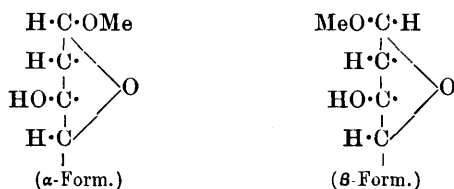


LX.—*Derivatives of a New Form of Glucose.*

By JAMES COLQUHOUN IRVINE, ALEXANDER WALKER FYFE (Carnegie Fellow), and THOMAS PERCIVAL HOGG (Carnegie Scholar).

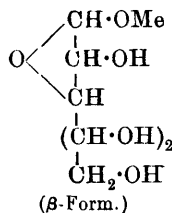
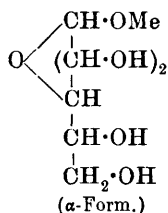
THE recent account given by Fischer (*Ber.*, 1914, **47**, 1980) of the isolation of a third isomeric form of methylglucoside marks a new development in the chemistry of the sugars of great importance. An outline of the present position of the subject and its future possibilities has already been published (*Ann. Report*, 1914, 86), but, in making a further contribution to the problem, it is necessary to review the situation in some detail.

Until the past year, the opinion has prevailed that glucosides may be classified into two types, termed α - and β -forms respectively, which correspond with the two mutarotatory varieties of the parent sugar from which they are derived. According to this view, the isomerism exhibited by such glucosides is dependent on the configuration of the groups attached to a terminal carbon atom of the chain, and is unconnected with the internal linking of the sugar molecule. Taking the well-defined crystalline α - and β -methylglucosides as examples, this difference in structure, adopting the configurations indicated by recent researches, may be represented by the skeleton formulæ shown below, which show that each compound contains the same γ -oxidic linking:



In practically every respect, the above formulæ may be regarded as satisfactory and consistent with the properties of the isomeric methylglucosides, their different solubilities, rotations, rates of hydrolysis, and their behaviour towards enzymes. Similar structures have also been applied to other artificial glucosides which have been isolated in two isomeric forms, and the same γ -oxidic linking has been shown to be present in several naturally occurring sugar derivatives, including salicin, sucrose, and maltose. The literature of the sugars certainly contains many other suggestions to account for the isomerism of glucosides, and the views expressed above were at first adopted with some hesitation, and only after a considerable amount of direct and collateral evidence had been

collected in their support has their acceptance become general. In a recent paper, however (Nef, *Annalen*, 1914, **403**, 204), arguments have been put forward in favour of the idea that the isomerism of α - and β -glucosides is due to a difference in the linking of the oxygen atom forming the internal ring in the sugar molecule. On this assumption, the formulæ suggested for α - and β -methylglucosides are:



Fischer has dealt so effectively with these ideas that it is unnecessary to produce any further argument to show that, whatever may be the cause of the isomerism of α - and β -methylglucosides, it is independent of the nature of the oxidic linking, which must be the same in each compound. It does not follow, of course, that all glucosidic compounds are derived from the γ -oxidic form of the parent sugar. Thus, the remarkable ease with which sucrose and other fructosides are hydrolysed indicates that these compounds are probably constituted on a different plan. As a result, the reasonable expectation has been held that, in addition to the fructosides, other hexosides would be discovered which, in constitution and properties, would differ from the standard forms represented by α - and β -methylglucosides. This expectation has been realised by Fischer, who obtained, from "glucose acetal," the new variety of methylglucoside, the instability of which towards hydrolysts closely resembles that of sucrose.

In the following communication, which shows that this methylglucoside is a mixture of isomeric hexosides derived from an entirely new variety of glucose, the expression " γ -methylglucoside" has been retained, but it should be understood that the name is provisional, and is used only to distinguish the substance from α - and β -methylglucosides. The index letter γ has thus no structural significance, either with regard to the configuration of the compound or to the coupling of the oxygen ring, and should not be confused with the expression " γ -oxidic linking."

At the date on which Fischer's paper on γ -methylglucoside was published, we had been engaged for some time on the investigation of derivatives of the new methylglucoside, and, in view of this collision of ideas, it is perhaps advisable to state the reasons which

led us into this line of work. With the object of synthesising glucosamine from glucose, a research was commenced in this laboratory in 1912 by one of us in collaboration with Mr. J. L. A. Macdonald, the first step of the proposed scheme being the preparation of trimethyl glucose in quantity. This involved a re-investigation of the preparation of glucosediacetone and of the general mechanism of the condensation of glucose with acetone. The reactions encountered were extremely complex, and it was evident that when glucose is treated with methyl alcohol and hydrogen chloride several products result, one being a form of methylglucoside much more reactive than the α - and β -varieties. This was shown by the result obtained when glucose acetal is extracted rapidly with a small quantity of acid acetone (a procedure which we imagined would yield glucosemonoacetone), as the product always contained a methylglucosidemonoacetone. A description of this product and of its dimethyl derivative has already been published (Macdonald, T., 1913, **103**, 1896), but it was subsequently recognised that the compound could not be derived from either α - or β -methylglucoside, as the latter compounds fail to react with acetone, and are, moreover, practically unaffected by heating at 40° with 0.25 per cent. hydrochloric acid. On the other hand, the methylglucosidemonoacetone referred to above was readily hydrolysed under these conditions, and was, moreover, characterised by its behaviour towards alkaline potassium permanganate solution, which it reduced instantaneously in the cold. Recognising that the properties of the parent methylhexoside must resemble those of a ketoside rather than those of an aldose, we undertook its detailed examination, and were engaged on the problem when Fischer's paper on γ -methylglucoside appeared.

