

### C.—*The Alkylation of Sugars.*

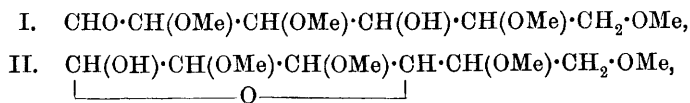
By THOMAS PURDIE, F.R.S., and JAMES C. IRVINE, Ph.D., D.Sc.

IN the course of the earlier researches on the synthesis of glucosides, attempts were no doubt frequently made to prepare alkyl ethers of the sugars. Berthelot (*Ann. Chim. Phys.*, 1860, [iii], 60, 103), by heating cane sugar with caustic potash and ethyl bromide, obtained a substance which he describes as a diethylglucosan ether. Practically, however, the only methods of alkylating sugars at present known are those of Fischer (*Ber.*, 1893, 26, 2400; 1895, 28, 1145) and of Koenigs and Knorr (*Ber.*, 1901, 34, 957); in the former process, the alkylation is effected by the direct action of alcohol on the sugar in the presence of hydrochloric acid, whilst the latter is due to the interaction of alcohol and the acetohalogen or acetonitro-derivative, and subsequent removal of the acetyl groups by hydrolysis with alkali. By these methods, as is well known, only one of the carbinol groups of the sugar is etherified, and the products are of a glucosidic nature. Alkyl ethers of the sugars in the stricter sense of the term, that is to say, ethers which retain the aldehydic or ketonic properties of the parent sugar and resist the action of hydrolysing agents, are, however, so far unknown. The main purpose of the following research was the preparation and investigation of compounds of this class.

In alkylating the esters of optically active hydroxy-acids, we found that the object could be attained, when other methods had failed, as in the case of malic, lactic, and tartaric esters (*Trans.*, 1899, 75, 153, 483; 1901, 79, 957) and of mandelic esters (McKenzie, *Trans.*, 1899, 75, 753),

by employing dry silver oxide and alkyl iodide, and the application of this method has been much extended since then by G. D. Lander (Trans., 1903, 83, 414, and earlier papers). Provided the oxidising effect of the silver oxide could be obviated, it seemed not improbable that the sugars might lend themselves to this reaction, and that we might thus obtain alkyl ethers of the above-mentioned class. Alkylated sugars should be compounds of considerable interest. A completely alkylated hexose, such as pentamethyl glucose, should be capable of existing, like penta-acetylglucose, in three stable forms. Of these, two should be glucosidic in structure and stereoisomeric, corresponding with the well-known penta-acetylglucoses (m. p. 112° and 131°), the relations of which as  $\alpha$ - and  $\beta$ -derivatives, in the sense of Fischer's nomenclature of the glucosides, have been recently established by Koenigs and Knorr (*loc. cit.*) and by Fischer and Armstrong (*Ber.*, 1901, 34, 2885). The third isomere, structurally different from the other two, should possess the properties of an ordinary aldehyde. Among the penta-acetylglucoses, Tanret's compound (*Bull. Soc. chim.*, 1895, [iii], 13, 268), melting at 86°, probably represents this form, although its aldehydic properties do not so far appear to have been definitely proved.

In their behaviour towards hydrolytic agents, however, the alkylated sugars should differ from the corresponding acyl derivatives. The penta-acyl glucoses are readily hydrolysed with production of the parent sugar. The pentamethyl glucose of aldehydic structure, on the other hand, should resist the action of these agents, whilst the corresponding glucosidic isomerides should lose on hydrolysis only one methyl group and yield a tetramethyl glucose ether. It seemed to us interesting to ascertain how far a sugar derivative of this kind exhibits the properties of an aldose. Adopting Fischer's view of the structure of the alkylglucosides, the derivative referred to might possibly possess a stable constitution represented by one or other of the following formulæ :



or, like the parent glucose, the substance might be tautomeric and exhibit the functions of both forms. Few acyl derivatives of this class appeared to have been prepared, and on account of their ready hydrolysis they would not be convenient for investigation. A further interest attaches to the tetra-alkyl aldose and ketose ethers of the above type. It is not improbable that they might lend themselves to the synthesis of alkylated disaccharides, a study of which might throw some light on the constitution of the common natural sugars of this class.

Although benzoin (Lander, *loc. cit.*) and salicylaldehyde (Irvine,

Trans., 1901, 79, 668) can be etherified, the latter almost quantitatively, by means of silver oxide and alkyl iodide, the method proved inapplicable to the reducing sugars. When silver oxide was added to a mixture of glucose, dissolved in methyl alcohol and methyl iodide, a vigorous reaction ensued, and when a large excess of the alkylating agent was used a product soluble in ether but having an acid reaction was obtained. On attempting to distil this, much decomposition occurred, and the only substance isolated was methyl oxalate. When ethyl iodide was employed in a similar reaction, the product was also acid, and an analysis of the silver residues showed that only 45 per cent. of the silver oxide taken was converted into iodide, the remainder having been reduced to the metallic state. The reaction was evidently a complex one. An attempt to alkylate *lævulose* by this method was also unsuccessful.

