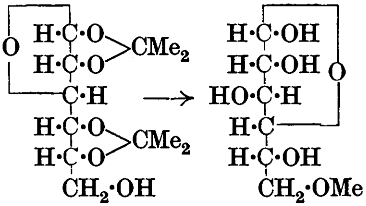
CLXXV.—*The Constitution of Glucose-monoacetone, Glucose-diacetone, and of the Derived 3 : 5 : 6-Trimethyl Glucose and 3-Monomethyl Glucose.*

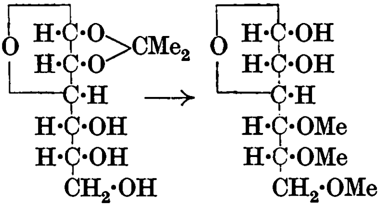
By Cameron Gordon Anderson, William Charlton, and Walter Norman Haworth.

In view of the preparation of sugar carbonates which exhibit many analogies with the sugar acetones (see forthcoming paper, Haworth and Porter), it has become imperative that the oxide-ring forms of sugars which participate in these types of condensation should be established.

Endeavours to provide an experimental proof of the structure of the glucose-acetones have hitherto been only partly successful. Recognising that glucose-monoacetone gave rise on methylation and hydrolysis to a product which was abnormal in its properties, Irvine and his collaborators (Irvine and Scott, J., 1913, **103**, 573; Irvine and Macdonald, J., 1915, **107**, 1710; Irvine and Patterson, J., 1922, **121**, 2146) considered the glucose-acetones to be derivatives of γ-glucose, and the following structures were advocated by the last-named authors for glucose-diacetone (I) and glucose-monoacetone (II).



(I.) (III.)



(II.) (IV.)

These formulæ were intended to supplant those (p. 1333) which had been supported by Macdonald (J., 1913, **103**, 1896) and by Karrer and Hurwitz (*Helv. Chim. Acta*, 1921, **4**, 728) and strong criticism (herein shown to be groundless) was applied by Irvine and Patterson (*loc. cit.*) to the structures adopted by Karrer.

The monomethyl glucose derived from (I) was assigned the constitution (III), indicating the presence of the methyl group in position 6 in the chain; whilst the trimethyl glucose derived from (II) is, on this view, to be represented as 4 : 5 : 6-trimethyl glucose (IV). The experimental results purporting to establish the structure (III) for the monomethyl glucose have frequently been quoted as evidence for the presence of a free hydroxyl group at position 6 in glucose-diacetone (I), whether the latter be represented, as is here the case, as a propylene-oxide sugar derivative or as an ethylene-oxide form (Irvine and Patterson, *loc. cit.*).

The above experimental conclusions have been called into question by other investigators, who have adduced convincing evidence (*a*) that in glucose-diacetone a free hydroxyl group is not situated at the terminal position 6, (*b*) that the oxide-ring of the sugar cannot be attached at position 3, since the free hydroxyl group is allocated to this position, and (*c*) that the monomethyl glucose isolated from glucose-diacetone is 3-methyl glucose and not 6-methyl glucose (Freudenberg and Brauns, *Ber.*, 1922, **55**, 3233; Freudenberg and Doser, *Ber.*, 1923, **56**, 1243; Levene and Meyer, *J. Biol. Chem.*, 1922, **54**, 805; 1923, **57**, 317; 1924, **60**, 173).

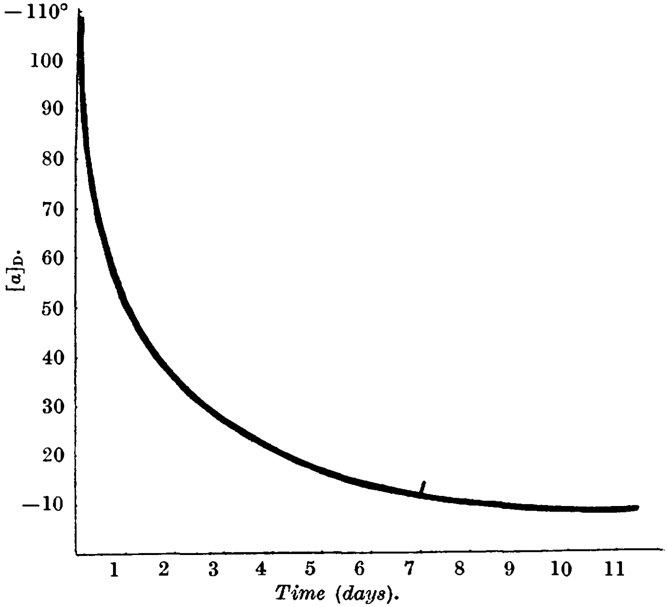
The alternative formulæ advocated by these later authors ascribed to the glucose-acetones a 1 : 4-oxide ring, but a final proof of this assumption has been lacking. The recognition of γ-methylglucoside as a five-atom ring form rendered this hypothesis highly probable (Charlton, Haworth, and Peat, J., 1926, 89; Haworth, Hirst, and Miller, J., 1927, 2436), as did also the preparation, from the glucose-acetones as initial materials (Micheel and Hess, *Annalen*, 1926, **450**, 21), of a tetramethyl sugar having a similar rotation to that of tetramethyl γ-glucose.

