

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF THE UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD, UNIVERSITY OF ST. ANDREWS]

A POSSIBLE SOURCE OF ERROR IN DETERMINING THE CONSTITUTION OF DI- AND POLYSACCHARIDES

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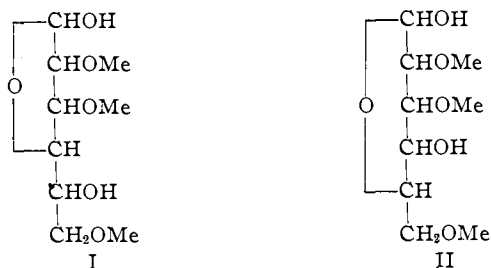
The results contained in the present communication confirm the idea expressed in former papers that the isolation of crystalline 2,3,6-trimethylglucose (m. p. 121°) from the hydrolysis products of a methylated carbohydrate does not provide decisive evidence as to the constitution of the parent compound. The evidence is, in fact, ambiguous as the compound under examination may equally be a derivative of normal glucose or of γ -glucose. This conclusion, which affects profoundly many investigations on the structure of disaccharides and of polysaccharides based upon glucose, creates a position which was not unforeseen by us.

From the time that Irvine and Black¹ proved that maltose gives the same methylated sugars as does cellobiose, it has been evident that it is insufficient merely to identify the sugars formed on hydrolyzing a methylated disaccharide and to determine the structure of these scission products. There remains another factor of equal importance, as proof must be forthcoming that the methylated hexoses isolated actually contain the same oxygen-ring systems that were present in the initial disaccharide. Unless this condition is fulfilled the conclusions drawn from the results of methylation may be misleading. This point was emphasized by one of us several years ago² in discussing the constitution of glucosediacetone but its importance has been frequently overlooked by other investigators.

In most constitutional studies of disaccharides by the method now under discussion, a trimethyl and a tetramethyl hexose are formed, and in many cases the accepted structure of the parent sugar has been arrived at merely by attaching two hexose residues in the position best suited to accommodate the result. Of the methylated sugars which function as reference compounds in this type of research, greatest importance must be attached to 2,3,6-trimethylglucose, which has been isolated from such sugars as maltose, cellobiose and lactose, to quote only prominent examples. Now although certain sugars (*e. g.*, 2,3,4,6-tetramethylglucose) are incapable under ordinary conditions of undergoing any shift in the internal oxygen-ring, a circumstance which renders their isolation of decisive value in constitutional studies, the same assurance does not extend to the case of 2,3,6-trimethylglucose. As Irvine and Black pointed out, this sugar can exist in an unstable modification (Formula I), which has only a transient existence owing to its transformation into the stable form (Formula II), actually isolated.

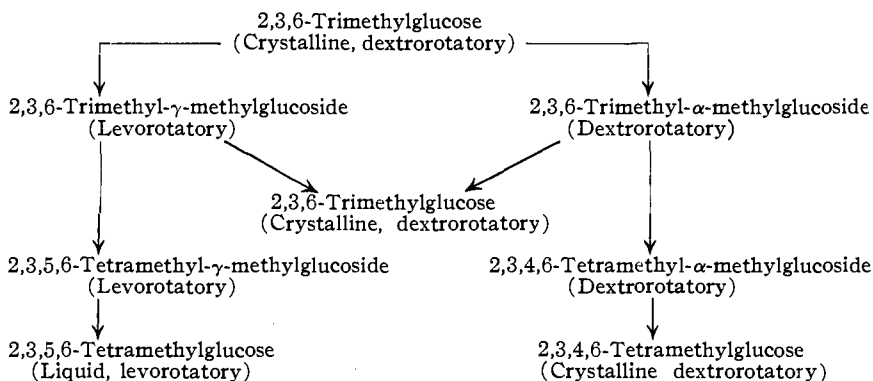
¹ Irvine and Black, *J. Chem. Soc.*, 129, 862 (1926).

² Irvine and Patterson, *ibid.*, 121, 2149 (1922).