To avoid oxidation, it was evidently requisite that the aldehydic or ketonic group of the sugar should be masked, and instead of glucose, therefore, we used Fischer's easily accessible  $\alpha$ -methylglucoside. Methyl iodide was employed throughout our experiments, as previous experience with tartaric esters had shown that the slower action of the higher iodides gave scope for the occurrence of oxidation which resulted in the production of oxalates in considerable quantity.

The methylglucoside in methyl alcoholic solution reacted readily with methyl iodide in the presence of silver oxide, and was found to be nearly proof against the oxidising action of the latter. The product, consisting of a mixture of methyl ethers of the glucoside, was a neutral, viscid syrup, soluble in ether, having no action on Fehling's solution and distilling without decomposition in a vacuum. The solubility in organic solvents and the volatility of these compounds, as was to be expected, increase with the number of the methoxyl groups present in the molecule, and it was found possible, therefore, to isolate the main constituent of the mixture by fractional distillation. This substance, which proved to be a trimethyl methylglucoside, boils at 167—170° under 17 mm. pressure and is readily hydrolysed by dilute hydrochloric acid, giving a syrup which reduces Fehling's solution vigorously. It is shown in the succeeding paper that three of the four methoxyl groups are retained throughout the hydrolysis, the product being a trimethyl glucose. Attempts to obtain a hydrazone or osazone from this compound having failed, evidence of its aldose nature was sought by oxidising it with bromine water according to Kiliani's method. The process gave an almost neutral syrup, an analysis of which after distillation gave figures approximating to those for trimethylgluconolactone. The lactonic nature of the compound was confirmed by titration with alkali and by the gradual change in the optical rotation of its solution.

As stated above, the main product of the methylation when it is

carried out in methyl alcohol is a trimethyl methylglucoside. The last remaining hydroxyl, probably that of the terminal primary carbinol group of the chain, alkylates more slowly than the others. Even when the alkylating agent was used in considerable excess, the tetramethyl derivative was produced in very small quantity. This is partly due to the fact, which is evident from the abundant production of dimethyl ether in the course of the process, that the alkylation extends to the solvent alcohol, and that much of the alkylating agent is thus lost. Complete alkylation of the glucoside can, however, be effected by taking advantage of the fact that the trimethyl methylglucoside is readily soluble in methyl iodide. Such a solution reacts readily with silver oxide, and under these conditions tetramethyl methylglucoside is obtained as a neutral, comparatively mobile liquid boiling at 144—145° under 17 mm. pressure and showing no action on Fehling's solution.

On hydrolysing this compound with dilute hydrochloric acid, the glucosidic methoxyl only is removed, and a tetramethylated glucose is produced, which distils without decomposition at 182—185° under 20 mm. pressure and gradually solidifies; by recrystallising from warm ligroin, it is obtained in long needles melting at 81—83°. The compound reduces both Fehling's solution and ammoniacal silver nitrate on warming, and has undoubtedly the structure of an aldose. To indicate this and to distinguish it from the isomeric trimethyl methylglucoside referred to above, it may be named tetramethyl glucose.

Although the substance reacted with phenylhydrazine, attempts to procure from it an osazone or crystallised hydrazone were not successful, but evidence of its nature was procured, as before, by Kiliani's process of oxidising aldoses to aldonic acids. The product was an acid oil, soluble in ether, but dissolving completely in water only on heating. Analysis of the substance dried at 100° in a vacuum showed it to be tetramethyl gluconolactone. This conclusion was confirmed by the analysis of a barium salt prepared from it, also by its behaviour on neutralisation, and by the gradual diminution in specific rotation shown by its aqueous alcoholic solution.

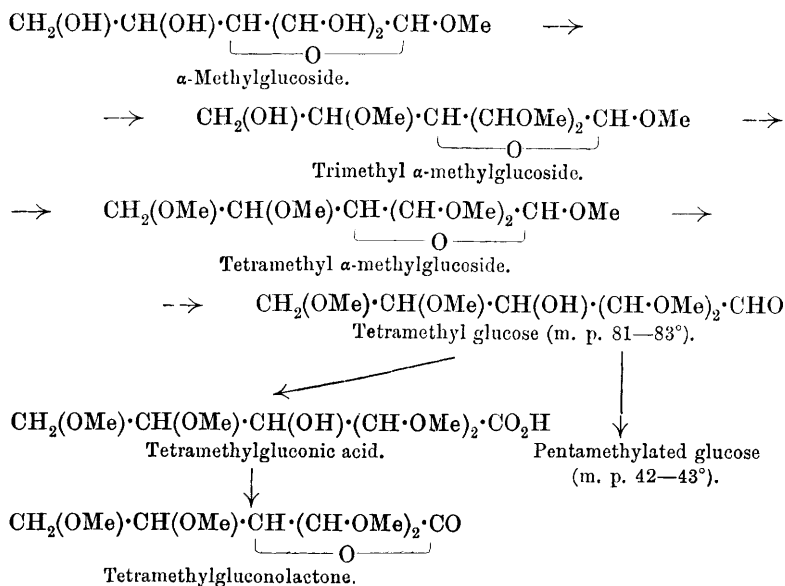
Tetramethyl glucose was obtained, as stated, by hydrolysing tetramethyl  $\alpha$ -methylglucoside. With the idea of ascertaining whether the methyl group lost in hydrolysis could be re-introduced by our method of alkylation, and, if so, whether this would result in the reproduction of the initial compound or an isomeride, the crystalline tetramethyl glucose was dissolved in methyl iodide and treated with silver oxide.