It seemed undesirable that the ring form of the sugar in the glucose-acetones should continue to be founded merely on analogy, and in the present communication it is experimentally demonstrated (1) that the above monomethyl glucose (a glucopyranose formed by ring-displacement from the furanose) is convertible into the usual crystalline tetramethyl glucopyranose; (2) that the trimethyl glucose derivable from glucose-monoacetone yields a crystalline *osazone*, and is 3 : 5 : 6-trimethyl glucose; (3) that this trimethyl glucose is a glucofuranose, since it is transformed readily into 2 : 3 : 5 : 6-tetramethyl γ-glucose (tetramethyl glucofuranose) and this again is converted into the crystalline 2 : 3 : 5 : 6-tetramethyl γ-gluconolactone, which yields the crystalline phenylhydrazide of the corresponding acid. In the following discussion of results these new data are taken into account along with evidence adduced by Levene and by Freudenberg and their co-workers (*locc. cit.*) for the recognition of the monomethyl glucose as 3-methyl glucose.

Curiously enough, on investigating the osazone of this monomethyl glucose we found its m. p. to be 178—179° and not 164—165° as given by Irvine and Scott (*loc. cit.*). This anomaly is disconcerting inasmuch as, on the evidence of its m. p. and other physical properties, this osazone is considered to be identical (Irvine and Hynd, J., 1909, **95**, 1220) with that obtainable from the monomethyl fructose isolated by methylation and hydrolysis of α-fructose-diacetone. This contradiction has led us to examine the monomethyl fructose more closely, and the experimental results are described in the succeeding paper. Still further is this problem complicated by the observations of Helferich and Becker (*Annalen*, 1924, **440**, 1), who have also described Irvine and Scott's osazone as having m. p. 164—166° and have differentiated this from the osazone, m. p. 178—179°, of the supposed authentic 6-monomethyl glucose (compare also Kuhn and Ziese, *Ber.*, 1926, **59**, 2314).

FIG. 1.

Mutarotation of the phenylosazone of 3-methyl glucose in ethyl alcohol (c = 1·1).



It is now shown that the osazone from 3-monomethyl fructose also has m. p. 178—179° and not 164—165°, and that this has properties similar to those of the osazone of 3-monomethyl glucose.

It would thus appear, on the basis of the work of Helferich and Becker, that the 6-monomethyl glucose yielded fortuitously an osazone of the same m. p. A mixture of the osazones from 3-monomethyl glucose and 3-monomethyl fructose also melts at 178—179° without depression. Caution should be exercised, however, in accepting " mixed melting point " determinations of osazones as a means of confirming their identity, since the m. p.'s given are frequently merely decomposition temperatures.

We have, however, determined the mutarotation of the osazone from 3-monomethyl glucose and from 3-monomethyl fructose and from either source the osazone gives almost identically the same curve (see Fig. 1), showing the change — 109° —> — 9°.

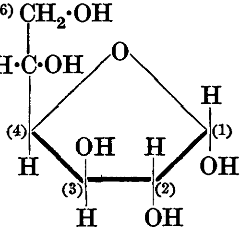
Discussion of Results.

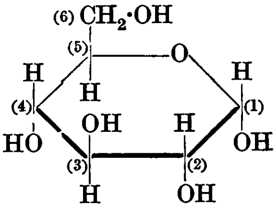
It became apparent that the glucose-acetones should be accommodated by either of the structural forms of glucose : the pyranose and furanose types.

