

CCCXXXVIII.—*New Crystalline Forms of Trimethyl Glucose and Dimethyl Glucose.*

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THE preparation of new crystalline reference compounds in the hexose series has been undertaken with the view of assisting the constitutional investigations of the di- and poly-saccharides. Progress in the determination of the structure of the higher sugars has been impeded by imperfect knowledge of the constitution of the simplest units, and formulæ assigned to methylated hexoses during 20 years are now amended by the recognition of the amylenoxide structure for most of the normal sugars (this vol., pp. 89, 1858).

In the series of partly methylated glucoses, two trimethyl glucoses have been recognised. These are the 2 : 3 : 6-trimethyl glucose, which is crystalline, and the 2 : 3 : 4-trimethyl glucose, which is a liquid, and each gives a crystalline glucoside. The latter appeared formerly in the literature as the 2 : 3 : 5-isomeride, but the allocation of the new ring formula to glucose introduces a corresponding amendment in the position of the third methyl group. Regarding normal glucose as an amylenoxide, one is able to deduce the possible existence of two other isomerides in the trimethyl series—the 2 : 4 : 6- and the 3 : 4 : 6-trimethyl glucoses, which have not hitherto been prepared.

Similarly, no fewer than six isomerides of dimethyl glucose may exist, of which only one has, up to the present, been isolated (Irvine and Scott, J., 1913, **103**, 575), and the structure of even this single representative is now indefinite, owing to the adoption of the amended formula for methylglucoside.

In an endeavour to explore this field completely, glucose has again been methylated with alkali and methyl sulphate under conditions selected as being favourable to the formation of partly methylated glucoses, and the first series of results is now communicated. From earlier work in this field (Haworth and Leitch, J., 1918, **113**, 194), it was known that the use of these reagents yields a preponderance of the β -glucosides. Under the procedure now described, chiefly the β -glucosides of tetramethyl glucose, trimethyl glucose, and dimethyl glucose were obtained. Separation of the various mixtures of products led to the isolation of two new crystalline varieties of trimethyl β -methylglucoside: (a), m. p. 67—68°, and (b), m. p. 64°.

The former (a) gave on hydrolysis a new crystalline *trimethyl glucose*, m. p. 123°, $[\alpha] + 89.7^\circ$, changing with acid catalysis to the equilibrium value $+71.9^\circ$ in water; or $+110^\circ \rightarrow 69.7^\circ$ in methyl alcohol. We have been unable to prepare an osazone from this sugar. The same variety of trimethyl glucose is also obtainable by an alternative method, *viz.*, hydrolysis of heptamethyl sucrose, which gives rise to a mixture of trimethyl glucoses and tetramethyl γ -fructose from which the latter can be largely removed by fractional distillation (Haworth, J., 1920, **117**, 206). The remaining liquid, which has a higher boiling point, gives rise to the trimethyl β -methylglucoside, m. p. 67—68°, already mentioned (a), and also to the corresponding trimethyl glucose, m. p. 123°, identical in all respects with the new sugar now described and giving in admixture with it no depression of m. p. In a previous paper, the isolation of 2 : 3 : 6-trimethyl glucose was recorded (Haworth and Mitchell, J., 1923, **123**, 310) as a product resulting from the hydrolysis of heptamethyl sucrose, and this was confirmed by two observers. The new trimethyl glucose, m. p. 123°, differs from 2 : 3 : 6-trimethyl glucose in an essential particular, in that it does not undergo inversion of sign during condensation with methyl-alcoholic hydrogen chloride at room temperature, a behaviour which is to be regarded as characteristic of the 2 : 3 : 6-variety. Although the melting point and rotation data of the two sugars are similar, the m. p. of either is depressed on admixture with the other.

We hesitate definitely to ascribe positions to the substituent groups in this crystalline trimethyl glucose, although the provisional formula suggested by the properties herein described for this sugar

is that of a 2 : 4 : 6-isomeride. We prefer, however, that the distribution of the methyl groups should be regarded as an open question for the present. The crystalline glucoside (*a*), m. p. 67—68°, may therefore be tentatively described as 2 : 4 : 6-trimethyl β -methylglucoside. The glucoside (*b*), m. p. 64°, appears to be a derivative of a different trimethyl glucose which we have not yet isolated in a crystalline form.