In addition to the properties recorded by Fischer, we find that γ -methylglucoside is characterised by (1) the remarkable ease with which it enters into condensation with acetone; (2) its capacity to reduce alkaline potassium permanganate solution, which is so striking as to suggest unsaturation; (3) its tendency to unite with one atomic proportion of oxygen to give a neutral product; and (4) the ready auto-condensation of this oxy-compound to give a product allied to the disaccharides. These properties, either individually or in combination, are practically unique in the sugar group, and introduced many serious complications into the methylation of the compound, a process which we adopted as likely to throw light on its constitution.

We find that γ -methylglucoside may be methylated by the silver oxide reaction in exactly the same manner as α - or β -methylglucoside, methyl alcohol being used as a solvent in the first and

second treatments with the alkylating mixture. Two subsequent methylations in methyl iodide solution sufficed to give tetramethyl γ -methylglucoside, which was purified by distillation in a high vacuum. The physical constants of this product are compared below with those of the fully methylated derivatives of α - and β -methylglucosides:

Tetramethyl α -methylglucoside.	Tetramethyl β -methylglucoside.	Tetramethyl γ -methylglucoside.
B. p. 108°/0.1 mm.	M. p. 40–41°.	B. p. 106°/0.25 mm.
$[\alpha]_D$ in water +147.4°	–17.3°	–14.6°
$[\alpha]_D$ in alcohol +153.9°	–17.4°	–3.0°
n_D^{20} 1.4454	1.4450	1.4458
D_4^{20} 1.1082	—	D_4^{15} 1.1064

On first inspection, the above figures might lead to the conclusion that the new compound was merely a mixture of α - and β -tetramethyl methylglucosides. Such is not the case. The compound reduces alkaline permanganate instantaneously in the cold, and is hydrolysed by *N*/100-hydrochloric acid at 40°, conditions which do not affect the normal alkylated glucosides. The different behaviour of the three isomeric methylated glucosides on hydrolysis is illustrated in the following curves, which give clear evidence that tetramethyl γ -methylglucoside is a mixture of isomeric compounds.

In the case of the curve *BE*, the rise and fall in dextrorotation has been shown to be due to the hydrolysis of the α - and β -forms of tetramethyl methylglucoside at different speeds (Purdie and Irvine, T., 1904, 85, 1049; see also Irvine and Cameron, T., 1904, 85, 1071). The curve *CF* shows a similar rise and fall in lævorotation, from which it would appear that tetramethyl γ -methylglucoside (and consequently also the methylhexoside from which it is prepared) is similarly a mixture of two isomerides, one of which is more readily hydrolysed than the other. In this case, however, it is a dextro-form which is the less stable variety, whereas in the normal alkylated glucosides the reverse is the case.

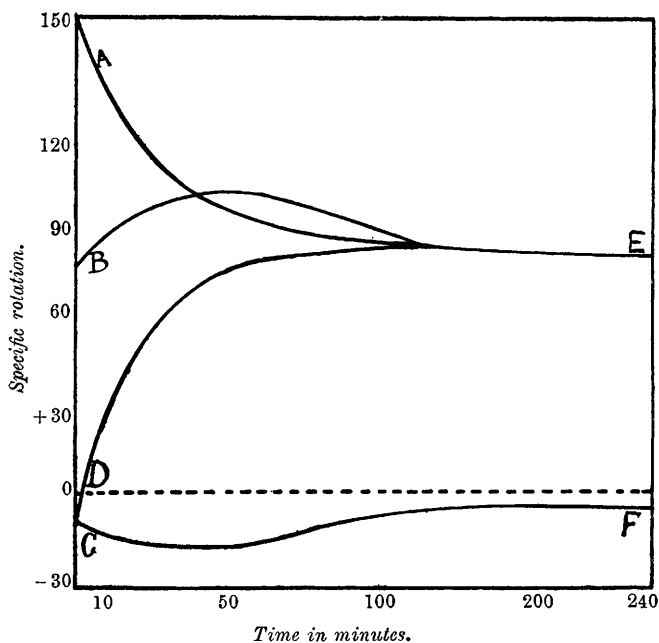
The product of hydrolysis is a tetramethylated hexose which, for want of a more appropriate name, may, in the meantime, be termed "tetramethyl γ -glucose." Unlike the characteristic crystalline tetramethyl glucose, the compound is a liquid, and is lævorotatory.

Comparison of the Tetramethyl Glucoses.

