CLX.—*The Addition of Alkyl Halides to Alkylated Sugars and Glucosides.*

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TETRAMETHYL glucose, in common with other methylated sugars, is converted into a mixture of the corresponding alkylated glucosides when subjected to the silver oxide and alkyl iodide reaction, and the β -form of the hexoside invariably predominates in the mixture. This reaction differs sharply in its results from the alternative method of obtaining the alkylated glucosides, in which the methylated sugar is condensed with an alcohol by means of small quantities of hydrogen chloride, as in the latter case the α -form of the product is obtained in much larger proportion. It seemed to us desirable to study more fully the mechanism of the silver oxide reaction, as applied in this way to alkylated sugars, and to elucidate if possible the remarkable tendency of the reaction to produce β -stereoisomerides. Tetramethyl glucose was in the first instance selected for experiment on account of its crystalline nature and its ready conversion into tetramethyl β -methylglucoside when it is dissolved in methyl iodide and treated with silver oxide.

This interaction may proceed in either of two distinct ways. The sugar undoubtedly possesses the γ -oxidic linking, and its unmethylated hydroxyl group is attached to the terminal carbon atom. It seemed possible therefore that, by the action of silver oxide, a silver derivative might be produced in which the metallic atom would occupy the glucosidic position, and that this intermediate compound and methyl iodide would then interact. In the event of the β -form of the sugar reacting in this fashion more readily than the α -isomeride, then the equilibrium mixture of the two forms might ultimately be transformed almost entirely into the alkylated β -glucoside. It was found, however, that no action took place when the equilibrium mixture of tetramethyl glucose was dissolved in pure benzene and shaken with dry silver oxide for several hours. This was carried out at temperatures ranging

from 20° to 50°, conditions which approximate to those which exist during the process of alkylation. The specific rotatory power of the solution remained constant, and the alkylated sugar, when recovered, was found to contain no combined silver and to possess the original melting point. The substitution of acetone and other indifferent solvents for benzene similarly gave negative results.

This observation supports the view that the alkyl iodide must play a specific part in the alkylation, either by altering the state of equilibrium of the two forms of the sugar, or by forming an additive compound from which silver oxide would subsequently abstract hydrogen iodide.

The first of these alternatives has been negated in a previous paper (Trans., 1904, 85, 1070), but the possibility of sugars and glucosides forming additive compounds in which the lactonic oxygen displays quadrivalency has already been pointed out, and E. F. Armstrong (Trans., 1903, 83, 1309) suggests that compounds of this type may play a part in effecting the transformation of the α - and β -forms of a reducing sugar, and in the interconversion of α - and β -glucosides.

The possible addition of methyl iodide to tetramethyl glucose and the subsequent removal of hydrogen iodide may be expressed in the following alternative schemes :

If the action followed the above course, the product would not possess a glucosidic structure, but would consist of a mixture of stereoisomeric methyl hexoses. Moreover, any modification of the above scheme which would account for the formation of a glucoside would be dependent on the transference of the methyl group from the γ -oxidic to the hydroxylic position. As this is most improbable, we conclude that the change can only proceed through the temporary opening of the γ -oxidic ring as shown below :

The change, involving as it does the addition of an alkyl halide and the removal of a different molecule, is not strictly comparable to the tautomeric change $\alpha \rightleftharpoons \beta$ in a reducing sugar, for which Armstrong's theory (*loc. cit.*), on which the first alternative is based, offers a satisfactory explanation.

With the view of testing this hypothesis we examined the rotatory powers of tetramethyl glucose in various alkyl halides, and contrasted the values obtained with those found in ordinary solvents.