The product was a neutral oil distilling without decomposition at 124—127° under 8 mm. pressure, which, after 3 months, deposited crystals melting at 42—43°. Analysis of the crystalline substance showed it to be a pentamethylated glucose; it reduced ammoniacal

silver nitrate, but did not reduce Fehling's solution even on boiling. That the substance is, however, isomeric and not identical with tetramethyl  $\alpha$ -methylglucoside is proved by its crystalline character, its lower boiling point, and its different optical activity. Of the three pentamethyl glucoses alluded to in the introduction, it must be either tetramethyl  $\beta$ -methylglucoside or the pentamethyl glucose of aldehydic structure. As a test made with our first preparations showed no action on Fehling's solution after warming with dilute aqueous hydrochloric acid, we concluded that the substance was the latter compound. On repeating the experiment on a second preparation, however, reduction of this solution was observed. The amount of material at our disposal being too small for further investigation, the structure of the compound must remain in doubt for the present. Its laevorotatory power favours the view that it is the  $\beta$ -glucoside.

Examination of the oil, which deposited the crystals just described, showed that it probably contained tetramethyl  $\alpha$ -methylglucoside. It reduced Fehling's solution only after being hydrolysed, and the product of hydrolysis yielded a minute quantity of crystals, which, from their melting point, seemed to be impure tetramethyl glucose. It appears, therefore, that by the methylation of this compound two of the three pentamethylated glucoses are produced.

Adopting Fischer's formula for methylglucoside and omitting the product of hydrolysis of the trimethyl derivative, the following scheme represents the relations of the compounds described:



With regard to the optical activity of the glucose derivatives described in this and the succeeding paper, all are dextrorotatory except the above-mentioned pentamethylated glucose, which is levorotatory. The specific rotations recorded later were determined for the most part in dilute solution, and are therefore subject to considerable experimental error. It must also be stated that the results obtained in different preparations of the same substance were not concordant. The figures quoted below, however, suffice to show that it is the methyl group in the glucosidic position that chiefly affects the optical activity, the conversion of glucose into glucoside causing in each case a great increase in the dextrorotation, whilst the introduction of methyl groups to form true ethers, whether in the glucose or the glucoside, produces a much less marked effect.

	Solvent.	$[\alpha]_D$ .
Glucose.....	H <sub>2</sub> O	+52.6°
Trimethyl glucose .....	CH <sub>4</sub> O	79.2
Tetramethyl glucose .....	C <sub>2</sub> H <sub>6</sub> O	78.2
Methylglucoside .....	H <sub>2</sub> O	157.5
Trimethyl methylglucoside...	C <sub>2</sub> H <sub>6</sub> O	150.2
Tetramethyl methylglucoside	C <sub>2</sub> H <sub>6</sub> O	140.5

The discordant observations of optical activity, exhibited more particularly in different preparations of tri- and tetra-methyl  $\alpha$ -methylglucosides, may be accounted for by the presence of impurities, as the fractionation of such viscid liquids was necessarily attended with much difficulty; or they may be due to partial conversion of the compounds into isomerides by intramolecular rearrangement during the repeated treatments with methyl iodide. The activity of these two substances was not impaired by redistillation.

We have formulated the tri- and tetra-methyl glucoses on the basis of the aldehydic formula commonly used for the parent sugar. It is, of course, probable that these compounds are subject to tautomeric change like glucose itself, although it is worthy of note in this connection that we obtained no distinct evidence of multirotation in the case of either compound. We hope to make a thorough examination of the crystalline tetramethyl glucose from this point of view, and in particular to ascertain whether, on hydrolysis, tetramethyl  $\beta$ -methylglucoside yields the same compound as the corresponding  $\alpha$ -glucoside or a stereoisomeride.

Our results supply evidence of some interest in support of the formula adopted by Fischer for his alkylglucosides (*loc. cit.*). The general correctness of this formula has been amply verified by subsequent research, but positive evidence with respect to the position of the oxygen coupling of the ring is still lacking. Fischer's view that the oxygen is linked to the  $\gamma$ -carbon atom is mainly based on the

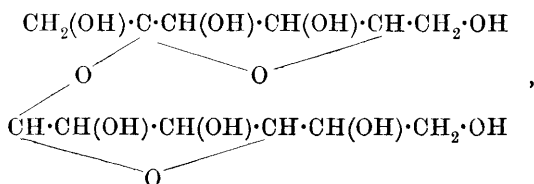
fact that benzoylcarbinol, benzoin, and glycolaldehyde (*Ber.*, 1897, 30, 3055) do not yield derivatives of a glucosidic nature, and that the group  $\text{CO}\cdot\text{CH}\cdot\text{OH}$ , therefore, does not suffice for the formation of glucosides. The alternative linkage, that of the ethylene oxide type, was supported by Marchlewski, and his arguments in favour of this formula were replied to by Fischer. Lobry de Bruyn and Ekenstein, however (*Ber.*, 1895, 28, 3078), consider that the interconversion of glucose, lævulose, and mannose by the action of alkalis lends support to Marchlewski's view. The fact that our tetramethylgluconic acid forms a lactone shows that its one unmethylated carbinol group is that in the  $\gamma$ -position; it follows, necessarily, that in the tetramethyl methyl glucoside from which the acid was derived, and, consequently, also in the parent methylglucoside, it is the  $\gamma$ -carbon atom which is united with the oxygen of the ring. Fischer's formula is thus confirmed.