Moreover the isolation of 3 : 5 : 6-trimethyl glucose as described in the preceding section is at variance with the propylene-oxide formulæ (I) and (II) proposed by Irvine for the glucose-acetones.

Reference to the perspective formulæ of the two structural types of glucose (Drew and Haworth, J., 1926, 2305) furnishes some explanation of the occurrence of the glucofuranose form (V) in glucose-diacetone, inasmuch as the hydroxyl groups in glucopyranose (VI) are less favourably situated for the union with acetone.

(V.)





(VI.)

cis-Positions available for condensation with acetone groups. } 1 : 2—5 : 6
1 : 2—3 : 5
1 : 2—3 : 6

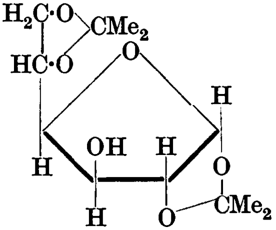
1 : 2—3 : 6

The formulation of glucose-diacetone as 1 : 2-3 : 6-di*iso*propylidene glucopyranose is inappropriate, since the monomethyl glucose derived from it should then be 4-methyl glucose, and this is rendered improbable by the work of Levene and his co-workers (*loc. cit.*). The glucofuranose having the acetone residues in positions 1 : 2-3 : 6 is also excluded as a possibility, since such a substance should yield a 5-monomethyl glucose and this is found not to be the case inasmuch as further methylation of the monomethyl glucose gives rise to 2 : 3 : 4 : 6-tetramethyl glucopyranose.

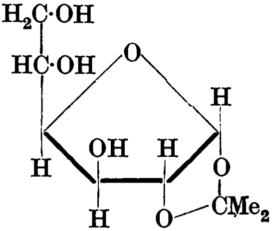
The latter result is consistent with the substitution of glucofuranose in the 1 : 2-5 : 6 or 1 : 2-3 : 5 positions (compare xylose-diacetone; Haworth and Porter, J., 1928, 611), in which case the monomethyl glucose would be substituted either at position 3 or 6. Now position 6 is excluded by the work of Freudenberg and of Levene (*loc. cit.*).

That the structural form of glucose in its acetone derivatives is that of glucofuranose is shown by the isolation of the 3 : 5 : 6-trimethyl glucose from glucose-monoacetone by methylation followed by hydrolysis. Earlier descriptions of this product lay stress on the ease with which it decomposes on distillation, and it is also credited with exceptional properties suggesting that it is not a trimethyl glucose but a trimethyl glucosone (Irvine and Macdonald, *loc. cit.*). None of these difficulties remains if the details for its preparation as given in the experimental section are adopted. The constitution of this trimethyl glucose is evident from its giving a crystalline *osazone* and also from its conversion into 2 : 3 : 5 : 6-tetramethyl glucofuranose. The latter is characterised by its transformation into the crystalline 2 : 3 : 5 : 6-tetramethyl γ-gluconolactone, and into the crystalline phenylhydrazide of the 2 : 3 : 5 : 6-tetramethyl gluconic acid. It may be recalled that the constitutions of the lactone and acid were proved by oxidation methods (Haworth, Hirst, and Miller, J., 1927, 2436).

These results are sufficient to decide the position of the oxide-ring in glucose-monoacetone, and consequently also in the diacetone, and the following constitutional formulæ are therefore supported :



Glucose-diacetone.



Glucose-monoacetone.

It is seen that the glucose is here depicted as α-glucofuranose. The β-form of glucose could not undergo interaction to yield a second stereochemical form of glucose-diacetone, and it is conceivable that, if a second form of the diacetone should exist, it would be the structural isomeride, 1 : 2-3 : 5-*iso*propylidene glucofuranose. There is at present no evidence for the existence of this possible second form.

EXPERIMENTAL.