The alkylated glucose required was prepared from tetramethyl α -methylglucoside (*loc. cit.*) by boiling an aqueous solution containing 10 per cent. of the alkylated glucoside and 12 per cent. of the hydrogen chloride for thirty minutes. In this way the yield of the crystalline sugar obtained was increased to 87 per cent. of the theoretical amount. The compound was recrystallised several times from light petroleum in order to convert it into the pure α -form. The solutions used for the determinations were uniformly 5 per cent., the concentrations being controlled by means of density determinations. In each case the initial rotatory power was determined as rapidly as possible, after which a trace of alcoholic ammonia was added to promote mutarotation. The permanent values found in the various solvents are contrasted in the following table:

Solvent.	$[\alpha]_D^{20^\circ}$.	Solvent.	$[\alpha]_D^{20^\circ}$.
Acetone	+89.6°	Methyl iodide	+75.2°
Benzene	88.9	Ethyl iodide	78.3
Carbon tetrachloride...	84.8	Ethyl bromide	78.7
Chloroform.....	84.1	Propyl iodide.....	77.5
Water	83.3	<i>iso</i> Propyl iodide.....	78.6
Alcohol ..	83.1		

It will be seen that the effect of alkyl halides is invariably to lower the optical rotatory powers considerably, and this was further demonstrated by examination of solutions in benzene and carbon tetrachloride of the sugar, together with 1 molecular proportion of methyl iodide. Even this small quantity of the alkyl halide lowered the specific rotatory powers notably, the values then observed being $[\alpha]_D^{20^\circ}$ 83.5° and $[\alpha]_D^{20^\circ}$ +81.0° respectively.

It has already been noted (*loc. cit.*) in the case of methyl iodide that this lowering of the rotatory power is not due to the establishment of a different equilibrium in the dissolved sugar, but to a specific effect of the solvent. It is only, however, when the changes undergone by the various solutions during cooling are taken into consideration that evidence is obtained which leads to the conclusion that alkyl iodides form oxonium derivatives with the sugar. For this purpose we utilised the various solutions, already referred to, which had attained the permanent rotatory powers, and determined these at

temperatures ranging from $+40^{\circ}$ to -20° . The conditions of the experiments, which were strictly uniform in every case, may be mentioned here. For temperatures above 0° , a 2-dm. jacketed tube was used, but at lower temperatures a 1-dm. tube, adapted for the use of freezing mixtures and provided with caps containing calcium chloride, was substituted. A thermometer reading to $1/20^{\circ}$ was used throughout, and the concentrations at the different temperatures were controlled by density estimations. Generally each solution was maintained at least one hour at 0° and at -10° before the observations were taken, and in each case, after cooling, the solutions were reheated to 20° and the rotatory powers at this temperature redetermined. Throughout the work precautions were taken to prevent either the access of moisture or evaporation of the solvent.

Our results show that in the case of solutions in acetone, chloroform, or carbon tetrachloride, a continuous and regular increase in specific rotatory power takes place on cooling from $+20^{\circ}$ to -20° , and the same holds true for solutions in benzene within the available range of temperature. Moreover, on reheating the cooled solutions once more to $+20^{\circ}$, the rotatory powers now found for the various intermediate temperatures corresponded with those previously determined for the same temperatures during the cooling process.

Solvent.	$[\alpha]_D^{20^{\circ}}$	$[\alpha]_D^{10^{\circ}}$	$[\alpha]_D^{5^{\circ}}$	$[\alpha]_D^{0^{\circ}}$	$[\alpha]_D^{-10^{\circ}}$	Behaviour on
						reheating to 20° .
Benzene	$+88.9^{\circ}$	$+89.7^{\circ}$	$+90.3^{\circ}$	—	—	Initial $[\alpha]_D$ constant
Carbon tetrachloride	84.8	87.3	—	$+87.8^{\circ}$	$+89.9^{\circ}$	„ „
Chloroform.....	84.1	85.1	—	86.2	87.2	„ „
Acetone	89.6	92.4	—	96.1	96.9	„ „

On the other hand, it was found that solutions in alkyl halides behaved in a different fashion, as the specific rotatory powers at first increased regularly with fall of temperature, and then suddenly diminished rapidly on further cooling.