From the direct methylation of glucose a liquid product was obtained corresponding to a dimethyl methylglucoside. It failed to condense with acetone, but gave a crystalline derivative with benzaldehyde, m. p. *ca.* 117—119°. Hydrolysis of the glucoside yielded a pale gum which was apparently a mixture of various forms of dimethyl glucose, and from this was isolated a new crystalline *dimethyl glucose*, m. p. 156—157°, $[\alpha]_D +93.1^\circ \rightarrow 62.4^\circ$ in water and $+110^\circ \rightarrow 64.7^\circ$ in methyl alcohol. That this was an amylenoxide sugar was demonstrated by its comparative stability towards permanganate and by its ready conversion into crystalline tetramethyl glucose. The new dimethyl glucose, from which we were unable to prepare an osazone, differs widely in physical properties from the α - and β -forms of the dimethyl glucose isolated by Irvine and Scott (*loc. cit.*), who give the m. p.'s 85—87° and 108—110°, respectively.

EXPERIMENTAL.

Preparation of Partly Methylated Glucoses by Direct Methylation of Glucose with Methyl Sulphate.—The methylation of glucose was conducted as described by Haworth (J., 1915, **107**, 8; compare J., 1918, **113**, 188), 27—50 g. of glucose being used in one operation. Initially, the solution was maintained at 35° in the presence of an excess of methyl sulphate over the amount of alkali required, and the mixture was thus kept neutral or slightly acid until all the reducing property of the sugar had disappeared. Thereafter the temperature was raised to 70° and the methylation completed in the manner described in earlier papers, but the greatest care was exercised to avoid the development of excessive alkalinity, since this condition was harmful to the partly methylated products. After being heated at 100° for $\frac{1}{2}$ hour, the solution was cooled, neutralised with dilute acetic acid, and then made faintly alkaline with sodium carbonate. Chloroform (10 c.c.) was stirred with the solution, which was then kept over-night; sodium sulphate crystallised in the interval and filtration was easy. Several extractions of the filtrate with chloroform were made and the extracts were combined with the chloroform washings of the sodium sulphate and dried. After evaporation of the solvent, the product was distilled under diminished pressure.

By varying the quantities of the methylating agent employed with 50 g. of glucose, it was found that, after one methylation using three times the theoretical quantities of methyl sulphate and alkali, 45 g. of a liquid product were obtained, but the major portion of this was the completely methylated tetramethyl β -methylglucoside. Twice the theoretical quantities for 50 g. of glucose having been used, the liquid product (37 g.) was extracted with chloroform, yielding on repeated distillation 16 g. of a fraction corresponding with tetramethyl methylglucoside, 14 g. corresponding with trimethyl methylglucoside, and 6.3 g. corresponding with dimethyl methylglucoside. When only theoretical quantities of methyl sulphate were used, a total weight of 26 g. of the methylated sugar was obtained; this was extracted with chloroform and divided into fractions of 11, 10, and 5 g.

Evaporation of the aqueous liquors to dryness gave a solid, slightly viscid mass, containing sodium sulphate, but consisting largely of sodium methyl sulphate along with partly methylated sugars. The latter were extracted with chloroform containing tetramethyl methylglucoside, the addition of which led to more complete extraction than with chloroform alone.

In view of these results, several such methylations were conducted on 50 g. of glucose, employing twice the theoretical quantities of methyl sulphate (121 c.c.) and sodium hydroxide (121 g. in 210 c.c. of water). By repeating these experiments, 150 g. of partly methylated glucose were accumulated, and submitted to six or more fractional distillations under 0.01 mm. pressure. In addition to intermediate fractions which were neglected, the material was divided into the following portions :

Fraction.	B. p.	Yield.	n_D .
I.	95°	40 g.	1.4455
II.	124—127	54 g.	1.4578
III.	146	24 g.	1.4730

The following constants of these fractions varied only slightly in different preparations, and constitute a trustworthy average based on several results.