Tetramethyl α -glucose.	Equilibrium mixture of α - and β -tetramethyl glucoses.	Tetramethyl γ -glucose.
M. p. 89°	M. p. $75-80^{\circ}$	Liquid.
B. p. —	$136^{\circ}/0.8$ mm.	$122^{\circ}/0.05$ mm.
$[\alpha]_D$ in water $+100.8^{\circ}$	$\rightarrow 83.3^{\circ}$	$-3.8^{\circ} \rightarrow -7.2^{\circ}$
$[\alpha]_D$ in benzene $+111.1^{\circ}$	$\rightarrow 88.9^{\circ}$	-17.1°
n_D	1.4588	1.4585

The new sugar retains the capacity to reduce alkaline potassium permanganate, which is characteristic of γ -methylglucoside, and is

FIG. 1.



A E: Hydrolysis of tetramethyl α -methylglucoside at 100° with $2N$ -hydrochloric acid.

D E: " " " " β -methylglucoside " " " "

B E: Hydrolysis of a mixture of α - and β -tetramethyl methylglucosides at 100° with $2N$ -hydrochloric acid.

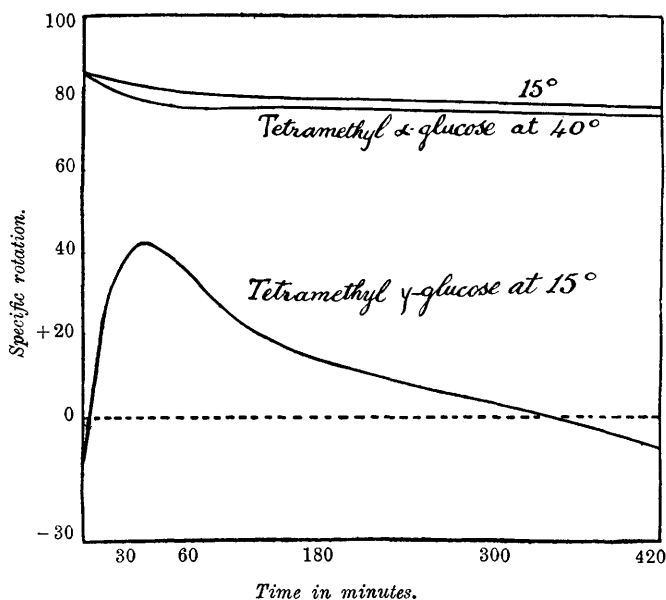
C F: Hydrolysis of tetramethyl γ -methylglucoside at 100° with $N/100$ -hydrochloric acid.

also distinguished from normal methylated glucoses in all its optical relationships. As, after distillation, it displays mutarotation, the compound presumably exists in two interconvertible forms, but the optical change observed thereafter on solution is

an increase in lævorotatory power. In the case of glucose, mono-, di-, and tetra-methyl glucose, the β -forms show, in solution, an increase in dextrorotation, and the equilibrium mixtures in each case are thus also dextrorotatory. Here the reverse holds true, and the only parallel which can be found in the substituted glucoses is furnished by trimethyl glucose (Irvine and Scott, T., 1913, **103**, 564), which displays the same optical irregularity.

Tetramethyl γ -glucose can be readily converted into the corresponding methylglucoside by the action at 15° of methyl alcohol containing 0.25 per cent. of hydrogen chloride. As an index of

FIG. 2.



the special reactivity of the sugar, it may be mentioned that the condensation takes place in a few minutes at this temperature, whereas, under parallel conditions, tetramethyl α -glucose requires twenty-four hours for complete reaction. During the formation of the alkylated γ -methylglucoside, the activity of the solution showed a double inversion (lævo \rightarrow dextro \rightarrow lævo), thus confirming the idea that the less stable form of the compound is dextrorotatory. The speed of this reaction, compared with that of the condensation of normal tetramethyl glucose under the same conditions, is best illustrated by the curve reproduced above.

It is evident that tetramethyl γ -glucose is a derivative of a much

more reactive form of glucose than the α - or β -variety, and the structure of the compound thus becomes an important question. The evidence available is, however, so far incomplete. The sugar reacts with phenylhydrazine and acetic acid, but is thereby resinified, and, in addition, a definite anilide or other crystalline derivative could not be obtained. On the other hand, the compound is readily reduced to give a tetramethyl hexitol, which is, presumably, tetramethyl sorbitol. The probable constitution of this compound and its bearing on the general problem will be referred to later. Again, when oxidised in the cold by the agency of alkaline potassium permanganate solution, tetramethyl γ -glucose gave rise to two distinct products. One of these was a neutral liquid, non-reducing and non-glucosidic, but nevertheless not a lactone or other recognisable derivative. It is possible that this substance is a pentitol ether or other degradation product of the sugar, and analysis certainly points to this conclusion. The second product was easily characterised, and consisted of a new form of tetramethyl gluconic acid, which was readily converted by heating in a vacuum into a tetramethyl gluconolactone.

Formation of Oxy-compounds from γ -Methylglucoside.