The following table contains the results obtained in the case of the solution in ethyl iodide, which serves as a typical example :

Temperature.	20° .	10° .	0° .	-5° .	-10° .
Specific rotatory power	$+78.4^{\circ}$	$+79.7^{\circ}$	$+81.6^{\circ}$	$+83.9^{\circ}$	$+75.3^{\circ}$

This abrupt fall in the values between -5° and -10° is naturally in itself no proof that association of the sugar and solvent had taken place. On reheating the cooled solution from -10° to $+20^{\circ}$, however, the initial specific rotatory power at the latter temperature was $[\alpha]_D^{20^{\circ}} + 81.2^{\circ}$, a value which is higher than that originally found ($+78.4^{\circ}$). On standing, moreover, at constant temperature, distinct mutarotation was observed until practically the original permanent value ($[\alpha]_D^{20^{\circ}} + 78.8^{\circ}$) was attained. As this change proceeded by itself very slowly, but was much hastened by the addition of a trace of

alcoholic ammonia, it seems to be due to the sugar partially undergoing tautomeric change in the sense $\alpha \rightarrow \beta$. The solution on reheating to 20° must therefore have contained excess of the α -isomeride, and this result is accounted for by the assumption that at the low temperature combination between the α -sugar and ethyl iodide had taken place, the removal of the α -form being then followed by a partial transformation of the uncombined portion of the sugar in the direction $\beta \rightarrow \alpha$ in order to restore the equilibrium. The first effect of reheating the solution would be to dissociate the unstable additive compound, and thus liberate the α -sugar. At 20° , the dissociation is practically complete, and the slower tautomeric change of the sugars is then indicated by mutarotation.

According to our explanation of the above results, the complete cycle of optical changes produced on cooling such solutions and then reheating them to the initial temperature should be: (1) a fall in rotatory power due to formation of an oxonium derivative. (2) Upward mutarotation at the low temperature, due to the change $\beta \rightarrow \alpha$ in the uncombined sugar. (3) On reheating, a rapid rise in rotatory power, resulting from the dissociation of the oxonium derivative. (4) Downward mutarotation at the higher temperature, due to the change $\alpha \rightarrow \beta$ in the sugar.

It might be expected that there would be a practical difficulty in observing all these optical effects, as the tautomeric change in the uncombined sugar must proceed simultaneously with the formation or dissociation of the oxonium derivative. As a matter of fact, the latter changes are extremely rapid, whilst the mutarotation of the sugar in alkyl halide solution is comparatively slow. It should thus be possible to observe in succession both series of optical changes. On cooling, the rotatory power of the solution should at first diminish rapidly, and afterwards increase slowly at the same temperature. The converse changes at constant temperature should be observed on heating the solution to a point at which the dissociation of the oxonium derivative takes place.

This cycle of changes was best realised in the case of a solution of tetramethyl glucose in isopropyl iodide, as the latter displays the readiest tendency to form an oxonium derivative with the sugar. The solution of the equilibrium mixture of the sugar was rapidly cooled in the polarimeter tube and maintained at 0° . An air thermometer was immersed in the liquid, and readings were taken as soon as the temperature was constant. The initial specific rotatory power observed at 0° was $[\alpha]_D^{0^\circ} + 80.1^\circ$, and this rapidly diminished to $[\alpha]_D^{0^\circ} + 74.1^\circ$. The change due to addition of the iodide was now complete. On adding a trace of alkali, mutarotation occurred, the specific rotatory power increasing to $[\alpha]_D^{0^\circ} + 77.1^\circ$. After standing for eight hours at 0° , the

solution was heated rapidly to 20° and maintained constantly at this temperature. The reverse optical changes were then observed; the rotatory power increased from the initial value, $[\alpha]_D^{20^\circ} + 78.4^\circ$, to a maximum, $[\alpha]_D^{20^\circ} + 80.6^\circ$, and afterwards diminished to $[\alpha]_D^{20^\circ} + 78.0^\circ$.

The complete results for this solution are tabulated below :

Changes in Specific Rotation at Constant Temperature.

Initial $[\alpha]_D^{0^\circ}$.		Minimum $[\alpha]_D^{0^\circ}$.		Final $[\alpha]_D^{0^\circ}$.
+ 80.1°	→	+ 74.1°	→	+ 77.1°
Initial $[\alpha]_D^{20^\circ}$.		Maximum $[\alpha]_D^{20^\circ}$.		Final $[\alpha]_D^{20^\circ}$.
+ 78.4°	→	+ 80.6°	→	+ 78.0°

We have observed a similar series of optical changes at constant temperature in solutions of the sugar in ethyl iodide or *n*-propyl iodide which had been cooled for three hours in a mixture of solid carbon dioxide and ether, and then rapidly heated to 20° and 30° respectively. The observations were :

Solution in Ethyl Iodide.