Fraction I. Colourless liquid, $[\alpha]_D +72^\circ$ in water ($c = 2$) [Found : OMe, 61.1. Calc. for $C_6H_7O(OMe)_5$: OMe, 62.0%]. Hydrolysis yielded the characteristic crystalline tetramethyl glucose, m. p. 86—87°, $[\alpha]_D$ in water $+90^\circ \rightarrow +84.1^\circ$.

Fraction II. Colourless liquid, which failed to crystallise on nucleation with a crystal of 2 : 3 : 4-trimethyl β -methylglucoside; $[\alpha]_D +4^\circ$ in water ($c = 2.8$) [Found : OMe, 50.6. Calc. for $C_6H_8O_2(OMe)_4$: OMe, 52.5%]. This corresponded with a trimethyl β -methylglucoside. It was unaffected by 0.25% hydrochloric acid

at 100°, but with 5% acid hydrolysis was complete in 3½ hours, the specific rotation being constant at +68°. This specimen was submitted to further methylation with Purdie's reagents, yielding tetramethyl methylglucoside, which hydrolysed to give crystalline tetramethyl glucose.

Fraction III was a colourless, viscid liquid, sparingly soluble in ether and benzene, $[\alpha]_D +1.0^\circ$ in water ($c = 5.9$). On repeated fractionation this value changed to $[\alpha]_D +12^\circ$ [Found: OMe, 41.5. Calc. for $C_6H_9O_3(OMe)_3$: OMe, 41.9%]. By hydrolysis with 3% hydrochloric acid at 100°, a constant value +62.4° was attained after 5 hours. Complete methylation of this fraction, followed by hydrolysis of the tetramethyl methylglucoside, yielded crystalline tetramethyl glucose.

Isolation of Trimethyl Glucoses.—Hydrolysis of fraction II with 5% hydrochloric acid at 100° gave the following polarimetric readings: $[\alpha]_D$ (initial) +4°; +16° (after 20 mins.); +30° (40 mins.); +41° (60 mins.); +59° (120 mins.); +65° (180 mins.); +66° (200 mins.). With a portion of the material of fraction II, hydrolysis was carried out with 8.8% hydrochloric acid during 2 hours. The product was a pale yellow syrup, n_D 1.4735, gradually depositing colourless needles which were separated. Distillation of the major portion of the sugar (b. p. 145—148°/0.04 mm.) yielded a colourless liquid which was collected in three portions. The middle fraction (n_D 1.4740) partly crystallised over-night, and addition of dry ether promoted further crystallisation. Two crystallisations from ether gave a constant m. p. of 123°. The colourless needles showed $[\alpha]_D$ in methyl alcohol ($c = 1.77$) +110° → 69.7°; in water ($c = 2.0$) +89.7° → 71.9°. In methyl alcohol containing 0.25% of hydrogen chloride at room temperature the sugar showed no inversion of rotation: $[\alpha]_D$ (initial) +78°; +71° (after 1 hr.); +70° (5 hrs.); +69° (12 hrs.); +69° (7 days); +68° (45 days). Thereafter this solution was heated at 40° for a further period of 5 days; it was then almost devoid of action towards Fehling's solution. At this stage the solution was neutralised with silver carbonate, the methyl alcohol distilled, and the product extracted with ether. Removal of the ether left a syrup which rapidly crystallised, and after being kept for 2 days on porous tile the colourless needles were washed several times with light petroleum and then melted at 67°. This compound was identical with another specimen prepared from a crystalline trimethyl glucose obtained by hydrolysis of heptamethyl sucrose. Two specimens of trimethyl methylglucoside showed $[\alpha]_D -12.3^\circ$ in water ($c = 0.5$).