One of the most remarkable properties of γ -methylglucoside is the ease with which it condenses with acetone, the reaction taking place on gentle warming and in the absence of any recognisable catalyst. The essential product of this reaction appears to be a γ -methylglucosidemonoacetone. The isolation of this substance in the pure state has not yet been accomplished, and, in order to convert it into a volatile derivative, the compound was methylated by means of the silver oxide reaction, with an altogether unexpected result. On fractionation of the methylated products, the lower boiling portion proved to be a trimethyl oxy- γ -methylglucosidemonoacetone (b. p. 105—106°/0.025 mm.), whilst the portion of higher boiling point (200°/1.4 mm.) consisted of a condensation compound allied to the disaccharides, which may be termed provisionally anhydrobis(dimethyl oxy- γ -methylglucosidemonoacetone). The methylation process was therefore accompanied by oxidation of a new type, and the consequent formation of an additional hydroxyl group in the γ -methylglucoside residue. The product of this change then undergoes normal methylation, but a secondary reaction, consisting of the auto-condensation of two molecules with the loss of a molecule of water, takes place simultaneously. This is an important reaction, as it indicates the possibility of synthesising complexes allied to the disaccharides without the agency of acid catalysts.

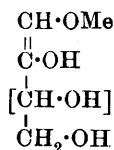
Constitution of the Compounds Described and of γ -Glucose.

Although the results now contributed throw a certain amount of light on the problem, further research will be necessary before definite conclusions as to the structure of γ -glucose and its derivatives can be drawn. Our deductions, therefore, cannot be regarded as final, and the structures suggested below are given with all reservation, and mainly with the object of rendering the scheme of reactions intelligible.

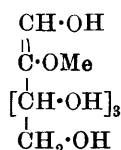
From the structural point of view, the most significant property common to all the derivatives of γ -glucose is the apparent unsaturation shown towards potassium permanganate. This at once suggests that the compounds may be allied to glucal, which, according to the most recent results (*Ber.*, 1914, **47**, 196), contains an ethylenic linking. No obvious modification of the glucal formula can, however, be found to accommodate the composition and reactions of the compounds under discussion without transferring the structures from the glucose to the fructose type. In the meantime, therefore, this possibility is passed over.

Obviously, the constitution of the form of glucose which gives rise to the new series of derivatives can be arrived at by determining the structure of γ -methylglucoside. Now, the results of methylation show that in the latter compound there are four unsubstituted hydroxyl groups, and, allowing for this factor and also for the behaviour towards potassium permanganate, the simplest possible formulæ fall into the three types shown below. In each case two stereoisomeric forms are possible.

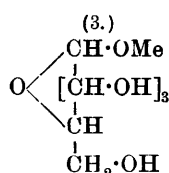
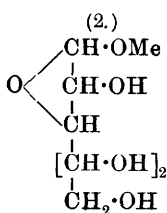
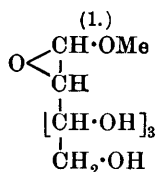
Type A (Enolic).



Type B (Enolic).

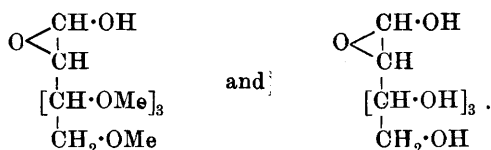


Type C (Oxidic).

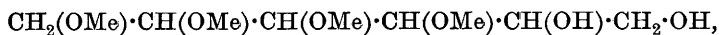


For several reasons, the types A and B are unlikely, as probably substances of this nature would act, not as glucosides, but as reducing sugars. Further, the formation of such derivatives would imply that glucose can undergo the aldose \rightleftharpoons enol \rightleftharpoons ketose change in an acid system, and although this possibility cannot altogether be excluded (T., 1914, **105**, 1275), it is opposed to the results obtained by Lobry de Bruyn. At the same time, the unsaturated formulæ offer a ready explanation of the formation of oxymethylglucoside derivatives, but the bulk of the evidence is in favour of the formulæ C (1), C (2), or C (3). One possibility is omitted from the latter list, as the sugar obtained by hydrolysing tetramethyl γ -methylglucoside is not identical with γ -oxidic tetramethyl glucose.

Of the three alternatives to which the discussion is now limited, formula C (1) seems in best agreement with all the facts. By the adoption of this structure, tetramethyl γ -glucose and the parent γ -glucose would be represented, respectively, by the structures:



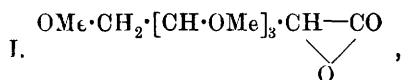
According to this view, the failure of tetramethyl γ -glucose to form a phenylosazone is explained, as the oxidation involved in osazone formation is due to the removal of hydrogen from the $\text{CH} \cdot \text{OH}$ group in the penultimate position in the sugar chain, or from a terminal $\text{CH}_2 \cdot \text{OH}$ group. Further, the optical properties of the hexitol formed from the sugar by reduction indicate that the compound contains two hydroxyl groups in spatial proximity. This was shown by the fact that the activity of the hexitol underwent a change of sign on the addition of boric acid, and, according to Böeseken (*Ber.*, 1913, **46**, 2612), this optical exaltation is only obtained when two hydroxyl groups are attached to neighbouring carbon atoms. This result, therefore, indicates that the tetramethyl hexitol may be represented by the formula



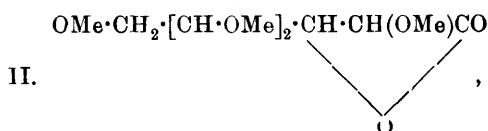
which is consistent with the above structure for γ -glucose.