Initial $[\alpha]_D^{30^\circ}$.		Maximum $[\alpha]_D^{30^\circ}$.		Final $[\alpha]_D^{30^\circ}$.
+ 77.4°	→	+ 79.5°	→	+ 76.8°

Solution in n-Propyl Iodide.

Initial $[\alpha]_D^{30^\circ}$.		Maximum $[\alpha]_D^{30^\circ}$.		Final $[\alpha]_D^{30^\circ}$.
+ 76.8°	→	+ 78.1°	→	+ 76.5°

In view of the above results, we accepted, in our experiments with other alkyl halides, the observation of a sudden diminution of rotatory power on cooling, together with subsequent mutarotation on reheating, as evidence of association of the sugar with the solvent. In addition to alkyl halide solutions, positive results were also obtained in the case of solutions of the sugar in chloroform or carbon tetrachloride containing a molecular proportion of methyl iodide or hydrogen chloride.

Solution in Methyl Iodide.

In this case, owing to the volatility of the solvent, it was found impossible to preserve the concentration of the solution accurately throughout the series of observations, and densities were therefore not taken. The observed rotatory powers are, however, quoted, as, in spite of the contraction of the liquid on cooling, the solution showed the same regularities as other alkyl iodides.

Temperature	20°.	10°.	5°.	0°.	-10°.
Observed rotatory power ...	+ 6.84°	+ 7.36°	+ 7.48°	+ 7.62°	+ 7.08°

Solution in n-Propyl Iodide.

Temperature	40°.	30°.	20°.	10°.	0°.
Specific rotatory power.....	+75·8°	+77·8°	+77·6°	+77·3°	+75·4°

In this case little evidence was given of addition, and the subsequent mutarotation at 20° was slight.

$$[\alpha]_D^{20^\circ} + 77.8^\circ \longrightarrow [\alpha]_D^{20^\circ} + 76.2^\circ.$$

Solution in isoPropyl Iodide.

Temperature	30°.	20°.	10°.	0°.	-10°.
Specific rotatory power.....	+77·7°	+78·6°	+79·2°	+72·8°	+70·6°

On reheating to 20°, $[\alpha]_D$ increased rapidly from +73·5° to +78·3° and then diminished slowly to +77°.

Solution in Carbon Tetrachloride containing one Molecular Proportion of Methyl Iodide.

Temperature.....	20°.	0°.	-10°.
Specific rotatory power	+81·0°	+81·2°	+77·0°

Solution in Carbon Tetrachloride containing one per cent. of Hydrogen Chloride.

Temperature	20°.	10°.	5°.	0°.	-5°.	-10°.
Specific rotatory power...	+79·6°	+79·9°	+80·2°	+81·8°	+79·9°	+79·4°

Rotations of α - and β -Modifications of Tetramethyl Methylglucoside in Alkyl Iodides.

Our results show that invariably the α -form of tetramethyl glucose becomes associated with alkyl halides more readily than the β -isomeride. This view was supported by experiments made with the α - and β -modifications of tetramethyl methylglucoside. In the case of glucosides, the problem under consideration is much simplified owing to the absence of ordinary mutarotation. In the cycle of optical changes already described for the case of a reducing sugar, conditions (2) and (3) are thus eliminated, and consequently any alterations in the rotatory power are due either to the formation or dissociation of the oxonium derivatives.

Tetramethyl α -methylglucoside, when cooled in acetone solution, showed practically a constant specific rotatory power. When dissolved in ethyl iodide, the value increased normally during cooling to 0°, but then diminished rapidly on further cooling. As in other cases in

which oxonium formation presumably occurred, heating the cooled solution to 0° had the effect of dissociating the additive compound and an increase of specific rotatory power at the constant temperature of 0° was thus observed. A solution of tetra-acetyl α -methylglucoside in *isopropyl* iodide showed the same regularities, but, on the other hand, tetramethyl β -methylglucoside gave no indication of addition when dissolved in ethyl iodide and similarly treated.