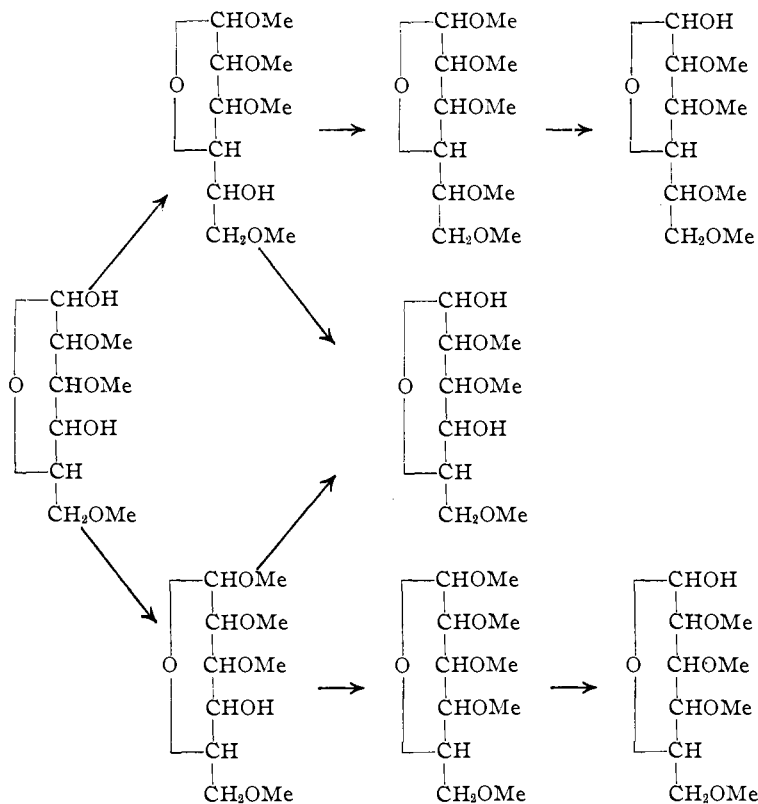


It follows that two distinct types of disaccharide containing, respectively, amylene oxide and butylene oxide rings in the reducing hexose residue (*e. g.*, glucose-5-glucoside and glucose-4-glucoside) would give precisely the same methylated sugars when the customary methods are applied and in order to ascertain if this view is valid we have examined a test case. We have converted 2,3,6-trimethylglucose into isomeric 2,3,6-trimethyl methylglucosides which differ only in the oxygen linkage present in each case. One of these compounds is definitely a γ -form (corresponding to Formula I) as it is convertible into 2,3,5,6-tetramethyl- γ -glucose, whilst the other belongs, equally definitely, to the normal type (corresponding to Formula II), as is shown by its transformation into 2,3,4,6-tetramethylglucose. Nevertheless these isomerides, when subjected to hydrolysis, gave crystalline 2,3,6-trimethylglucose as the only product. The result is convincing and shows that the isolation of the crystalline variety of 2,3,6-trimethylglucose in any structural investigation can be just as misleading as the isolation of levorotatory fructose by the hydrolysis of sucrose. The cases are analogous. It cannot be too frequently emphasized that the interconversion of a sugar into isomeric forms of the same sugar is not restricted to change in α - or β -configuration of the reducing group, but includes in addition alteration in the position of the internal oxygen-gering where such a change is possible.

The scheme of this part of the research may be summarized as



When these results are expressed in terms of structural formulas the intramolecular changes involved may be followed.



The test case submitted above is sufficiently decisive to show that much further work and the application of new methods are alike necessary before definite constitutions can be assigned to the disaccharides and polysaccharides which are convertible into 2,3,6-trimethylglucose and, for the time being, an arbitrary choice should be made between the two alternative oxygen-ring systems present in starch and cellulose, respectively; it has been, in fact, the detailed study of these polysaccharides which has led to the revision of the structural formulas of the corresponding disaccharides.

