183. *The Simultaneous Preparation of* 2 : 3 : 4- *and* 2 : 3 : 6-*Trimethyl Glucose.*

By George J. Robertson.

The primary object of this investigation was a synthesis of 2 : 3 : 6-trimethyl glucose which would give easy access to this important reference compound. The scheme of reactions achieved its purpose, but owing to the catalysed migration of an acetyl group from position 4 to position 6 during the process of methylation, the way was opened to the simultaneous preparation of 2 : 3 : 4- and 2 : 3 : 6-trimethyl glucose. These isomeric sugars were formed in practically equal amount and were separated in a state of purity.

A convenient starting point was found in 2 : 3-dimethyl α-methylglucoside (Irvine and Scott, J., 1913, **103**, 575), which on treatment with one molecular proportion of triphenylchloromethane (cf. Helferich, *Annalen*, 1924, **440**, 2) readily gave a *triphenylmethyl* derivative in which it can be concluded, from the work of Helferich (*loc. cit.*; *Annalen*, 1926, **450**, 219), that the triphenylmethyl radical is attached in position 6.

4-*Acetyl*-6-*triphenylmethyl*-2 : 3-*dimethyl* α-*methylglucoside* was readily convertible into 4-acetyl-2 : 3-dimethyl α-methylglucoside. The above structure is postulated, as it appears improbable that the conditions prevailing during the isolation are conducive to the migration of the acetyl group. In the subsequent methylation of the free hydroxyl group, at least five consecutive treatments with the reagents were necessary. During this protracted process, however, there was not the slightest indication of the loss of acetyl content. The acetyl group and the glucosidic methyl group were eliminated by the usual methods of hydrolysis, and a clear syrup was obtained, which showed all the physical characteristics of a trimethyl glucose, but failed to crystallise even after nucleation with 2 : 3 : 6-trimethyl glucose. Consideration of the work of Helferich (*Annalen*, 1926, **450**, 219; 1927, **455**, 173; **458**, 111) immediately suggested the idea that the faintly alkaline nature of the methylating medium had induced a migration of the acetyl group from position 4 to position 6, and that the product was an equilibrium mixture of 2 : 3 : 4- and 2 : 3 : 6-trimethyl glucose.

The catalytic migration or rearrangement of acyl groups in partly substituted glucoses is now well authenticated and has been shown to be conditioned by the presence of minute traces of alkali. Helferich (*loc. cit.*) has shown that 1 : 2 : 3 : 4-tetra-acetyl β-*d*-glucose is converted into an isomeric tetra-acetyl β-*d*-glucose to which he ascribed the structure of a 1 : 2 : 3 : 6-tetra-acetyl β-*d*-glucose. Haworth, Hirst, and Teece (J., 1930, 1405) point out that position 4 is remote from position 6 in that the hydroxyl groups are situated in

different planes in the β-glucopyranose configuration, and express the opinion that the new isomeride is derived from 1 : 2 : 3 : 4-tetra-acetyl β-*d*-glucose by interaction in positions 1 and 6 with the production of a derivative of orthoacetic acid. Now Helferich (*Annalen*, 1927, **458**, 111), in showing that 2 : 3 : 4-triacetyl β-methylglucoside was similarly converted into an isomeric triacetyl β-methylglucoside, which he considered to be 2 : 3 : 6-triacetyl β-methylglucoside, had already demonstrated that position 1 need not necessarily be involved in the above acyl rearrangement. When this evidence is considered in conjunction with the fact that Helferich's supposed 1 : 2 : 3 : 6-tetra-acetyl β-*d*-glucose is not identical with the 2 : 3 : 4 : 6-tetra-acetyl β-*d*-glucose obtained by Fischer and Delbrück (*Ber.*, 1909, **42**, 2778), there is little reason for the formulation of a derivative of orthoacetic acid by interaction in positions 1 and 6 to explain the existence of Helferich's tetra-acetate. Helferich's explanation of the conversion of his 1 : 2 : 3 : 6-tetra-acetyl β-*d*-glucose into 2 : 3 : 4 : 6-tetra-acetyl β-methylglucoside on methylation with methyl iodide and silver oxide as being due to a further rearrangement of acyl groups is quite adequate. The results of the present investigation strongly support Helferich's view that the 4- and the 6-position are involved in the above two cases and that 1 : 2 : 3 : 4-tetra-acetyl β-*d*-glucose and 2 : 3 : 4-triacetyl β-methylglucoside readily undergo acyl rearrangement to give 1 : 2 : 3 : 6-tetra-acetyl β-*d*-glucose and 2 : 3 : 6-triacetyl β-methylglucoside respectively.