Conversion of 3-Monomethyl Glucose into 2 : 3 : 4 : 6-Tetramethyl Glucose.—The glucose-diacetone used throughout the following preparations had the constants m. p. 109—110° and $[\alpha]_D^{17°}$ $-$ 18·6°. Methylation either with Purdie's reagents or with sodium and methyl iodide (Freudenberg) yielded monomethyl glucose-diacetone, b. p. 105—106°/0·3 mm., $[\alpha]_D^{21°}$ $-$ 31·4°, $n_D^{17°}$ 1·4518, OMe, 11·4 (Calc., 11·3%). Hydrolysis of this led to removal of the acetone groups, and the monomethyl glucose obtained (Irvine and Hogg, *loc. cit.*) had m. p. 160—161°, $[\alpha]_D^{17°}$ $+ 104·3° \longrightarrow 55·3°$ (after 19½ hours) (c = 1·33 in water) (Found: C, 43·3; H, 7·2; OMe, 15·9. Calc.: C, 43·3; H, 7·2; OMe, 16·0%).

1·2 G. of monomethyl α-glucose (m. p. 160—161°) were converted into the glucoside by heating in boiling methyl-alcoholic hydrogen chloride (1% HCl) for 4½ hours. The solution, which was then almost non-reducing, was neutralised with silver carbonate, filtered, and evaporated to a thick syrup, which contained colloidal silver. After the product had been dissolved in a little methyl alcohol, methyl iodide was added (not enough to cause precipitation of the glucoside) along with silver oxide and methylation was partly effected by heating at 45—50°. After another similar methylation the material was almost completely soluble in methyl iodide. Three further treatments with the Purdie reagents yielded a mobile oil.

This oil was hydrolysed by heating at 100° with 10 c.c. of 5% hydrochloric acid. The solution was neutralised with barium carbonate, evaporated to dryness, and the residue was extracted with chloroform. This solution yielded on evaporation a thick syrup which became solid. This was recrystallised and identified as tetramethyl glucose, m. p. 90—94° (yield, 0·6 g.), and gave the anilide, m. p. 135° (compare Irvine and Gilmour, J., 1908, **93**, 1429).

The phenylosazone of 3-monomethyl glucose was prepared and recrystallised several times from aqueous alcohol (Found: C, 61·4; H, 6·7; N, 15·25; OMe, 8·5. Calc.: C, 61·3; H, 6·5; N, 15·05; OMe, 8·3%). Its m. p. was 178—179° and not 164—165° as quoted by Irvine and Scott (*loc. cit.*). Its change of rotation in ethyl alcohol was compared with that of the osazone derived from 3-monomethyl fructose and the values are expressed in the form of a graph in the introduction. It is conceivable that the osazones of a 6-monomethyl glucose and of a 3-monomethyl glucose might show great similarity both in the rate of mutarotation and in m. p. But the close agreement of the initial and the final rotation values of each product appears in this case to suggest that the osazones are identical.

3 : 5 : 6-*Trimethyl Glucose and its Osazone.*—The use of β-glucose was found to be most advantageous for the rapid preparation of glucose-diacetone (Fischer and Rund, *Ber.*, 1916, **49**, 88). Glucose-monoacetone was prepared from the diacetone (Irvine and Scott, *loc. cit.*) and had the accepted physical constants (Fischer, *Ber.*, 1895, **28**, 2496).

In the preliminary methylation of glucose-monoacetone it is advisable to avoid the use of silver oxide and methyl iodide in acetone solution, because under these conditions there is a tendency for the glucose-diacetone to be regenerated. The methylated glucose isolated from this product by hydrolysis distils with decomposition and is far from homogeneous. It is possible that the difficulties of earlier authors (Irvine and Scott, Irvine and Macdonald, *locc. cit.*) are traceable to this cause. Consequently the methylation was conducted as follows: Glucose-monoacetone (30 g.) was dissolved in 150 c.c. of water and to this was admitted, with stirring, methyl sulphate (97 c.c.) and 33% sodium hydroxide solution (180 c.c.), the temperature being gradually raised from 20° to 60°. After the final heating at 60° for an hour, the cooled solution was extracted repeatedly with chloroform. The dried extracts were evaporated at 60° and yielded a pale yellow syrup, which was again submitted to similar methylation treatment. Thereafter the product had $[\alpha]_D$ $-$ 29·5° ($c = 1{\cdot}55$ in methyl alcohol); n_D 1·4470; OMe, 35·3%.