	Solvent.	$[\alpha]_D^{20^\circ}$	$[\alpha]_D^{10^\circ}$	$[\alpha]_D^{0^\circ}$	$[\alpha]_D^{-10^\circ}$
Tetramethyl α -methylglucoside	Acetone	+143.2°	—	+144.6°	+144.6°
"	Ethyl iodide ...	+138.1	+138.7°	+139.6	+132.9
Tetramethyl β -methylglucoside	Ethyl iodide ...	-17.3	-17.7	-18.6	-18.8
Tetra-acetyl α -methylglucoside	<i>iso</i> Propyl iodide	+127.8	+127.6	+129.0	+126.5

Specific Rotatory Powers of Tetramethyl Mannose at Different Temperatures.

Tetramethyl mannose and tetramethyl α -methylmannoside were found to behave in a similar manner to the corresponding glucose derivatives when dissolved in alkyl iodides, but the optical changes were not so pronounced.

	Solvent.	$[\alpha]_D^{20^\circ}$	$[\alpha]_D^{10^\circ}$	$[\alpha]_D^{0^\circ}$	$[\alpha]_D^{-10^\circ}$	$[\alpha]_D^{-15^\circ}$	Change in $[\alpha]_D$ on reheating to 20° .
(1) Tetramethyl mannose	Carbon tetra-chloride	+34.4°	+30.6°	+25.8°	+21.1°	—	nil
(2) Tetramethyl mannose	Ethyl iodide..	45.6	43.6	40.9	40.7	—	+48.0° +45.7°
(3) Tetramethyl α -methylmannoside	Carbon tetra-chloride	82.3	80.4	77.4	75.3	—	nil
(4) Tetramethyl α -methylmannoside	Carbon tetra-chloride + HCl	80.6	78.6	76.0	75.7	+75.8°	—

In experiments (2) and (4), the optical effect of association is to counterbalance the regular decrease in rotatory power observed on cooling solutions in non-associating solvents.

Experiments made with non-alkylated sugars or glucosides gave no positive results. Glucose, mannose, α -methylglucoside, and sucrose were selected for experiment, and the specific rotatory powers of each compound determined at the usual temperatures in methyl alcohol containing methyl iodide. The values found were in some cases slightly different from those obtained in pure methyl alcohol, but in no case was a change of rotatory power at constant temperature observed. It would thus appear that the presence of the etheric groups in the alkylated sugar increases the basicity of the γ -oxidic oxygen atom.

Similarly, we find that the specific rotatory power of a typical

hydroxy-etheral salt such as ethyl tartrate, although much diminished in ethyl iodide, shows no fluctuations corresponding to oxonium formation.

Rotations of Ethyl Tartrate at Different Temperatures.

Solvent.	$[\alpha]_D^{36^\circ}$	$[\alpha]_D^{30^\circ}$	$[\alpha]_D^{20^\circ}$	$[\alpha]_D^{10^\circ}$	$[\alpha]_D^0$	$[\alpha]_D^{-10^\circ}$	$[\alpha]_D^{-20^\circ}$
Carbon tetrachloride...	—	—	+0.98°	-1.1°	-3.4°	-4.7°	—
Ethyl iodide	+0.95°	inactive	-2.21	-4.47	-7.3	-8.8	-10.1°

Our results are best expressed graphically in the form of curves, the abscissæ representing temperatures and the ordinates specific rotatory powers.

In Fig. 1 the behaviour of solutions of tetramethyl glucose in various solvents is contrasted with that of the ethyl iodide solution.

FIG. 1.

The curves for ordinary solvents are seen to be quite normal, but in the case of the alkyl halide the sharp fall *AB* represents oxonium formation between -5° and -10° , whilst *CD* corresponds with the subsequent mutarotation at $+20^\circ$.

Fig. 2 shows the effect of adding one molecular proportion of either methyl iodide or hydrogen chloride to a solution of tetramethyl glucose in carbon tetrachloride. The initial rotatory power is much reduced, and the sharp descent of the curves below 0° indicates the oxonium formation.

In Fig. 3 the curve for the *isopropyl iodide* solution descends steeply from *A* to *B*, indicating that addition begins above 0° . The rapid change *CD* at 20° corresponds with the dissociation of the oxonium derivative.