On the other hand, the fact that tetramethyl γ -glucose may be oxidised to give a definite unimolecular lactone is somewhat disconcerting, and is opposed to the evidence cited above. The lactone is certainly different from that obtained from tetramethyl α -glucose, but is not a lactide or other bimolecular α -lactone, as it

shows a normal molecular weight. The two simplest structures for this lactone are:



indicating that γ -glucose belongs to type C (1).

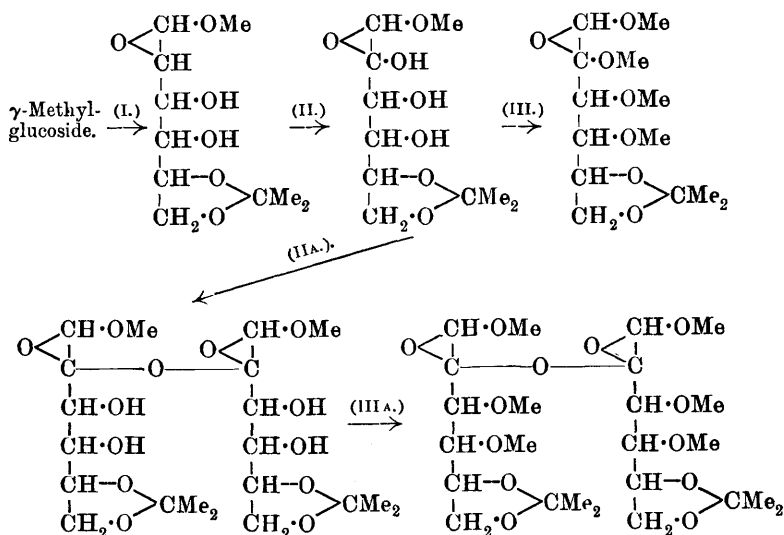


indicating that γ -glucose belongs to type C (2).

It is difficult to determine which result is of greater value in the solution of this problem, the exaltation in the specific rotation of tetramethyl sorbitol in the presence of boric acid or the formation of a unimolecular lactone on oxidation. In the meantime, the question may be left open until further evidence regarding the application of Böeseken's methods to the sugar group is available, and, in the structural scheme subsequently given, a β -oxidic linking would apply equally well to explain the formation of all the compounds now described.

Structure of the Oxy-derivatives.

The addition of one oxygen atom to γ -methylglucoside, which takes place under the conditions described in the experimental part, introduces a new hydroxyl group into the molecule. Although this is a most unexpected result, there can be no reasonable doubt that this is the case, as, after methylation in the presence of acetone, a trimethyl oxy- γ -methylglucosidemonoacetone results. This compound is quite unique, as it is evidently derived from a reducing hexose containing six in place of five hydroxyl groups. Application of the provisional formula C (1) for γ -methylglucoside offers a feasible explanation for the formation of the oxy-compound, and also of the oxy-disaccharide derivative.



Stage I.: Condensation with Acetone.—No proof exists as to the location of the isopropylidene group, but the position provisionally selected appears to be the most probable one. Fructose forms a similar compound, which can be isolated by distillation.

Stage II.: Oxidation by Silver Oxide.—This product has not been isolated, as, under the conditions of the experiments, its existence is transitory.

Stage II.A: Auto-condensation.—The union of the hexose residues doubtless depends on the interaction of two tertiary hydroxyl groups, as, on the analogy of fructose, this group should be the most reactive part of the molecule.

Stages III. and III.A: Normal Methylation.

We are continuing the same line of investigation, and, in particular, hope to examine further the auto-condensation products of γ -methylglucoside and similar substances with a view to ascertaining if the synthesis of disaccharides can be accomplished through the agency of these compounds.

EXPERIMENTAL.

Methylation of γ -Methylglucoside.

The γ -methylglucoside used was prepared in essentially the manner described by Fischer, special care being taken to ensure that all the reagents used were free from acetone. This is a very necessary precaution. As the products of methylation are readily volatile, it was considered unnecessary to distil the glucoside, as

this process involves considerable loss. The compound was accordingly used in the form of a colourless syrup, which was practically devoid of action on Fehling's solution, and, when dried at $30^{\circ}/15$ mm., gave $\text{OMe}=15.90$. ($\text{C}_7\text{H}_{14}\text{O}_6$ requires $\text{OMe}=15.98$ per cent.)