The investigation has also revealed that the oxidation reactions of methylated sugars which are frequently employed in determining constitution are likewise invested with complications. In such reactions, precisely as in glucoside formation, the oxygen-ring of a methylated sugar or of its derivatives may alter from one position to another so that, for example, the starting material may be an amylen oxide and the final product a γ -lactone containing the butylene oxide ring. In fact, the oxidation

of one and the same substance may give rise under varying conditions to either γ - or δ -lactones, thus rendering the structural evidence ambiguous. One example may be quoted. Crystalline 2,3,6-trimethylglucose if oxidized with bromine water under conditions which permit of the accumulation of hydrogen bromide yields directly the γ -lactone of 2,3,6-trimethylgluconic acid as the main product. In sharp distinction, when the sugar is oxidized by the same reagent but in the absence of halogen acid, the δ -lactone is produced in preponderating amount. There is probably no reaction of a reducing sugar in which similar changes of the internal oxygen ring do not take place to some extent provided the necessary hydroxyl groups are unsubstituted and this possibility cannot with safety be overlooked.

This consideration raises the question of what factors are operative in converting sugars into their γ -forms. Once more selecting 2,3,6-trimethylglucose as a test case, we find that change of temperature has little or no effect in altering the amount of the γ -form present in solution. The customary experimental procedure in which the γ -derivatives of a sugar are prepared at low temperatures thus seems to be dictated by the instability of these compounds rather than by alteration of the equilibrium stable form \rightleftharpoons γ -form. On the other hand, the influence of halogen acid in converting a sugar into γ -forms is profound and we have shown that both hydrogen bromide and hydrogen chloride are particularly effective. Having engaged on this problem, we are now making a systematic survey of the conditions under which all types of sugars can react in γ -modifications and in the course of the work have examined cases where, on theoretical grounds, no such conversion is possible. One of these examples is furnished by 2,3,4,6-tetramethylglucose which, when dissolved in acid methyl alcohol under conditions favorable to the formation of a γ -glucoside, shows a steady diminution in dextro-rotation until the reducing action upon Fehling's solution vanishes. These results might be regarded as sufficient to indicate that the sugar was actually reacting in a γ -form, which it could do only by transference of a methoxyl group from one position to another. We find, however, that such is not the case and that the changes mentioned are due to the formation of the corresponding semi-acetal which readily breaks down to regenerate the parent sugar. The result is quoted as an additional example emphasizing the caution which must be exercised by workers in this field even when employing processes apparently well-defined and decisive.

Experimental

Preparation of 2,3,6-Trimethylglucose.—Cotton cellulose was subjected to graded acetolysis according to the method described by Irvine and Robertson³ and the amor-

³ Irvine and Robertson, *J. Chem. Soc.*, 129, 1488 (1926).

phous mixture of acetates thus obtained was methylated by the joint use of methyl sulfate and 60% sodium hydroxide, the product being isolated in the usual manner. Six methylations with 30% caustic soda were necessary in order to raise the methoxyl content to 45.8%. In this way a mixture of trimethyl dextrins was obtained in the form of a yellow viscous sirup which weighed, on an average, 50% of the cellulose originally taken. The process is convenient, provided the conditions of acetolysis have been determined for the particular form of cellulose employed.

The sirup was then hydrolyzed by boiling with 8% hydrochloric acid for thirty minutes and the liberated sugar was thereafter isolated and purified in the usual manner. The yield of crystalline product, showing m. p. 121° and $[\alpha]_D +70.9^\circ$, amounted to 40% of the methylated sirup from which it was prepared.

Conversion into 2,3,6-Trimethyl- γ -methylglucoside.—The following is an account of one typical preparation. The sugar (10 g.) was dissolved in a liter of methyl alcohol containing 0.3% of hydrogen chloride and the solution was maintained at the temperature of the room, samples being abstracted at intervals in order to determine changes in specific rotation and in the reaction toward Fehling's solution. After remaining constant for an initial period, the optical activity diminished regularly and ultimately became levo, a constant value being observed when the reaction had proceeded for one hundred hours. At this stage the product behaved like a glucoside toward Fehling's solution. On plotting specific rotations against time a smooth curve was obtained and only significant figures are therefore quoted.