Preliminary experiments show that methylfructoside behaves like the corresponding glucoside, and yields, when completely methylated, tetramethyl methylfructoside, a syrup boiling without decomposition at  $132\text{--}136^\circ$  under 10 mm. pressure. The method of alkylation has also been applied satisfactorily to acetone rhamnoside. According to Fischer's formula (*Ber.*, 1895, 28, 1150), the substance contains two unetherified secondary carbinol groups. By carrying out the alkylation first in acetone and then in methyl iodide solution, the hydroxyl of both groups is methylated with the production of dimethyl acetone rhamnoside. The substance is an oil of pleasant odour, distilling readily at  $115\text{--}118^\circ$  under 11 mm. pressure. The introduction of the methyl groups changes the sign of rotation, the compound being lævorotatory. A detailed description of the results obtained with the fructoside and rhamoside will be given in a later communication.

Our method of alkylation can also be applied to bioses. In the case of maltose, as was to be expected, the reaction is complicated by the occurrence of oxidation, and we have not been able as yet to isolate any of the products in a pure state. Cane sugar, however, gives results of some interest. It was to be expected that this sugar, owing to the absence of free aldehydic groups in its composition, would lend itself readily to the reaction; on the other hand, the very slight solubility of the substance in all solvents in which the process can be carried out seemed an insurmountable difficulty. The solubility of a sugar in organic solvents, however, increases as the methylation proceeds, and we found, accordingly, that by repeated alkylations, first in aqueous methyl alcohol and then in dry alcohol, a syrup entirely soluble in methyl iodide was produced, and the methylation was therefore completed in the latter solvent. In this manner, a neutral oil was finally obtained which showed no action on Fehling's solution until it was hydrolysed. The product of hydrolysis was a

viscid liquid which, after a time, partly crystallised. The crystalline substance, when purified by recrystallisation from ligroin, was recognised by its melting point and by analysis to be identical with the tetramethyl glucose previously prepared from glucose. The uncrystallisable portion of the oil no doubt contains the corresponding derivative of lævulose, which may possibly be isolated by distillation or otherwise.

Fischer (*Ber.*, 1893, 26, 2404), after developing the constitution of the alkylglucosides, concludes that the complex carbohydrates probably possess a similar structure. Modifying the formula suggested by Tollens (*Ber.*, 1883, 16, 923), he accordingly represents the constitution of cane sugar as follows:



and Perkin has recently shown (*Trans.*, 1902, 81, 185) that this view is corroborated by the magnetic rotation of the sugar.

The fact, just mentioned, that methylated cane sugar and methylated methylglucoside give, on hydrolysis, the same tetramethyl glucose, proves that the constitution and linkage of the glucose group of the biose is the same as that of the simple glucoside. This, coupled with the evidence given above of the constitution of tetramethyl glucose, furnishes conclusive evidence, at least so far as the glucose half of the molecule is concerned, of the correctness of Fischer's formula.

#### *Trimethyl α-Methylglucoside.*

The α-methylglucoside used was prepared by Fischer's method (*loc. cit.*), the yield of product obtained (m. p. 165—167°) being 73 per cent. of the weight of glucose used.

The method of alkylation finally adopted was as follows: the dry silver oxide (5 mols.) was added to the mixture of methyl iodide (10 mols.) and methylglucoside (1 mol.) dissolved in six to seven times its weight of pure methyl alcohol. The methyl iodide was kept in excess of the oxide during the process, and to obviate precipitation of the glucoside it was added in several instalments, each addition being followed by the corresponding amount of the oxide. The action, which was started after each addition by slightly warming the mixture, was then allowed to proceed spontaneously, and finally completed by heating for some time on a water-bath under a reflux condenser.



The silver residues having been filtered off and washed with hot methyl alcohol, the filtrate was evaporated to dryness, and the residual syrup was then extracted with ether, the alkylated products being thus removed and any unaltered glucoside precipitated. The ethereal extract, dried with anhydrous sodium sulphate and then evaporated, left a viscid syrup, which was distilled on a graphite bath under reduced pressure. The total distillate, boiling at 157—165° under 14 mm. pressure, amounted to about half the weight of glucoside taken. After several fractional distillations, a liquid boiling at 167—170° under 17 mm. pressure was collected, which was analysed with the following results:

0·1999 gave 0·3723 CO<sub>2</sub> and 0·1506 H<sub>2</sub>O. C=50·79; H=8·37.

C<sub>10</sub>H<sub>20</sub>O<sub>6</sub> requires C=50·85; H=8·47 per cent.

That the substance was not merely a mixture of different alkylated products is proved by the fact that the same liquid of constant boiling point was obtained in other experiments when different proportions of the alkylating agent were used, and even when the glucoside employed was a crude, syrupy mixture of the  $\alpha$ - and  $\beta$ -forms. In the latter preparation, a better method of isolating the product was apparently employed, because combustions of successive distillations gave the following results:

I. C=50·84; H=8·61. II. C=50·87; H=8·58.

As the various methylated derivatives do not differ very much in elementary composition, the methoxyl was determined by Zeisel's method:

0·4704 gave 1·7864 AgI. CH<sub>3</sub>O=50·13.