A further portion of fraction II (20 g.) was submitted to repeated fractional distillation and the products were collected in six portions,

the first of which distilled at $123^{\circ}/0.01$ mm., and the last at $128^{\circ}/0.01$ mm. The first five portions crystallised on nucleation with a specimen of the trimethyl methylglucoside obtained above, but the third fraction, b. p. 126° , n_D 1.4575, crystallised completely and these crystals were examined after being washed with light petroleum: large fine needles, m. p. $67-68^{\circ}$, $[\alpha]_D -19.1^{\circ}$ in water ($c = 2.25$); -13.5° in methyl alcohol ($c = 0.77$) [Found: C, 50.8; H, 8.5; OMe, 51.1. Calc. for $C_6H_8O_2(OMe)_4$: C, 50.85; H, 8.5; OMe, 52.5%]. The glucoside was readily soluble in all organic solvents, but no crystallising medium was found. Hydrolysis was effected at 100° with 5% hydrochloric acid during 4 hours. The following rotation values were observed during the course of the hydrolysis: $[\alpha]_D$ (initial) -17.1° ; $+7.4^{\circ}$ (after 30 mins.); $+30^{\circ}$ (60 mins.); $+46.8^{\circ}$ (90 mins.); $+56.5^{\circ}$ (120 mins.); $+70^{\circ}$ (180 mins.); $+71.3^{\circ}$ (240 mins.). The product derived from this hydrolysis was isolated by the usual methods, and the syrup, dried at $60^{\circ}/15$ mm., immediately crystallised. On recrystallisation from dry ether, colourless needles were obtained, m. p. 123° , showing no depression of m. p. with the specimen of the trimethyl glucose obtained as described above.

The fractions (4) and (5) in the previous fractionation of the glucoside had partly crystallised, and the crystals were separated on porous tile, washed with light petroleum, and then melted at 50° with softening at 30° . Further washing with light petroleum did not affect the m. p. and the crystals were evidently the methylglucoside (Found: C, 50.8; H, 8.5%); $[\alpha]_D -21^{\circ}$ in water ($c = 1.0$). By mechanical means the mixed crystals were separated into two portions, and from one of these, after repeated washing with light petroleum, a small quantity was obtained, m. p. 64° . When this was mixed with the specimen of trimethyl methylglucoside already described as melting at $67-68^{\circ}$, the m. p. was depressed to $35-50^{\circ}$. In admixture with a specimen of 2:3:4-trimethyl β -methylglucoside, m. p. 92° , a m. p. $48-52^{\circ}$ was recorded. Hydrolysis of the original mixture of crystals was carried out in the usual way, yielding a syrup which partly crystallised. The crystals were identical with those of the trimethyl glucose described above, m. p. 123° .

Dimethyl Glucose.—The fraction III obtained on distillation (p. 2577) showed $[\alpha]_D +1.1^{\circ}$ in water ($c = 5.0$), but after repeated distillation a value of $+12.2^{\circ}$ was obtained. In a preliminary experiment an attempt was made to condense this glucoside with dry acetone containing a trace of hydrogen chloride, but, as no alteration of rotation occurred during 24 hours, it appeared that little, if any, condensation had occurred. Hydrolysis of the dimethyl methylglucoside was conducted with 3% hydrochloric acid at 100° :

$[\alpha]_D$ (initial) $+1.0^\circ$; $+19.1^\circ$ (after 30 mins.); 30.3° (1 hr.); 47.1° (2 hrs.); 54.0° (3 hrs.); 59.1° (4 hrs.); 60.0° (5 hrs.). Hydrolysis then appeared to be complete, but for the isolation of the corresponding sugar in quantity the hydrolysis was conducted with 10% hydrochloric acid for 30 minutes in a boiling water-bath, the specific rotation then increasing from $+1.0^\circ$ to $+62.6^\circ$. After neutralisation of the mineral acid, evaporation, and extraction of the sugar with dry acetone, a viscid gum remained, n_D^{20} 1.4867, which is hereinafter referred to as specimen (A). After 12 hours' drying at 60° in a vacuum, crystallisation occurred, and when the syrup was maintained at 40° for a week a semi-solid mass was obtained. The adhering syrup was removed by extraction with cold ethyl acetate and the remaining crystals were purified also from this solvent, giving prismatic needles, m. p. $156-157^\circ$.