The evidence which is at present available in connection with the catalysed migration of acyl groups points to the idea that no generalisation can be drawn. The problem is complicated by the fact that in addition to acyl wandering, loss of acyl content often occurs in these reactions. For example, recent work in this laboratory (Irvine and Miller, unpublished result) has shown that when 2 : 3-diacetyl α-methylglucoside is methylated with the Purdie reagents 2 : 3-dimethyl α-methylglucoside and 2 : 3 : 4-trimethyl α-methylglucoside occur among the products. Miller has suggested the idea that there is a general tendency for acetyl groups to migrate from positions 2, 3, and 4 towards position 6 whenever a free hydroxyl group renders such rearrangement possible. The conversion of 2 : 3 : 4-triacetyl α-methylglucoside into 3 : 4 : 6-triacetyl-2-methyl α-methylglucoside (Haworth, Hirst, and Teece, J., 1931, 2858) may not represent a simple migration of an acetyl group from position 2 to position 6, but may be the result of a general migration of groups towards the 6 position, *i.e.*, 4 to 6, 3 to 4, and 2 to 3.

The problem is being further explored.

Experimental.

6-*Triphenylmethyl*-2 : 3-*dimethyl* α-*Methylglucoside*.—2 : 3-Dimethyl α-methylglucoside (8·95 g.) in 70 c.c. of dry pyridine was treated with triphenylchloromethane (11·23 g.; 1 mol.), and the mixture heated on a boiling water-bath for 1 hr. After cooling and filtration of the pptd. pyridine hydrochloride, the mixture was poured slowly into ice-water (800 c.c.). The sticky yellow solid pptd. became hard and granular in 12 hr. and, after washing with H_2O, was dried (17 g., m. p. 152°). One crystn. from abs. EtOH gave 11·1 g. of pure 6-*triphenylmethyl*-2 : 3-*dimethyl* α-*methylglucoside*, transparent plates, m. p. 169—170°. It had $[\alpha]_D$ + 66·4° in $CHCl_3$ (Found : C, 72·3; H, 6·6; OMe, 19·8. $C_{28}H_{32}O_6$ requires C, 72·4; H, 6·9; OMe, 20·05%).

4-*Benzoyl*-6-*triphenylmethyl*-2 : 3-*dimethyl* α-*methylglucoside* was obtained by treating 6-triphenylmethyl-2 : 3-dimethyl α-methylglucoside (8·7 g.) with benzoyl chloride (2·5 c.c.) in dry pyridine (30 c.c.). The product, isolated as described above, was an amorphous white powder, m. p. 60°, and had $[\alpha]_D$ + 62·7° in $CHCl_3$ (Found : OMe, 15·3. $C_{35}H_{36}O_7$ requires OMe, 16·4%). The triphenylmethyl residue is easily removed, but a separation of the resulting 4-benzoyl-2 : 3-dimethyl α-methylglucoside from triphenylmethylcarbinol proved to be difficult.

4-*Acetyl*-6-*triphenylmethyl*-2 : 3-*dimethyl* α-*Methylglucoside*.—6-Triphenylmethyl-2 : 3-dimethyl α-methylglucoside (10 g.) in dry pyridine (25 c.c.) was treated with Ac_2O (5 c.c.), and the mixture kept at the ordinary temp. for 12 hr. and then poured into cold H_2O. The ppt. was washed and dried (10·65 g., m. p. 150—152°). 4-*Acetyl*-6-*triphenylmethyl*-2 : 3-*dimethyl* α-*methylglucoside* (8·7 g.) was obtained by crystn. from light petroleum (b. p. 60—80°) in clusters of needles, m. p. 153—154°, $[\alpha]_D$ + 83·4° in $CHCl_3$ (Found : OMe, 18·0; Ac, 9·0. $C_{30}H_{34}O_7$ requires OMe, 18·4; Ac, 8·5%).