0·3292 „ 1·2480 AgI. CH<sub>3</sub>O=50·04.\*

C<sub>6</sub>H<sub>8</sub>O<sub>2</sub>(OCH<sub>3</sub>)<sub>4</sub> requires CH<sub>3</sub>O=52·54 per cent.

A determination of the molecular weight of the substance by the cryoscopic method in aqueous solution gave 209, the calculated value being 236. The substance is therefore trimethyl  $\alpha$ -methylglucoside. When warmed, it is a colourless, fairly mobile liquid, but on cooling it becomes a viscid syrup, which, after the lapse of a year, shows no sign of crystallising. The substance has a slightly sweet taste; it is soluble in water, alcohol, and ether, and has no action on Fehling's solution.

Observations of the specific rotation in alcoholic solution gave:  $l=1$ ,  $c=15\cdot86$ ,  $\alpha_D^{20}+19\cdot96^\circ$ , hence  $[\alpha]_D^{20}$  is  $+125\cdot9^\circ$ ; a solution obtained by diluting 5 c.c. of this to 15 c.c. gave  $[\alpha]_D^{20}+126\cdot8^\circ$ .† An

\* The quantity of substance used in these determinations was too large. A better result is recorded in the succeeding paper.

† An observation showing a much higher specific rotation is recorded in the succeeding paper.

observation of the specific rotation of the pure liquid, made at  $30^\circ$  so as to admit of the substance being manipulated, gave:  $d_{30^\circ/4^\circ} = 1.1656$ ,  $\alpha_D^{30^\circ} + 75.66^\circ$ ;  $l = 0.5$ ;  $[\alpha]_D^{30^\circ} + 129.8^\circ$ .

When the alkylating agent is used in the proportion given above, little or no unchanged glucoside is left, and the undistilled residues and less volatile fractions consist of mono- and di-methylated derivatives, the percentage of carbon in which is raised by repeated alkylation. When a larger proportion of alkylating agent is used, the more volatile tetramethyl ether is produced in small quantity. It was, however, extremely difficult, even by repeated alkylation, to extend the process beyond the trimethyl stage so long as any methyl alcohol was present. The further examination of this compound is described in the succeeding paper.

*Tetramethyl  $\alpha$ -Methylglucoside.*

On alkylating again some of the lower methylated ethers from the previous experiments without the use of other solvent than methyl iodide, we found that the final distilled product, which was comparatively mobile, had a much lower boiling point than the trimethyl ether, and its composition approximated to that of a tetramethyl methylglucoside. The same process was therefore applied to the pure trimethyl ether, the following experiment being quoted as an example of the method employed. A very large excess of alkylating agent was used, the quantities taken being 15 grams of trimethyl ether (1 mol. reckoned as methylglucoside), 115 grams of methyl iodide (10 mols.), and 90 grams of dry silver oxide (5 mols.). The ether was dissolved in half the total amount of iodide, and then half the oxide was added in small quantities, the mixture being heated after each addition. The action was feeble, and when the rest of the alkylating material had been similarly added the mixture was heated for some hours on a water-bath. The liquid obtained after filtering and extracting the silver residues with ether was dried with anhydrous sodium sulphate and evaporated. On distilling the residual neutral oil, 10 grams were collected which boiled at  $144\text{--}152^\circ$  under about 20 mm. pressure, and fractionation yielded 6.2 grams boiling steadily at  $144\text{--}145^\circ$  under 17 mm. pressure. The results of analysis and of the methoxyl determination in two different preparations were as follows:

0.1794 gave 0.3480  $\text{CO}_2$  and 0.1426  $\text{H}_2\text{O}$ . C = 52.90; H = 8.83.

0.2144 ,, 0.4134  $\text{CO}_2$  ,, 0.1673  $\text{H}_2\text{O}$ . C = 52.59; H = 8.67.

0.1378 ,, 0.6484 AgI.  $\text{CH}_3\text{O} = 62.11$ .

0.1822 ,, 0.8494 AgI.  $\text{CH}_3\text{O} = 61.54$ .

$\text{C}_{11}\text{H}_{22}\text{O}_6$  requires C = 52.80; H = 8.80.  $\text{C}_6\text{H}_7\text{O}(\text{OCH}_3)_5$  requires  $\text{CH}_3\text{O} = 62.0$ .

Analysis of a third preparation gave C = 52.45; H = 8.86; CH<sub>3</sub>O = 61.04 per cent.

In preparing this compound, it is unnecessary to isolate the trimethyl ether. The crude syrup containing the latter, obtained from the alkylation in methyl alcohol solution, may be alkylated after drying by heating in a vacuum in methyl iodide solution in the manner described above. If the less volatile fractions are again alkylated, the yield is about 55 per cent. of the glucoside taken.

Tetramethyl  $\alpha$ -methylglucoside is a colourless, neutral, syrupy liquid possessing a burning taste; it is soluble in water, alcohol, acetone, ether, and methyl iodide, and has no action on Fehling's solution. Determinations of the specific rotation made on different preparations gave discordant results, as mentioned in the introduction. The following observations were made in a 2 dm. tube:

	$c.$	$\alpha_D^{20}$ .	$[\alpha]_D^{20}$ .
I. In ethyl alcohol.....	5.4233	+13.86°	+127.8°
II. " " .....	5.0090	14.08	140.5
Water.....	5.005	13.63	136.2.

