198. *Monomethyl Hexoses. Part I. The Constitution of the Supposed 4-Methyl Glucose.*

By John Munro and Edmund G. V. Percival.

During the investigation of the alkali addition compounds of the carbohydrates (J., 1934, 1160) it became clear that the assignment of structure by a methylation method depended on the isolation of derivatives of partly methylated sugars, usually in the form of the crystalline phenylhydrazones or phenylosazones. Whereas well-characterised derivatives of 2-, 3-, and 6-methyl glucose were already available, there was dubiety about the existence of such reference compounds for 4- and 5-methyl glucose, and it was considered desirable to remove all doubt on this point.

In 1925 Pacsu (*Ber.*, **58**, 1455) reported the isolation of 4-methyl glucose and of 4 : 5 : 6-trimethyl glucose by the methylation of acetone compounds of glucose dibenzyl mercaptal. This work was, however, challenged by Schinle (*Ber.*, 1931, **64**, 2361), who revealed that the so-called 4-methyl glucosazone was, in reality, impure glucosazone, an observation which led to the conclusion that the parent monomethyl sugar was 2-methyl glucose identical with that previously described by Hickinbottom (J., 1928, 3140) and Brigl and Schinle (*Ber.*, 1929, **62**, 1716; 1930, **63**, 2887). Schinle followed up these observations (*Ber.*, 1932, **65**, 318) by a study of the 4 : 5 : 6-trimethyl glucose reported by Pacsu, and found it to be a monomethyl glucose yielding an osazone, m. p. 158°. Accordingly this sugar was designated 4-methyl glucose, since the osazone was different from the apparently well-characterised derivatives obtained from 3-, 5- and 6-methyl glucose. Unfortunately, however, Schinle carried out no conclusive experiments to characterise the sugar in question, and the position became indefinite once more when Levene and Raymond (*J. Biol. Chem.*, 1932, **97**, 751) proved by the isolation of 2 : 3 : 4 : 6-tetramethyl glucopyranose by methylation of the supposed 5-methyl glucose of Ohle and v. Vargha (*Ber.*, 1929, **62**, 2435), that the supposed 5-methyl glucose was in reality 6-methyl glucose. Obviously when these new facts came to light Schinle's method of assignment of the 4-position to the methyl group in the sugar under review did not exclude a selection of the 5-position. As was to be expected, Levene and Raymond (*J. Biol. Chem.*, 1932, **97**, 763) re-examined the position and adduced evidence supporting the original conclusion of Schinle (*loc. cit.*), but a survey of this evidence reveals the fact that it too is not conclusive.

Instead of a critical examination of the " trimethyl glucose " of Pacsu, Levene and Raymond synthesised a crystalline compound described as 2 : 3 : 6-triacetyl 4-methyl β-methylglucoside and compared it with the corresponding derivative prepared directly from the sugar in question. The stages of their synthesis are: β-methylglucoside (I) ⟶ 4 : 6-benzylidene β-methylglucoside (II) ⟶ 2 : 3-dibenzoyl 4 : 6-benzylidene β-methylglucoside (III) ⟶ 2 : 3-dibenzoyl β-methylglucoside (IV) ⟶ 2 : 3 : 6-tribenzoyl β-methylglucoside (V) ⟶ 2 : 3 : 6-tribenzoyl 4-methyl β-methylglucoside (VI) ⟶ 4-methyl β-methylglucoside (VII) ⟶ 2 : 3 : 6-triacetyl 4-methyl β-methylglucoside (VIII). Levene and Raymond (*loc. cit.*) accept the view of Ohle and Spencker (*Ber.*, 1928, **61**, 2387) that (II) has a pyranoside form and argue therefore that positions 2 and 3 are available for benzoylation. They consider that, since (VIII) is originally derived from a normal glucoside, it cannot be substituted in position 5. But it is clear that no direct evidence is presented, at any rate after stage (II), that glucopyranosides are concerned. In addition, the possibility of the wandering of acyl groups during the methylation with methyl iodide and silver

oxide was not considered, and though Helferich and Günther (*Ber.*, 1931, **64**, 1276) record that 2 : 3 : 4-tribenzoyl β-methylglucoside passes on methylation into the corresponding 6-methyl derivative, it is well known that acetyl groups migrate during such treatment (Haworth, Hirst, and Teece, J., 1930, 1405; 1931, 2858). Since, although the interpretation of Levene and Raymond was by no means improbable, in our opinion the question at issue was not decisively proved, it was determined to put the matter to a critical test, from which the fact emerges that the 4-methyl glucose of Schinle has indeed that structure.