Twelve grams of the glucoside were boiled under a condenser with 75 grams of methyl iodide, and, on the addition of 10 c.c. of pure methyl alcohol, a clear solution was obtained. To this, 55 grams of silver oxide were gradually added, and the alkylation was continued for eight hours, methyl alcohol being afterwards used as the extracting agent. The syrupy product, isolated as usual, was subjected to a second methylation, in which the same proportions of the alkylating mixture were employed, and, in this case also, a small quantity of methyl alcohol was necessary to obtain complete solution. After this treatment, the product was freely soluble in methyl iodide, and in the third methylation, in which 30 grams of oxide and 45 grams of iodide were employed, no extraneous solvent was necessary. The methylated glucoside was extracted with ether and isolated by distillation at the Gaede pump. In this way, 7 grams of a colourless, mobile liquid were obtained, whilst a viscous residue (1.4 grams) remained undistilled. The boiling point of the distilled product was, however, indefinite, and, in addition, the refractive index (n_D 1.4475) and methoxyl content ($\text{OMe}=58.1$ per cent.) showed that the methylation was still incomplete. The methylated glucoside was accordingly subjected to a fourth alkylation by solution in 45 grams of methyl iodide and treatment with 30 grams of silver oxide. On distillation of the resulting syrup, 6.3 grams of tetramethyl γ -methylglucoside were collected at $115\text{--}116^{\circ}/0.5$ mm., and from this specimen, on further fractionation, the pure compound was obtained (b. p. $106^{\circ}/0.25$ mm.).

Found: $\text{C}=52.42$; $\text{H}=8.79$; $\text{OMe}=61.1$.

$\text{C}_{11}\text{H}_{22}\text{O}_6$ requires $\text{C}=52.80$; $\text{H}=8.80$; $\text{OMe}=62.0$ per cent.

It was evident that small quantities of other products possessing a lower carbon content were also produced in the reaction, judging from analyses conducted on fractions of both lower and higher boiling point than the main fraction referred to above. For this reason, the re-fractionation of tetramethyl γ -methylglucoside must be carried out with great care, and, in our experience, it is better to control the progress of the distillation by determination of the refractive index rather than by variations in the boiling point, as little trust can be placed in the latter factor in fractionations under highly diminished pressure.

Tetramethyl γ -methylglucoside is a colourless, mobile liquid

readily soluble in water and in organic solvents. The compound is non-reducing, but is hydrolysed by very dilute acids with extreme ease. The most striking property of the compound is its capacity to reduce alkaline potassium permanganate solution in the cold. The following constants were determined:

$$n_D 1.4458, D_4^{15} 1.1064, M_D 60.23 \text{ (Calc. } 60.65).$$

Solvent.	c.	$[\alpha]_D^{20}$.
Water	2.4995	-14.6°
Alcohol	2.4985	- 3.0
Acetone	2.6215	- 5.5
Benzene	2.6665	- 4.3

The above values are initial specific rotations determined without delay. In the case of the aqueous and the benzene solutions, no change in activity was observed on keeping, but the acetone and the alcoholic solutions showed considerable variation, the former increasing in fifteen hours to $[\alpha]_D -7.6^\circ$, and the latter to -11.8° . These alterations are doubtless due either to oxidation or to reaction with the solvent.

Hydrolysis of Tetramethyl γ -Methylglucoside. Tetramethyl γ -Glucose.

A 5 per cent. solution of the alkylated glucoside in *N*/100-hydrochloric acid showed an increase in specific rotation when preserved at 40° , but, as the hydrolysis at this temperature was slow, the solution was thereafter heated at 100° . The specific rotation increased to a maximum and then diminished to practically the initial value, some of the figures indicating this rise and fall being reproduced below, the value being calculated on the concentration of glucoside originally present:

Initial specific rotation :—	— 9.2°
After 30 minutes at 40°	—12.5
„ 30 „ „ 100°	—17.5
„ 60 „ „ 100°	—10.0
„ 90 „ „ 100°	— 8.2 (constant).

At this stage, although the hydrolysis was apparently complete, the acid concentration was raised to *N*/10 and the heating continued at 100° for forty-five minutes, during which time the specific rotation diminished to the constant value -5.4° . On removal of the acid with silver carbonate, and evaporation of the solvent under diminished pressure, a clear syrup remained. This was dissolved in ether, and the solution was dried over magnesium sulphate and evaporated. The residue consisted of tetramethyl γ -glucose in the form of a clear, viscous syrup, which was purified by distillation (b. p. $122^\circ/0.05$ mm.).

In subsequent preparations of the sugar, the hydrolysis of the glucoside was carried out from start to finish with *N*/10-acid at

100°. Although under these conditions the reaction is complete in sixty minutes, it is somewhat difficult to determine the end-point polarimetrically, as, with the higher concentration of acid, the rise and fall of rotation is obliterated, so that the optical value remains practically steady.

Tetramethyl γ -glucose is a colourless liquid resembling glycerol in appearance. The compound possesses solubilities similar to those of the glucoside from which it is derived, reduces Fehling's solution actively on warming, and also alkaline potassium permanganate in the cold.

Found: C=50.65; H=8.47; OMe=50.6.

C₁₀H₂₀O₆ requires C=50.85; H=8.47; OMe=52.5 per cent.

Owing to the viscosity of the liquid and the small quantity of material available, the following density determination may be regarded as only approximate:

D₄¹⁵ 1.1644, n_D 1.4585, M_D 55.36 (calc. 56.03).

Before determining the specific rotations, the sugar was re-distilled, so as to increase the proportion of one of the possible mutarotatory forms. Mutarotation was, however, only detected in the case of the aqueous solution.