Time	$[\alpha]_D$	Time	$[\alpha]_D$
3 Minutes	+70.5°	39 Hours	+ 7.1°
10 Minutes	+70.5	72 Hours	-14.0
45 Minutes	+70.5	88 Hours	-17.4
15 Hours	+32.5	100 Hours	-23.5

It may be mentioned that the same condensation has already been carried out on a small scale by Denham and Woodhouse⁴ and by Irvine and Hirst.⁵ These observers obtained, however, a different end-point, *viz.*, $[\alpha]_D -33$ and -36° , respectively, the increased levorotation being due in all probability to the slow formation of secondary products. After neutralizing with silver carbonate and removal of the solvent, the residual sirup was dissolved in water and extracted with chloroform in order to free the glucoside from traces of unchanged sugar. On evaporation of the solvent, trimethyl- γ -methylglucoside remained as a sirup which was purified by distillation at low pressures. The yield was nearly quantitative (b. p. 180° (0.05 mm.); OMe, 51.8%; n_D^{17} 1.4581; $[\alpha]_D$ in water -26.3° for $c = 1.20$).

Anal. Calcd. for $C_{10}H_{20}O_6$: C, 50.85; H, 8.47. Found: C, 50.79; H, 8.44.

Proof that the Above Glucoside Belongs to the γ -Series.—The specific rotation of the compound and its instability to dilute acid might be accepted as sufficient evidence that the form of trimethyl methylglucoside described above is a derivative of γ -glucose, but it was considered advisable to confirm this point by conversion into tetramethyl- γ -methylglucoside. The glucoside was accordingly subjected to two successive treatments with silver oxide and methyl iodide, the product being isolated in the usual manner and purified by distillation (b. p. 115° (0.35 mm.)). The clear sirup thus obtained gave the correct analytical figures and was identical with the tetramethyl- γ -methylglucoside first described by Irvine, Fyfe and Hogg.⁶

⁴ Denham and Woodhouse, *J. Chem. Soc.*, 111, 249 (1917).

⁵ Irvine and Hirst, *ibid.*, 121, 1213 (1922).

⁶ Irvine, Fyfe and Hogg, *ibid.*, 107, 524 (1915).

	Found	Quoted by Irvine, Fyfe and Hogg
n_D^{15}	1.4454	1.4458
$[\alpha]_D$ in water.....	-16.0°	-14.6°
B. p., °C.....	115 (0.35 mm.)	106 (0.25 mm.)
OMe.....	61	61 (Calcd. 62%)

In order to obtain an additional proof the tetramethyl- γ -methylglucoside was hydrolyzed by heating at 100° with *N*/100 hydrochloric acid. The action was followed polarimetrically, the curve of the optical changes being identical with that plotted from the results of Irvine, Fyfe and Hogg for the hydrolysis of their original preparation of tetramethyl- γ -methylglucoside. The highly characteristic change in which the specific rotation first increased to a maximum negative value and then decreased to a constant was duly observed.

Time of heating	$[\alpha]_D$	Time of heating	$[\alpha]_D$
0	-11.1°	90 Minutes	-19.6°
30 Minutes	-25.9	150 Minutes	- 9.8
60 Minutes	-24.4	200 Minutes	- 9.0 (constant)

The sugar formed in the reaction was isolated by the usual processes and distilled under diminished pressure. A clear viscous sirup was thus obtained which decolorized alkaline potassium permanganate solution in the cold and proved to be tetramethyl- γ -glucose (found: OCH_3 , 51.3%; n_D^{15} 1.4590; $[\alpha]_D$ in benzene -15.4°; b. p. 130° (0.15 mm.); quoted for tetramethyl- γ -glucose: OCH_3 , 52.5%; n_D^{15} 1.4585; $[\alpha]_D$ in benzene -17.0°; b. p. 122° (0.05 mm.)). It follows from the above sequence of reactions that the parent trimethyl methylglucoside definitely belongs to the γ -type.