The solutions did not exhibit multirotation, and the optical activity was but slightly altered by redistilling the substance.

The specific rotations of the two preparations in the form of pure liquids were:

- I.  $l = 0.5$ ,  $\alpha_D^{20} + 70.5^\circ$ ;  $d_{20^\circ/4^\circ} = 1.1006$ ,  $[\alpha]_D^{20} + 128.1^\circ$ .  
 II.  $l = 0.5$ ,  $\alpha_D^{20} + 77.5^\circ$ ;  $d_{20^\circ/4^\circ} = 1.1025$ ,  $[\alpha]_D^{20} + 140.6^\circ$ .

The specific rotation of the liquid substance is nearly the same as in alcoholic solution; in aqueous solution, it is considerably lower.

#### *Tetramethyl Glucose.*

To prepare this substance, tetramethyl  $\alpha$ -methylglucoside is boiled with 8 per cent. aqueous hydrochloric acid for half an hour and the dark coloured solution is then neutralised with sodium hydroxide and evaporated. As evaporation proceeds, a part of the product of hydrolysis separates as an oil and must be removed by extraction with ether. The residue left on complete evaporation is boiled with alcohol and, sodium chloride having been filtered off, the alcoholic liquid is evaporated. The residual syrup is then extracted with boiling ether, which leaves the greater portion of the colouring matter undissolved; the ethereal solution, to which is added the solution containing the above-mentioned oil, after being decolorised with animal charcoal and dried with sodium sulphate, is completely evaporated. The residue is a pale yellow oil consisting mainly of tetramethyl

glucose and unaltered tetramethyl methylglucoside. To separate these, the mixture may be extracted with boiling ligroin, which dissolves the former, or it may be distilled. In the latter case, the unaltered glucoside ether passes over first, after which the thermometer rises quickly, when the tetramethyl glucose is collected as a viscid liquid boiling at 182—185° under 20 mm. pressure and slowly crystallising in long needles. This less volatile distillate contains, however, a considerable quantity of uncrystallisable oil, from which the crystals have to be separated by means of a porous tile. A further quantity of substance is obtained by extracting the tile with ether, evaporating, and extracting the residual syrup with boiling ligroin. When recrystallised from this liquid, it is deposited in beautiful tufts of radiating needles melting at 81—83°. The yield of the recrystallised compound was 35 per cent. of the weight of tetramethyl methylglucoside taken.

The analysis of two different preparations and a methoxyl determination were made with the following results :

- I. 0.1705 gave 0.3165 CO<sub>2</sub> and 0.1344 H<sub>2</sub>O. C = 50.63 ; H = 8.69.  
 0.1537 ,, 0.6137 AgI. CH<sub>3</sub>O = 52.70.
- II. 0.1933 ,, 0.3578 CO<sub>2</sub> and 0.1460 H<sub>2</sub>O. C = 50.48 ; H = 8.39.  
 0.1612 ,, 0.3010 CO<sub>3</sub> ,, 0.1250 H<sub>2</sub>O. C = 50.92 ; H = 8.62.
- C<sub>10</sub>H<sub>20</sub>O<sub>6</sub> requires C = 50.85 ; H = 8.47. C<sub>6</sub>H<sub>8</sub>O<sub>2</sub>(OCH<sub>3</sub>)<sub>4</sub> requires  
 CH<sub>3</sub>O = 52.54 per cent.

The substance has a bitter taste and is neutral to litmus ; it is readily soluble in all ordinary organic solvents, but sparingly so in ligroin. Fehling's solution is reduced on boiling, and ammoniacal silver nitrate on gently warming. The aqueous solution becomes yellow and finally brown on boiling with dilute alkali, and with *α*-naphthol and concentrated sulphuric acid (Molisch reaction) the substance behaves like glucose.

Observations of the specific rotation gave the following results :

In alcohol :  $l = 2$ ,  $c = 5.0083$ ,  $\alpha_D^{20} + 7.83^\circ$ , hence  $[\alpha]_D^{20} 78.2^\circ$ .

In water :  $l = 2$ ,  $c = 5.0183$ ,  $\alpha_D^{20} + 8.11^\circ$ , hence  $[\alpha]_D^{20} 80.8^\circ$ .

After 24 hours, the observed rotation of this solution rose by 0.22°, the specific rotation thus becoming 83.0°; 24 hours later the reading appeared to be constant. The compound therefore exhibits the property of multirotation to a very slight extent, if at all.

Trimethyl glucose and phenylhydrazine readily interact in molecular proportions with the production of an oil insoluble in water, very soluble in alcohol, ether, and benzene. The substance could not be made to crystallise, but, as indicated below, it is doubtless a hydr-azone.