Solvent.	c.	$[\alpha]_D^{20}$.
Water	2.080	— 3.85° \rightarrow — 7.21
Methyl alcohol	1.827	— 19.7
Benzene	1.641	— 17.1

Reactions of Tetramethyl γ -Glucose.

In practically every respect the reactions of the new form of tetramethyl glucose are abnormal. Its behaviour towards alkaline permanganate and its optical irregularity have already been referred to, and are opposed to all precedent in compounds possessing the glucose configuration.

Action of Phenylhydrazine.—An aqueous solution of the sugar when heated in boiling water with phenylhydrazine and acetic acid reacted very readily. Gas was evolved, and a dark-coloured oil separated. Attempts to purify this compound failed, but, from its solubilities and reactions, we are inclined to the opinion that it is of the nature of a hydrazone, and not an osazone.

Action of Aniline.—The anilides of alkylated sugars are usually well defined and crystalline, but, although the standard conditions (Irvine and M'Nicoll, T., 1910, **97**, 1449) were followed in the case of tetramethyl γ -glucose, the sugar was recovered unaltered from the reaction.

Condensation with Methyl Alcohol.—A 1 per cent. solution of the sugar in methyl alcohol containing 0.25 per cent. of hydrogen chloride showed immediate and extensive alterations in rotatory

power, indicating that condensation proceeded rapidly at the temperature of the room. The rotation altered from lævo to dextro, and then underwent a second inversion from dextro to lævo, the reducing action on Fehling's solution meanwhile disappearing. Some of the optical observations which are embodied in the curve reproduced in the introduction are given below, together with the similar changes in rotation shown during the condensation of tetramethyl α -glucose with methyl alcohol under the same conditions and at 40°. In each case the specific rotations are calculated on the concentration of the sugar originally present.

Solvent: Methyl Alcohol containing 0.25 per cent. of Hydrogen Chloride.

Time from first reading.	Tetramethyl γ -glucose. T = 15°.	Tetramethyl α -glucose.	
		T = 15°.	T = 40°.
0 minutes.	-10.4°	+85	+84
2 "	7.5	—	—
3 "	3.8	—	—
5 "	+3.8	—	—
13 "	24.6	—	—
40 "	43.2	81	79.1
85 "	32.0	—	—
200 "	12.0	—	—
260 "	6.6	78	76.5
Constant	-22.5	(incomplete in 30 days) 75.1	

The tetramethyl γ -methylglucoside isolated from the above experiment showed n_D 1.4470.

Oxidation with Potassium Permanganate.—A solution of 2 grams of the sugar in 200 c.c. of water was rendered alkaline by the addition of 16 c.c. of 2*N*-sodium hydroxide, and thereafter 56 c.c. of potassium permanganate solution (1 c.c. = 0.01575 gram KMnO_4) were gradually added, with frequent shaking. Carbon dioxide was then bubbled through the liquid, which was filtered, and evaporated to dryness under diminished pressure. The solid residue was extracted with boiling ether, and the solution was dried and evaporated, a colourless, mobile liquid (0.6 gram) being thus obtained. As this quantity of material did not permit of further purification, we are unable to identify the product, but the following facts regarding it may be stated. The compound is neutral, and practically devoid of action on Fehling's solution at the boiling point. It still reduces alkaline permanganate, but is neither a lactone nor an ester, and contains 55.2 per cent. of methoxyl. As stated in the introduction, these results indicate that the compound is possibly a tetramethyl pentitol.

The main oxidation product remained in the solid residue, referred to above, in the form of a potassium salt, and was isolated by acidification with hydrochloric acid and extraction with ether

in Hagemann's apparatus. After drying the ethereal solution and evaporation of the solvent, an acid syrup remained, which weighed 1.4 grams. This was dried until constant in weight at $60^{\circ}/1$ mm. Analysis and titration showed the compound to be a *tetramethylgluconolactone* (n_D 1.4519).

Found: C=51.03; H=7.66.

$C_{10}H_{18}O_6$ requires C=51.28; H=7.69 per cent.

The molecular weight, determined in benzene by the freezing-point method, was 228. (Calculated for a unimolecular lactone, 234.) The behaviour of the compound on titration was characteristic of a lactone.

0.1200 Dissolved in dilute alcohol was titrated with sodium hydroxide solution (1 c.c.=0.00411). Found: (1) by direct titration in the cold, that 5.00 c.c. alkali were required, and (2) after heating with excess of alkali and titration to the neutral point with acid, that 5.13 c.c. alkali were used. $C_{10}H_{18}O_6$ requires 5.00 c.c.

The lactone differs widely in rotation from all the other compounds now described. Solvent: ethyl alcohol, $c=1$, $[\alpha]_D +59.4^{\circ}$. A solution in aqueous alcohol showed the usual diminution in rotatory power, which is a common property of lactones allied to the sugars.

Initial $[\alpha]_D +59^{\circ} \rightarrow +46^{\circ}$ in four hours.

Reduction of Tetramethyl γ -Glucose.—This reaction was carried out in practically the same manner as already described for the reduction of tetramethyl mannose (Irvine and Paterson, T., 1914, 105, 898), except that the ethereal solution of the sugar was very dilute, and only 2.5 per cent. sodium amalgam was used. After two successive reductions, the product, isolated by vacuum distillation (b. p. $125^{\circ}/0.4$), proved to be a *tetramethyl sorbitol*.

