A*.—A portion of the syrup was boiled with 2% methyl-alcoholic hydrogen chloride until the sugars were converted into the corresponding methylglucosides. The mixed glucosides (1·8 g.) were dissolved in dry pyridine (25 c.c.), and *p*-toluenesulphonyl chloride (1·6 g.) added. The solution was kept at 50° for 12 hours and then poured into water. The aqueous solution was extracted with benzene and the benzene was washed successively with concentrated hydrochloric acid, aqueous sodium carbonate, and water. The solution was dried over magnesium sulphate and evaporated to a syrup (2·6 g.), which was dissolved in acetone (25 c.c.) containing sodium iodide (1 g.). This solution was heated in a sealed tube at 100° for 5 hours. The precipitated sodium *p*-toluenesulphonate was filtered off, washed with dry acetone, and weighed (yield, 0·068 g., corresponding to the presence of 4·7% of 2 : 3 : 4-trimethyl glucose in syrup A). The solution and the washings were evaporated to dryness and the iodine content of the mixed sugars so obtained was estimated by heating the syrup with silver nitrate in acetonitrile according to the method of Oldham and Rutherford (*J. Amer. Chem. Soc.*, 1932, **54**, 366). The yield of silver iodide was 0·079 g., corresponding to the presence of 4·5% of 2 : 3 : 4-trimethyl glucose in the syrup A, in good agreement with the other value recorded above.

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THE UNIVERSITY, BRISTOL.

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