This specimen of trimethyl glucose-monoacetone (30 g.) was digested for 2 hours under reflux with 300 c.c. of aqueous methyl alcohol containing 0·5% of hydrogen chloride. The cooled solution was neutralised with silver carbonate, filtered, treated with charcoal and then with silica to remove traces of silver, and evaporated at 50°. The resulting trimethyl methylglucoside was collected (OMe, 50%) and hydrolysis was effected by digestion with 0·3% hydrochloric acid at 100° for 1½ hours, followed by neutralisation with barium carbonate and evaporation of the filtered solution at 60°. The trimethyl glucose was extracted with ether, and the product was distilled under 0·04 mm. without decomposition from a bath heated at 150—160° (b. p. about 134°). The distillate was a clear, almost colourless liquid (yield, 60%), showing $[\alpha]_D$ $-$ 44·1° ($c = 1{\cdot}49$ in ethyl alcohol) and $-$ 25·9° ($c = 1{\cdot}3$ in water); $n_D = 1{\cdot}4675$ (Found: OMe, 41·1. Calc.: OMe, 41·9%).

Phenylosazone. 1 G. of the above 3 : 5 : 6-trimethyl glucose yielded 1·8 g. of crude *osazone*, which was dissolved in ethyl alcohol; the solution was treated with charcoal and diluted slightly with water; matted yellow needles separated which, after recrystallisation from aqueous alcohol and drying in a vacuum at 45° until constant in weight, had m. p. 70—72° (Found: C, 62·8; H, 7·2; N, 14·15. $C_{21}H_{28}O_4N_4$ requires C, 62·95; H, 7·0; N, 14·0%).

Conversion of 3 : 5 : 6-*Trimethyl Glucose into* 2 : 3 : 5 : 6-*Tetramethyl Glucose.*—The trimethyl methylglucoside (10 g.) was methylated by solution in 50 c.c. of water and treatment at 60° with 20 c.c. of methyl sulphate and 17 c.c. of 50% sodium hydroxide solution. The extracted product (9·9 g.) was distilled, b. p. about 96°/0·025 mm., and yielded 8·2 g. of a colourless distillate having the constants $n_D^{16°}$ 1·4440, $[\alpha]_D^{16°}$ $-$ 20·4° (c = 2·1 in water) (Found: OMe, 61·2. Calc. for tetramethyl methylglucoside: OMe, 62·0%).

Hydrolysis. The above product was hydrolysed by digestion at 95° with 0·3% hydrochloric acid for 1½ hours. The resulting sugar was isolated in the usual manner and on distillation under 0·08 mm. (bath temperature 150°) gave a colourless liquid having $n_D^{24°}$ 1·4500, $[\alpha]_D^{19°}$ $-$ 14·3° (c = 1·26 in water) (Found: OMe, 51·5. Calc. for 2 : 3 : 5 : 6-tetramethyl glucose: OMe, 52·6%). About 60% of the product was distilled over, leaving a residue which crystallised, m. p. 97—98° (Found: OMe, 53·9%). This by-product has not yet been identified and is under investigation. It is probably a condensation product of the above tetramethyl glucose.

Oxidation. The above 2 : 3 : 5 : 6-tetramethyl methylglucoside (3 g.) was treated with an aqueous solution of bromine (1·5 c.c. in 20 c.c. of water) at 20° during 1½ days. It then no longer reduced Fehling's solution even after a preliminary heating with mineral acid. The solution was aerated to remove bromine, neutralised with silver carbonate, and filtered and the organic acid was liberated from its silver salt by titration with hydrochloric acid. The aqueous filtrate was then evaporated at 50°, the residue extracted with ether and evaporated, and the syrupy product thus isolated was heated at 70° for 5 hours and then distilled (2 g.). The colourless liquid crystallised on nucleation with 2 : 3 : 5 : 6-tetramethyl γ-gluconolactone (compare Haworth and Long, J., 1927, 544) and had m. p. 25·5—26°, alone or in admixture with an authentic specimen prepared from octamethyl methyl-lactobionate.

Phenylhydrazide. The identification of the above 2 : 3 : 5 : 6-tetramethyl γ-gluconolactone was assisted also by the preparation of this crystalline derivative. The lactone (0·4 g.) in ether was digested with 0·2 g. of phenylhydrazine. The resulting oil crystallised on cooling and from hot benzene gave colourless needles which, either alone or in admixture with an authentic specimen of the phenylhydrazide of 2 : 3 : 5 : 6-tetramethyl gluconic acid (Haworth and Long, *loc. cit.*), melted at 136°.

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UNIVERSITY OF BIRMINGHAM,
EDGBASTON.

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