4-*Acetyl*-2 : 3-*dimethyl* α-*Methylglucoside*.—A solution of 4-acetyl-6-triphenylmethyl-2 : 3-

dimethyl α-methylglucoside (8·7 g.) in C_6H_6 was saturated with dry HCl. The initial rotation declined and became const. in 30 min. The C_6H_6 solution was extracted repeatedly with H_2O until the C_6H_6 layer was inactive. The combined aq. extracts, which had been poured on solid NaOAc to depress the acidity, were filtered and extracted with $CHCl_3$ until the H_2O was inactive. The $CHCl_3$ extract was dried, filtered, and evaporated to dryness under diminished press. and a clear mobile syrup (4·3 g.; calc., 4·54 g.) was obtained, $n_D^{15°}$ 1·4590 (Found: Ac, 18·3. Calc. for $C_{11}H_{20}O_7$: Ac, 16·3%).

Methylation of 4-Acetyl-2 : 3-dimethyl α-Methylglucoside.—Methylation was effected by means of MeI and Ag_2O. On one occasion, after seven consecutive treatments with the methylating agents, 8·0 g. of initial material yielded 7·9 g. of a mobile syrup, $n_D^{15°}$ 1·4510 (Found: OMe, 43·6; Ac, 19·7. Calc. for $C_{12}H_{22}O_7$: OMe, 44·6; Ac, 15·5%).

Trimethyl α-Methylglucoside.—The acetyl group was eliminated from the above monacetyltrimethyl α-methylglucoside (7·9 g.) by boiling with $N/10$-alkali for 20 min. The cooled solution was extracted with $CHCl_3$, the extract dried, filtered, and evaporated to dryness under diminished press., and 5·8 g. of a syrup obtained, b. p. 115—120°/0·2 mm., $n_D^{15°}$ 1·4585, $[\alpha]_D$ + 156·6° in $CHCl_3$ (Found: OMe, 51·4. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

Trimethyl Glucose.—Trimethyl methylglucoside (5·4 g.) was hydrolysed with 5% HCl (initial rotation + 150·7°; const. value + 71·4° after 3 hrs.' boiling). The solution was neutralised with $BaCO_3$, filtered, extracted with $CHCl_3$ to remove traces of unhydrolysed material, and evaporated to dryness under diminished press. at 60°. The dry residue was extracted with $CHCl_3$ and the extract, on evaporation to dryness, yielded 4·9 g. of a clear syrup, $n_D^{15°}$ 1·4724, which did not crystallise even after nucleation with 2 : 3 : 6-trimethyl glucose (Found: OMe, 41·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). The syrup (4·42 g.) was dissolved in MeOH (100 c.c.) containing 1% dry HCl. The initial rotation was + 67·4°; after 20 hr. the solution still reduced Fehling's solution but the rotation was const. at + 37·5°. The acid was neutralised with $BaCO_3$, most of the MeOH distilled away, the residue diluted with H_2O, and the filtered aq. solution extracted with $CHCl_3$ until the optical activity of the aq. layer was const. The united $CHCl_3$ extracts, on evaporation to dryness, gave 2·4 g. of a mobile syrup (A). The aq. solution, on evaporation to dryness, gave 1·8 g. of a syrup (B).

The mobile syrup (A) was hydrolysed in the usual way and yielded 2·03 g. of a product which crystallised spontaneously on the removal of the solvent. After one crystn. from Et_2O it had m. p. 113—115°, alone or mixed with authentic 2 : 3 : 6-trimethyl glucose (m. p. 112—115°).

The syrup (B) had $[\alpha]_D^{15°}$ + 79° in H_2O (cf. Irvine and Oldham, J., 1921, **119**, 1748) and $n_D^{15°}$ 1·4724. It (1·8 g.) was identified as 2 : 3 : 4-trimethyl glucose by conversion into the cryst. 1 : 6-dinitrate (1·0 g.), m. p. 84°, and 86° after recrystn. from abs. EtOH (Oldham, J., 1925, **127**, 2840, gives m. p. 86°).

The author is grateful to Sir James C. Irvine, C.B.E., F.R.S., for his interest and kindly criticism.

THE UNIVERSITY, ST. ANDREWS. [*Received, April 19th,* 1933.]