Hydrolysis of Trimethyl- γ -methylglucoside.—This reaction was carried out under varying conditions in order to ascertain if, under any circumstances, the glucoside yields the corresponding γ -sugar.

I. A 5% solution of the glucoside in *N*/10 aqueous hydrochloric acid was kept at 100°. The rotation altered regularly from levo to dextro, and the end value $[\alpha]_D$ +65.4° was reached.

II. In this case the acid concentration was diminished to *N*/100 but otherwise the conditions were the same as in No. I. The hydrolysis was naturally slower and after twelve hours' treatment the solution had acquired the optical value $[\alpha]_D$ +40.1°, when the reaction was arrested.

III. Duplicate with Experiment II, but conducted at 60°. Here again the rotation, after the usual initial rise and fall in the levo sense, altered regularly to dextro.

In each of the above experiments the sugar was isolated by the customary processes and the product, which crystallized with unusual ease, proved to be the stable form of 2,3,6-trimethylglucose. Finally, the hydrolysis of the glucoside was conducted under the mildest possible conditions (solvent *N*/100 hydrochloric acid; *T.* 40°) and the reaction was arrested before completion. This procedure enabled the initial optical changes to be observed and revealed the presence of the α - and β -forms of the γ -type.

$[\alpha]_D$	Initial	Maximum levo	Maximum dextro
	-24.8°	-45°	+65°

A sample of the liquid was withdrawn when the specific rotation was -5°, the acid was neutralized and the sugar isolated together with unaltered glucoside. The latter was extracted from aqueous solution by means of chloroform and showed $[\alpha]_D$ -27°, while from the aqueous portion trimethylglucose was obtained. This crystallized at once on evaporation of the solvent, and proved to be the normal variety melting at 121° and showing $[\alpha]_D$ +70° in water.

Hydrolysis of 2,3,6-Trimethyl α - and β -Methylglucoside.—This compound in α - and β -forms was prepared from the sugar and hydrolyzed according to the methods used by Irvine and Macdonald.⁷ The results obtained were exactly as described and the dextrorotatory sugar was regenerated on heating with acids, it being observed that when obtained in this way the compound crystallized with great ease.

Oxidation of 2,3,6-Trimethylglucose to 2,3,6-Trimethylglucono- γ -lactone.—Six grams of crystalline trimethylglucose (m. p. 121°) was dissolved in 30 cc. of water and 7.4 g. of bromine was added drop by drop with constant shaking. During the reaction, which extended for eight hours, the liquid was thoroughly cooled in ice. The subsequent procedure was exactly as described by Purdie and Irvine,⁸ the final product being purified by distillation. In this way a clear viscous liquid, b. p. 140° (0.15 mm.), was obtained while a thick sirup which also possessed the properties of a methylated lactone remained undistilled. As the molecular weight of this residue was 409 it evidently represented either a polymerized lactone or a lactide. On the other hand, the distillate proved to be the monomolecular form of 2,3,6-trimethylglucono- γ -lactone (calcd. for $C_9H_{16}O_6$: OCH_3 , 42.2. Found: 42.6). The behavior of the compound toward sodium hydroxide was characteristic of a lactone and the correct amount of alkali was required. In addition, when dissolved in aqueous alcohol ($c = 1.054$) the specific rotation showed the usual change, $[\alpha]_D$ decreasing from +81.5° \rightarrow 74° in twenty hours. In a second preparation of the lactone by means of bromine the procedure was varied, the treatment of the acid solution with silver oxide being omitted so as to exclude the possibility of silver trimethylgluconate being formed. Obviously, the intervention of this reaction would invalidate the evidence of the experiment. After removal of the excess of bromine the product of the oxidation was extracted with chloroform and isolated. Once more the same trimethylglucono- γ -lactone was formed and the specific rotation in aqueous alcohol showed the characteristic change +91.5 \rightarrow 70.3°.

Proof that the Lactone Belongs to the γ -Series.—The trimethyl lactone was methylated in the customary manner with silver oxide and methyl iodide and, after two such treatments, the product was distilled. The clear mobile liquid thus obtained, b. p. 100–105° (0.15 mm.), n_D 1.4460, proved to be tetramethylglucono- γ -lactone.