By a modified method the syrupy methylated glucose of Schinle (*loc. cit.*) was isolated. Complete methylation, followed by hydrolysis, yielded crystalline 2 : 3 : 4 : 6-tetramethyl glucopyranose in good yield, which thus excluded the possibility of the presence of 5-methyl glucose. Oxidation of the monomethyl glucose with bromine water yielded a monomethyl gluconolactone which on account of its rapid hydrolysis in aqueous solution was shown to be a δ-lactone (Haworth, " Constitution of Sugars," London, 1929). The inference is, therefore, that the possibility of the formation of the more stable γ-lactone was ruled out by the presence of a methyl group in the 4-position. Furthermore, complete methylation of the monomethyl δ-gluconolactone yielded 2 : 3 : 4 : 6-tetramethyl δ-gluconolactone identified as the crystalline phenylhydrazide, proving that the original oxidation product was indeed 4-methyl δ-gluconolactone.

In addition, crystalline 2 : 3 : 6-triacetyl 4-methyl β-methylglucoside (Levene and Raymond, *loc. cit.*) was prepared from the monomethyl glucose, and this on deacetylation and methylation, followed by hydrolysis, again yielded 2 : 3 : 4 : 6-tetramethyl glucopyranose. There is thus no room for doubt that the monomethyl glucose is indeed 4-methyl glucose.

Experimental.

Preparation of 4-Methyl Glucose Dibenzyl Mercaptal.—The methods described by Pacsu (*Ber.*, 1924, **57**, 851; 1925, **58**, 1455) and Schinle (*loc. cit.*) were followed except for modifications of detail. Glucose dibenzyl mercaptal (30 g.) was condensed with dry acetone (300 g.) containing concentrated sulphuric acid (6 g.) for 42 hours at 15°. The acetone compound (20 g.) obtained in the form of a syrup after neutralisation and removal of solvent was dissolved in dry ether (130 c.c.) and treated with excess of sodium shavings for 24 hours. After filtration and removal of the ether by distillation the resulting glass was methylated with methyl iodide (35 c.c.) at 40° for 24 hours. The solution on extraction with ether, filtration and evaporation yielded a syrup, which was dissolved in ten times its weight of 90% alcohol and hydrolysed by boiling for 20 minutes with *N*-hydrochloric acid (6 c.c.). On cooling, 2-methyl glucose dibenzyl mercaptal (3·5 g.) crystallised, m. p. 191°, *i.e.*, the " 4 "-methyl glucose dibenzyl mercaptal of Pacsu (*loc. cit.*). The 4-methyl glucose dibenzyl mercaptal, *i.e.*, the trimethyl glucose dibenzyl mercaptal of Pacsu, was obtained by addition of water to the filtrate until a turbid solution was produced, which on standing at 0° gave place to a crystalline precipitate. This was dissolved in alcohol, treated with silver carbonate to remove hydrochloric acid, and decolourised with animal charcoal. Concentration yielded 4-methyl glucose dibenzyl mercaptal (7 g.), m. p. 73°.

Isolation of 4-Methyl Glucose.—For the removal of the mercaptan residue, 4-methyl glucose dibenzyl mercaptal (8 g.) was dissolved in acetone (100 c.c.), and a concentrated acetone solution of mercuric chloride (13 g.) added. After refluxing for an hour, the insoluble $C_6H_5 \cdot CH_2 \cdot S \cdot HgCl$ was filtered off, and the acetone removed by evaporation (diminished pressure). The syrup was dissolved in water, and the solution filtered from a further crop of the insoluble mercury compound. The excess of mercuric chloride was then removed by treatment with hydrogen sulphide, and the hydrochloric acid formed during the reaction was neutralised with silver carbonate. The solution, after filtration, was concentrated to a syrup (2·5 g.), $[\alpha]_D^{20°}$ + 53° (equil.) in water (*c*, 2·1) (Found: OMe, 14·8. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). Treatment with phenylhydrazine and acetic acid yielded an osazone, m. p. 158° after recrystallisation from aqueous alcohol (cf. Pacsu, *loc. cit.*; Schinle, *loc. cit.*).

Preparation and Identification of the Fully Methylated Glucose from 4-Monomethyl Glucose.—*Tetra-acetyl 4-methyl glucose.* 4-Monomethyl glucose (1 g.) was dissolved in warm pyridine (4·5 c.c.), and acetic anhydride (4·5 c.c.) slowly added. The solution was warmed to 50°, kept at room temperature for 36 hours, poured into ice-water (50 c.c.), and extracted with ether. The ethereal solution was washed, first with dilute sulphuric acid, then with sodium bicarbonate solution, and finally with water. After drying over calcium chloride and removal of solvent a yellow syrup (1·5 g.) was obtained.

Triacetyl 4-Methyl Glucosidyl Bromide.—To the acetyl compound (1·5 g.) dissolved in glacial acetic acid (2 c.c.), glacial acetic acid saturated with hydrogen bromide at 0° (3 c.c.) was added. After 2 hours, cold chloroform (15 c.c.) was added, and the mixture poured into ice-water (40 c.c.). The chloroform solution was washed with sodium bicarbonate solution and water and dried, and the solvent removed at 45° (diminished pressure) to yield a pale yellow syrup (1·15 g.).