When the pure base and the methylated sugar were mixed in ethereal solution in the proportion indicated, only a slight coloration ensued, which was not much increased when the solution was heated at 55° in a sealed tube. Reaction had, however, occurred, as the oil which was left on evaporating the ether, after having been washed with dilute acetic acid, had no action on Fehling's solution. When a dilute acetic acid solution of the base was added to the sugar derivative in the same proportions as before, the latter dissolved at once, and the solution subsequently deposited a light yellow oil. The interaction of the substance was evidently complete, as only a minute quantity of phenylhydrazine acetate was found in the aqueous layer. Although the oil, after having been washed with water, had no action whatsoever on Fehling's solution, even on boiling, yet that it nevertheless contained both the sugar and hydrazine residues was proved by the positive results obtained on applying the Zeisel test for methoxyl and the ordinary test for nitrogen. Attempts to recover the methylated glucose by decomposing the compound with benzaldehyde or with fuming hydrochloric acid were unsuccessful, but it behaved towards the latter reagent like a hydrazone, as the product of the action at once reduced Fehling's solution in the cold.

*Tetramethylgluconic Acid.*

Tetramethyl glucose is readily converted into this acid by the action of bromine water. The oxidation was carried out according to the method of Kiliani and Kleemann (*Ber.*, 1884, 17, 1298) for the preparation of gluconic acid, the quantities of material used being 4·3 grams of tetramethyl glucose, 10·6 grams of bromine, and 21·5 grams of water. The bromine was added gradually with frequent shaking, and after 15 hours the small quantity of this element left was boiled off; the hydrobromic acid was then removed with silver oxide and the dissolved silver by means of sulphuretted hydrogen. The residue left on evaporation was dissolved in ether in order to remove some barium salt formed from traces of barium carbonate contained in the silver oxide, and the ethereal solution, after being treated with anhydrous sodium sulphate, was evaporated to dryness. The residue was a pale yellow oil weighing 2·6 grams, which consisted mainly of tetramethylgluconolactone; it was prepared for analysis by heating at 100° under reduced pressure, but no further attempt was made to purify the substance.

The following analytical results were obtained with different preparations:

0·1771 gave 0·3288 CO<sub>2</sub> and 0·1228 H<sub>2</sub>O. C = 50·63; H = 7·70.

0·3156 „ 0·5946 CO<sub>2</sub> „ 0·2204 H<sub>2</sub>O. C = 51·38; H = 7·75.

C<sub>10</sub>H<sub>18</sub>O<sub>6</sub> requires C = 51·28; H = 7·69 per cent.

The result of a determination of methoxyl showed that these groups had not been affected by the oxidation :

0.1455 gave 0.5934 AgI.  $\text{CH}_3\text{O} = 53.83$ .

$\text{C}_6\text{H}_6\text{O}_2(\text{OCH}_3)_4$  requires 52.99 per cent.

The lactone, which was found to volatilise at  $100^\circ$  under reduced pressure, condensed as an oil ; it formed oily globules in water which disappeared on warming, and produced an acid solution. When treated with alkali, it showed the characteristic behaviour of a lactone. An alcoholic solution containing 0.2646 gram of the substance was titrated with an aqueous solution of barium hydroxide (1 c.c. = 0.01052), phenolphthalein being used as indicator. The pink colour produced on adding a small quantity of the alkali gradually disappeared, and the solution after some time was again distinctly acid. After adding 5 c.c., the colour was persistent for about a minute in the cold ; it finally remained quite permanent, even on boiling, after the addition of 9.50 c.c.  $\text{C}_{10}\text{H}_{18}\text{O}_6$ , calculated as lactone, requires 9.22 c.c. for neutralisation.

It was found impossible to isolate the acid or to obtain crystalline salts. The calcium salt is a gum, the cadmium salt a glass, and both are soluble in alcohol.

The barium salt was obtained for analysis by the following process : the solution prepared by digesting the aqueous solution of the lactone with barium carbonate was evaporated to dryness ; the residual glass was powdered, dried at  $110^\circ$ , treated with boiling ether to remove extraneous organic matter, and then taken up in alcohol. On the addition of ether to the solution thus obtained, the salt separated as a perfectly white, bulky, gelatinous precipitate, which was collected, washed with ether, and dried at  $115^\circ$  for analysis :

I. C = 37.69 ; H = 5.99 ; Ba = 21.46.

II. C = 37.49 ; H = 5.85 ; Ba = 21.50.

$\text{C}_{20}\text{H}_{38}\text{O}_{14}\text{Ba}$  requires C = 37.54 ; H = 5.94 ; Ba = 21.49 per cent.

The optical activity of the lactone was determined in an aqueous alcoholic solution containing 0.4837 gram in 20 c.c. The rotation observed immediately after the solution was prepared was  $+4.87^\circ$  in a 2 dm. tube ; this decreased in 1 hour 45 minutes to  $3.58^\circ$ , and after three days to  $1.91^\circ$ , the specific rotation having thus fallen from  $100.7^\circ$  to  $39.5^\circ$ .

#### *Methylation of Tetramethyl Glucose.*

In a preliminary attempt to methylate tetramethyl glucose with silver oxide and methyl iodide, a mobile oil was obtained which boiled considerably lower and showed on analysis a higher percentage of

carbon than the original substance; after three months, the liquid deposited slender prisms melting at 39—40°. The experiment was accordingly repeated, the material used being 2 grams of tetramethyl glucose, 20 grams of methyl iodide, and 12 grams of silver oxide. The substituted glucose dissolved easily in the iodide, and on adding the oxide a feeble although appreciable reaction ensued which was completed by heating for 6 hours on a water-bath under a reflux condenser. The ethereal solution of the product, after drying with sodium sulphate, was evaporated, and the residual oil was distilled; the total distillate between 124° and 135° under 8 mm. pressure weighed 1·7 grams, and of this, 1·09 grams were collected at 124—127°. The crystallisation of this fraction was induced at once by introducing a small fragment of the previously prepared substance. After being freed from the oil in which they were imbedded by drying on a porous tile, the crystals weighed 0·48 gram and melted at 42—43°. On account of the small quantity of available material, the substance had to be analysed without further purification:

0·1318 gave 0·2546 CO<sub>2</sub> and 0·1057 H<sub>2</sub>O. C = 52·68; H = 8·91.