This crystalline specimen of a dimethyl glucose reduced Fehling's solution on warming to 90° , but did not reduce cold neutral permanganate. It showed $[\alpha]_D$ in methyl alcohol ($c = 0.8$) $+110.7^\circ \rightarrow 64.7^\circ$ (after catalysis); in water ($c = 0.5$), $93.1^\circ \rightarrow 62.4^\circ$ [Found: C, 46.0; H, 7.9; OMe, 28.2. $C_6H_{10}O_4(OMe)_2$ requires C, 46.15; H, 7.7; OMe, 29.8%].

The new crystalline dimethyl glucose was methylated several times with Purdie's reagents, and on hydrolysis of the distilled product, crystalline tetramethyl glucose was isolated, m. p. 84° , giving no depression in admixture with an authentic specimen of the latter sugar.

The unchanged portion of the dimethyl glucose which, as indicated above, was removed from the crystals with ethyl acetate, was placed in contact with methyl alcohol containing 0.25% hydrogen chloride. A change in specific rotation occurred after 9 days at room temperature from $+64.3^\circ$ to $+27.1^\circ$, and after 45 days condensation appeared to be complete. The mixture of glucosides isolated showed n_D 1.4737. A portion of this liquid product was heated with methyl alcohol containing 0.5% of hydrogen chloride at 110° , and the specific rotation increased from $+27^\circ$ to $+82^\circ$. This change evidently represented interconversion of the glucosides, and, in view of the subsequent details, represented also a structural change from the γ -glucoside to the more stable form of α - and β -isomerides. The remaining major portion of the mixture of dimethyl methylglucosides was subjected to partial hydrolysis by digestion for 2 hours at 100° with 0.4% hydrochloric acid. After neutralisation and isolation of the products in the usual way, any unchanged glucoside was extracted with small quantities of dry benzene, and was obtained as a viscid liquid, b. p. $155^\circ/0.05$ mm., $[\alpha]_D +57.9^\circ$ in water ($c = 0.81$) (Found: OMe, 40.1. Calc.: 41.9%).

A further specimen of the liquid dimethyl glucose (A) was dissolved in dry methyl alcohol containing 0.25% of hydrogen chloride and maintained at 20° for 10 days ($[\alpha]_D +27^\circ$), and the syrup isolated (n_D 1.4782) was repeatedly extracted with benzene.

The extract was distilled, b. p. 140—144°/0.01 mm., and gave a colourless liquid, n_D 1.4710, which instantly decolorised neutral permanganate but was devoid of action on Fehling's solution. It showed $[\alpha]_D -7.9^\circ$ ($c = 1.4$) [Found : C, 48.4; H, 8.2; OMe, 43.0. $C_6H_9O_3(OMe)_3$ requires C, 48.6; H, 8.1; OMe, 41.9%]. Hydrolysis with 0.4% hydrochloric acid at 90° gave a syrup, n_D 1.4820, which gave analyses for a dimethyl glucose (Found : OMe, 30.1%).

A portion of this dimethyl γ -methylglucoside was subjected to complete methylation with methyl iodide and silver oxide, and the resulting tetramethyl methylglucoside was isolated as a mobile liquid, n_D 1.4440, which decolorised permanganate, but had no effect on Fehling's solution. It showed $[\alpha]_D -3.2^\circ$ in water ($c = 0.95$) (Found : OMe, 60.0. Calc. : 62.0%). Hydrolysis of this glucoside, which appeared to be identical with tetramethyl γ -methylglucoside, was conducted with 0.4% hydrochloric acid for 2 hours at 100°, the specific rotation changing from -3.2° to -6° . The corresponding sugar was isolated in the usual way, and this showed n_D 1.4523, $[\alpha]_D -6.1^\circ$ in water ($c = 1.0$) (Found : OMe, 52.6. Calc. : 52.5%). The constants are similar to those recorded for tetramethyl γ -glucose, and the sugar decolorised permanganate and reduced Fehling's solution actively.

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[Received, July 31st, 1926.]