Found: C=50.57; H=9.19; OMe=51.5.

$C_{10}H_{22}O_6$ requires C=50.42; H=9.25; OMe=52.1 per cent.

n_D 1.4568, $[\alpha]_D$ in water -6.2° ($c=1.463$).

The above specific rotation was permanent, but a solution of the compound in $N/2$ -boric acid showed curious optical changes, indicating that interaction of the solutes took place.

Time from the addition of boric acid.	Specific rotation.
10 minutes	-15.0°
25 "	8.2
35 "	inactive
50 "	$+6.8$
300 "	-2.7 (constant).

The significance of this result is discussed in the introduction.

Condensation of γ -Methylglucoside with Acetone.

On heating γ -methylglucoside with pure acetone under a condenser, the compound passes into solution, owing to condensation with the solvent. On alkylating a solution obtained from 12 grams of the glucoside, in the manner described above, by the addition of methyl iodide (6 mols.) and silver oxide (3 mols.), simultaneous oxidation and methylation took place. Acetone was used as the extracting agent, and the syrup left on evaporation of the solvent was freely soluble in methyl iodide. No extraneous solvent was thus required for the second methylation, in which the same proportions of oxide and iodide were used.

On distilling the product under 0.05 mm. pressure, 7.9 grams of a colourless distillate were obtained between 115° and 122° , whilst 4 grams of a viscous syrup remained undistilled. Two distinct products were evidently present, and these were separately re-methylated and re-fractionated until pure. The compound of lower boiling point ($105\text{--}106^{\circ}/0.025$ mm.) proved to be *trimethyl oxy- γ -methylglucosidemonoacetone*.

Found: C=53.63; H=8.41; OMe=41.3.

$\text{C}_{13}\text{H}_{24}\text{O}_7$ requires C=53.42; H=8.21; OMe=42.4 per cent.

n_D 1.4493, D_{15}^{15} 1.1133, M_D 69.33 (calc. 70.37).

The divergence of the molecular refraction from the calculated value is not great, and may be accounted for by the uncertainty as to which constants should be included in the calculation. Greater trust is placed in the analytical figures, which are so far removed from those required for a fully methylated glucoside that there is no possibility of such a compound being present. The specimen described above contained, however, at least two isomeric compounds, as, on distilling the liquid in two equal fractions, the following results were obtained:

n_D of liquid distilled=1.4500.

	B. p.	Pressure.	n_D	OMe
Fraction I.	110–113°	0.05 mm.	1.4493	40.7
Fraction II.	105–106°	0.025 mm.	1.4491	41.3 per cent.

Despite the apparent identity of the two fractions and the constancy of refractive index and analytical composition, they differed in rotatory power as shown below ($c=2.5$):

	Acetone.	Ethyl alcohol.	Benzene.	Methyl alcohol.
Fraction I.	—	—	—	—3.4°
Fraction II.	+7.6°	+5.3°	+3.2°	inactive

Hydrolysis.—On heating a 5 per cent. solution of trimethyl oxy- γ -methylglucosidemonoacetone in *N*/10-hydrochloric acid

at 90°, the rotation altered from lævo to dextro, and in fifty minutes attained the constant value $[\alpha]_D + 41^\circ$. At this stage, only the isopropylidene residue had been removed, as the liquid was without action on Fehling's solution, and the product, isolated in the usual manner, had the composition of a *trimethyl oxy- γ -methylglucoside*.

Found: OMe=48.7.

$C_{10}H_{20}O_7$ requires OMe=49.2 per cent.

Prolonged heating under the same conditions removed the glucosidic group, but the products of the change were not further examined.

Examination of the Distillate of High Boiling Point.—The second product of higher boiling point, obtained in the simultaneous alkylation and oxidation of γ -methylglucoside in the presence of acetone, was methylated five times and fractionated. It consisted of a very viscous, clear syrup boiling at 200°/1.4 mm., and was readily soluble in organic solvents.

Found: C=53.57; H=8.12; OMe=37.5, 37.1.

$C_{24}H_{42}O_{13}$ requires C=53.53; H=7.81; OMe=34.6 per cent.

Although the analytical figures are doubtless affected by the presence of higher methylated products, they point to the substance being *anhydrobisdimethyl oxy- γ -methylglucosidemonoacetone*. The relationship of the compound to a disaccharide is also indicated by the viscosity, high boiling point, refractive index (n_D 1.4587), and the value of the molecular weight.

Found: In alcoholic solution by the ebullioscopic method, M.W.=532; in benzene solution by the cryoscopic method, M.W.=366.

$C_{24}H_{42}O_{13}$ requires M.W.=538.

One molecular-weight determination thus gave an abnormal result, which we are unable to explain, but the same irregularity was encountered on a former occasion in the case of octamethyl diglucose, and the bulk of the evidence shows that the compound described above is not a derivative of a hexose, but of a disaccharide.

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CHEMICAL RESEARCH LABORATORY,
UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD,
UNIVERSITY OF ST. ANDREWS.

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