2 : 3 : 6-*Triacetyl 4-Methyl β-Methylglucoside.*—The acetobromo-compound (1·15 g.) was dissolved in dry methyl alcohol (20 c.c.), and dry silver carbonate (3 g.) added. The solution was shaken for 12 hours, until no bromine remained in solution. The solution was filtered and evaporated to a thin syrup. This crystallised on standing and the long colourless needles (0·7 g.) were washed free from syrup with alcohol. They showed m. p. 106°, $[\alpha]_D^{20°}$ — 34·0° in chloroform (*c*, 1·2) (Found: OMe, 16·9. Calc. for $C_{14}H_{22}O_9$: OMe, 18·55%) (cf. Levene and Raymond, *J. Biol. Chem.*, 1932, **97**, 763).

Methylation of Triacetyl 4-Methyl β-Methylglucoside.—The triacetyl 4-methyl β-methylglucoside (0·7 g.), dissolved in acetone, was methylated in the usual way (Haworth, J., 1915, **107**, 8) with methyl sulphate (15 c.c.) and sodium hydroxide solution (40 c.c., 30%). The syrup obtained was methylated during 6 hours at 40° in contact with methyl iodide (10 c.c.) and silver oxide (4 g.). After extraction with ether and removal of solvent the syrup yielded on distillation at 0·03 mm. tetramethyl methylglucopyranoside (0·3 g.) at 100° (bath temp.), $n_D^{15°}$ 1·4450.

2 : 3 : 4 : 6-*Tetramethyl Glucopyranose.*—The tetramethyl methylglucoside was hydrolysed with 5% hydrochloric acid (2 c.c.) for 8 hours. After neutralisation with barium carbonate the solution was evaporated. After the addition of alcohol to precipitate most of the barium chloride, and filtration, the solid was extracted three times with boiling ether. The ethereal solution was evaporated, and the syrup extracted with boiling light petroleum (b. p. 60—80°). From this solution the characteristic crystals of 2 : 3 : 4 : 6-tetramethyl glucose were deposited, m. p. 81—82° alone or in admixture with an authentic specimen. It was thus established that Levene and Raymond's (*loc. cit.*) 2 : 3 : 6-triacetyl 4-methyl β-methylglucoside yielded 2 : 3 : 4 : 6-tetramethyl β-methylglucoside on methylation.

Direct Methylation of 4-Methyl Glucose.—The 4-monomethyl glucose (0·35 g.), dissolved in acetone (10 c.c.), was twice methylated as before with methyl sulphate (10 c.c.) and sodium hydroxide solution (20 c.c., 30%). During the first three additions the temperature was maintained at 30° in order to facilitate the initial formation of the glucoside. The product was extracted with chloroform, and the chloroform removed by evaporation. The second methylation was followed by two treatments with methyl iodide (10 c.c.) and silver oxide (5 g.). The resulting syrup (0·15 g.) distilled at 100—110° (bath temp.)/0·03 mm. to yield a mobile colourless liquid (0·07 g.), $n_D^{15°}$ 1·4445. The glucoside was hydrolysed as before to yield 2 : 3 : 4 : 6-tetramethyl glucose, and this was recrystallised twice from light petroleum (b. p. 60—80°) (0·04 g.), m. p. 82—83° alone or in admixture with an authentic specimen (Found: OMe, 51·2. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

Oxidation of 4-Methyl Glucose to 4-Methyl δ-Gluconolactone.—4-Methyl glucose (0·8 g.) was oxidised in water (7 c.c.) with bromine (1·5 c.c.) at 35° for 3 days until all reducing action had ceased. The excess of bromine was then removed by aëration, and the solution neutralised with silver carbonate. To obtain the lactone, the silver was precipitated with hydrogen sulphide and the solution after filtration was evaporated to dryness (diminished pressure) at about 80°. $[\alpha]_D^{20°}$ + 54·6° (3 mins.); 47·0° (4 mins.); 39·5° (6 mins.); 37·6° (15 mins.); 35·7° (50 mins.); + 33·9° (280 mins.; constant value) (Found: OMe, 14·0. Calc. for $C_7H_{12}O_6$: OMe, 16·1%).

From the hydrolysis curve it is evident that the lactone belongs to the δ-series and that the methyl group is in the 4-position.

Methylation of 4-Methyl δ-Gluconolactone.—The lactone (0·4 g.) was dissolved in the minimum quantity of methyl alcohol and treated with methyl iodide (10 c.c.) and silver oxide (5 g.) during 20 hours at 40°. This process was repeated four times for shorter periods of 5 hours until the lactone became completely soluble in methyl iodide; a final methylation in absence of methyl alcohol was then carried out. After isolation in the usual way the syrup was distilled at 0·03 mm., the fraction distilling at 110—115° (bath temp.) being collected (0·15 g.). This lactone was digested with phenylhydrazine at 100° for 3 hours and on extraction of the product with an ether–light petroleum mixture crystals of the phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl gluconic acid were isolated, m. p. 114° (cf. Charlton, Haworth, and Peat, J., 1926, 89).

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