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.28; H, 7.69; OCH_3 , 52.99. Found: C, 51.0; H, 7.9; OCH_3 , 52.1; $[\alpha]_D$ in absolute ethyl alcohol +52.4° for $c = 1.867$ and in aqueous alcohol +48.9° \rightarrow 48.4° in twelve hours for $c = 1.40$. On titration, 0.1375 g. required 56.5 cc. of $N/100$ sodium hydroxide (calcd., 58.5 cc.).

Oxidation of 2,3,6-Trimethylglucose to 2,3,6-Trimethylglucono- δ -lactone.—To a solution of 5 g. of the sugar in 50 cc. of water were added 8 g. of calcium bromide and excess of finely powdered calcium carbonate. Chlorine was led into the solution at intervals under thorough cooling and agitation, and the reaction was continued for eight hours. The calcium salts in solution were decomposed by the addition of the required amount of oxalic acid, the product extracted with chloroform and isolated in the usual manner, and finally methylated by the silver oxide reaction. On distillation, a specimen of tetramethylgluconolactone, b. p. 130° (0.8 mm.), n_D 1.4534, was obtained.

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.28; H, 7.69; OCH_3 , 53. Found: C, 51.08; H, 7.79; OCH_3 , 52.8.

The material was a mixture of γ - and δ -forms as shown by the value of the rotation, $[\alpha]_D$ +86.0° in alcohol, and by the optical change on dissolving in aqueous alcohol, when the initial specific rotation of +81.6° diminished in the course of two days to the constant value +49.6°.

⁷ Irvine and Macdonald, *J. Chem. Soc.*, 127, 1517 (1926).

⁸ Purdie and Irvine, *ibid.*, 83, 1033 (1903).

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Summary

1. 2,3,6-Trimethyl- γ -methylglucoside has been prepared and its constitution determined by conversion into 2,3,5,6-tetramethyl- γ -glucose. The glucoside therefore conforms to the γ -type.

2. When hydrolyzed, the liberated 2,3,6-trimethyl- γ -glucose transforms into the stable crystalline variety which is the only form isolated.

3. The oxidation of 2,3,6-trimethylglucose by bromine may lead to either the corresponding γ - or δ -lactones according to variations in the concentration of hydrogen bromide present.

4. The presence of halogen hydride is a determining factor in converting 2,3,6-trimethylglucose into the γ -form.

5. The combined results show that the formation of 2,3,6-trimethylglucose in the constitutional studies of carbohydrates by the methylation method is ambiguous as are also the results of oxidation methods in certain cases.

ST. ANDREWS, SCOTLAND

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

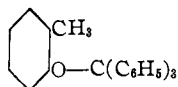
THE REARRANGEMENT OF TRIPHENYLMETHYL ORTHO-TOLYL ETHER

BY GEORGE S. PARSONS AND C. W. PORTER

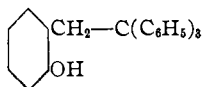
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In 1926 Schorigin¹ prepared the triphenylmethyl ether of *o*-cresol and a year later Van Alphen² made the corresponding derivative of phenol. These ethers rearrange when heated with hydrochloric acid or with zinc chloride. In the case of phenyl triphenylmethyl ether the triphenylmethyl group migrates from the oxygen atom to the *p*-position in the ring, as would be expected, but the change in the case of *o*-tolyl triphenylmethyl ether was reported by Schorigin and by Van Alphen as a migration of the triphenylmethyl group from the oxygen atom to the ortho side chain.



o-Tolyl triphenylmethyl ether



α -2-Hydroxyphenyl- β,β,β -triphenylethane

The evidence in support of this mechanism comprised the isolation of triphenylcarbinol as an oxidation product and triphenylmethane as a

¹ Schorigin, *Ber.*, 59, 2506 (1926).

² Van Alphen, *Rec. trav. chim.*, 46, 287 (1927).