0·1464 „ 0·2835 CO<sub>2</sub> and 0·1178 H<sub>2</sub>O. C = 52·81; H = 8·91.

0·1333 „ 0·6213 AgI; CH<sub>3</sub>O = 61·52.

C<sub>6</sub>H<sub>7</sub>O(OCH<sub>3</sub>)<sub>5</sub> requires C = 52·80; H = 8·80; CH<sub>3</sub>O = 62·00.

The compound is therefore a pentamethylated glucose isomeric with the tetramethyl  $\alpha$ -methylglucoside already described; we are unable, however, at present to say whether it is the glucosidic or the aldehydic isomeride.

The substance became brown on boiling with alkali, gave the Molisch reaction, and reduced ammoniacal silver nitrate, but it did not reduce Fehling's solution even on boiling. In alcoholic solution, it was feebly laevorotatory; for  $c = 5\cdot002$ , and  $l = 1$ ,  $\alpha_D^{20} = -0\cdot7^\circ$ , hence  $[\alpha]_D^{20} = -13\cdot99^\circ$ .

The neutral oil, which yielded the crystals of pentamethylated glucose, was recovered from the porous tile by extraction with ether. It was indifferent to Fehling's solution, but the product of its hydrolysis, a viscid liquid which was isolated by the process used in previous cases, reduced this reagent on warming. A ligroin extract of the syrup, when evaporated, deposited crystals which, from their appearance and solubility in this solvent, were taken to be tetramethyl glucose. Their low melting point, 55—57°, much higher, however, than that of the above-mentioned pentamethylated derivative, may very well have been due to adhering oil from which it was impossible to free them on account of the minute quantity of the material. An explanation of the probable production of this substance is given in the introduction.

*Alkylation of Cane Sugar.*

The materials used in a preliminary experiment were: three grams of cane sugar (1 mol.), 20 grams of methyl iodide (20 mols.), and 16 grams of silver oxide (10 mols.). The sugar, previously dissolved in 3 c.c. of warm water, was mixed with 20 c.c. of pure methyl alcohol, and in order to avoid the precipitation of the sugar by the iodide and, as far as possible the oxidising effect of the oxide, the same precautions were taken in mixing the materials as in the methylation of methyl glucoside. A brisk reaction was set up on slightly warming. After all the iodide and oxide had been added, the mixture was heated for 4 hours on a water-bath under a reflux condenser, and then extracted with methyl alcohol. The residue left on evaporating the alcohol was a viscid, neutral oil, partially soluble in methyl iodide and dissolving readily in methyl alcohol. After being dried at 100° in a vacuum, this was dissolved in 10 c.c. of the latter liquid and the process of alkylation and extraction was repeated. The solubility of the substance in methyl iodide had now so far increased that only 2 c.c. of methyl alcohol were required to keep it in solution, and after a third alkylation with the same quantity of materials as before, ether could be used for the extraction of the product. On a fourth alkylation, it was found possible to dispense entirely with alcohol, and the reaction produced on adding the oxide was very feeble. The product, obtained as in previous alkylations, weighed 2 grams; it had a neutral reaction, was not very soluble in water, and did not reduce Fehling's solution. The decreasing weights of the silver residues from the successive alkylations, 32, 30, 28, and 22 grams respectively from 16 grams of oxide, showed that the conversion into iodide became less complete as the alkylation proceeded.

As the oil thus procured failed to crystallise, it was hydrolysed by boiling for half an hour with 50 c.c. of about 1.5 per cent. aqueous hydrochloric acid. The product of hydrolysis, obtained as in previous cases, was a yellow oil which, on being nucleated with tetramethyl glucose, deposited the long, crystalline needles characteristic of this substance. The crystals, after being dried on porous tile, recrystallised from ligroin, and left in a vacuum over paraffin wax, melted at 83—84°, the melting point previously found for tetramethyl glucose being 81—83°.

The tile used in absorbing the mother liquor of the crystals was extracted first with ligroin and then with ether. As neither extract crystallised on being nucleated, the material was again hydrolysed and treated as before, when an additional quantity of the crystalline needles was obtained. The total yield of crystals from the 2 grams of cane sugar ether was 0.32 gram.



The analysis of the crystals gave C = 50.72 ; H = 8.50 ; the required figures for tetramethyl glucose being C = 50.85 ; H = 8.47 per cent.

The uncrystallised part of the product of hydrolysis probably contains tetramethyl fructose, and the alkylation is being repeated on a larger scale with the view of isolating and identifying this substance.

We are applying our methods of alkylation to other members of the sugar group and to natural glucosides, and we purpose making a more complete study of the compounds already obtained, including their possible application to the synthesis of alkylated disaccharides.

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