FIG. 2.

Fig. 4 shows the complete cycle of changes observed with a solution of tetramethyl glucose in *isopropyl iodide*. The rapid fall *AB*

FIG. 3.

is due to oxonium formation, the subsequent rise *BC* at the same temperature indicates the conversion $\beta \rightarrow \alpha$ in the uncombined sugar, whilst at 20° the rise *DE* and subsequent fall *EF* correspond with the reverse changes.

In Fig. 5 the regular curve for tetramethyl α -methylglucoside in acetone solution is contrasted with the irregular curve obtained for the ethyl iodide solution. The curve for the β -isomeride dissolved in ethyl iodide falls, on the other hand, quite regularly.

There seems to be little doubt that it is the oxygen atom of the γ -oxidic ring which participates in the formation of oxonium compounds from alkylated sugars. Collie and Tickle have pointed out (*Trans.*, 1899, 75, 710) that compounds like dimethylpyrone, in which oxygen

FIG. 4.

Tetramethyl glucose in isopropyl iodide. Changes in specific rotatory power at 0° and +20°.

is linked to a penta-carbon ring, display the readiest tendency to form oxonium derivatives, whilst Bredig (*Zeit. Elektrochem.*, 1896, 3, 116) and Walker (*Ber.*, 1901, 34, 4117) find that ethylene oxide has only slight basic properties. It would thus appear that within certain limits the basicity of the oxygen atom increases with the introduction of more carbon atoms into the ring. Alkylated reducing sugars which possess a γ -oxidic structure, and therefore contain an oxygen atom linked in a tetra-carbon ring, might also be expected to form oxonium compounds. In view of the fact that not only alkylated sugars but

also alkylated glucosides enter into combination with alkyl halides, it is evident that the aldose does not react with these solvents in the aldehydic form, but as a γ -oxide.

It is, moreover, unlikely that any of the etheric oxygen atoms play a part in the addition of the alkyl halides, in view of the fact that the specific rotatory power of ethyl tartrate in ethyl iodide solution, although much lower than in carbon tetrachloride, undergoes a perfectly regular change between $+36^\circ$ and -20° .

Alkylation of Tetramethyl Glucose at Low Temperatures.

In confirmation of our results we have alkylated tetramethyl-glucose with silver oxide and methyl iodide at -10° and find that

FIG. 5.

although the action is slow, the sole product of the change is tetramethyl β -methylglucoside unmixed with the α -isomeride. The materials used were α -tetramethyl glucose (1 mol.), methyl iodide (10 mols.), and dry silver oxide (5 mols.). The sugar was dissolved in the iodide and cooled in a mixture of ice and calcium chloride. The silver oxide was then added in small quantities and the mixture kept actively stirred by a mechanical stirrer, precautions being taken to exclude moisture. After eight hours' treatment, during which the temperature varied from -15° to -10° , the product was extracted with ether. After removal of the solvent, the residue was extracted with light

petroleum, and in this way the product was separated from the sparingly soluble sugar. The extract on evaporation gave an oil which crystallised completely on standing. As the substance melted at 39—41° and behaved like a glucoside towards Fehling's solution, it was evidently tetramethyl β -methylglucoside, which was apparently the only product of the reaction.

Mutarotation of α -Tetramethyl Glucose.

As explained in the introduction, the permanent specific rotatory power of the sugar was determined in several solvents, and, as the material used consisted of the pure α -form, the mutarotation of each solution was observed.

The following table contains the results found in solvents in which the mutarotation of this compound has not hitherto been observed:

Solvent.	Initial $[\alpha]_D^{20^\circ}$.	Permanent $[\alpha]_D^{20^\circ}$.
Chloroform *	+ 87.1°	+ 84.1°
Carbon tetrachloride	92.8	84.9
Benzene	114.5	88.9
Methyl iodide	107.3	75.3
Ethyl iodide	86.7	78.3
Ethyl bromide.....	86.0	78.7

* The specimen of chloroform used contained free acid. This seems to have accelerated the change.

We are extending our work with the view of securing other examples in which oxonium formation may be detected by means of the polarimeter.

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