

be accompanied to some extent by alteration in the position of the oxygen ring in the glucose component.

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

SYNTHESIS OF 2,3,6-TRIMETHYLGLUCOSE

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2,3,6-Trimethylglucose was first prepared by Denham and Woodhouse¹ who, working in this Laboratory, obtained the sugar by hydrolyzing methylated cellulose; in justice to these workers whose pioneer efforts have been ignored by others, it is advisable to recall that we also owe to them the use of methyl sulfate as a methylating agent applicable to carbohydrates.

Obviously the constitution of 2,3,6-trimethylglucose is of unusual importance as the structural formulas meanwhile assigned to many disaccharides and to all the polysaccharides derived from glucose are based ultimately on the capacity of these particular compounds to be converted into this variety of trimethylglucose. The point is elaborated in a previous paper² where it is, however, emphasized that the formation of 2,3,6-trimethylglucose by the hydrolysis of a methylated saccharide is not conclusive evidence of structure as it fails to discriminate between the normal and γ -types of glucose residues. This much is nevertheless certain—when 2,3,6-trimethylglucose is obtained in a structural study conducted by the methylation method the parent compound must have contained unsubstituted hydroxyl groups in positions 2, 3 and 6; no further conclusions are justifiable.

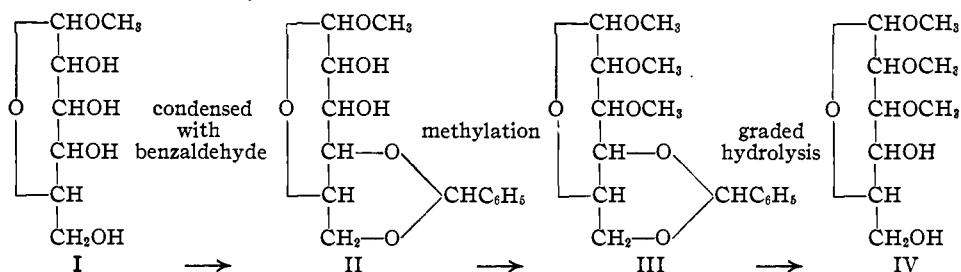
The evidence upon which the constitution of this methylated sugar depends has been accumulated gradually. In the first place Denham and Woodhouse¹ showed that the compound failed to form an osazone and that when converted into the corresponding heptonic lactone a methoxyl group was eliminated. In this way, methyl groups are definitely assigned to positions 2 and 3 in the glucose chain and the proof was completed by Irvine and Hirst,³ who found that when the sugar was oxidized to a dibasic acid one of the methyl groups was removed and this group must have occupied position 6. Confirmation of the formula was supplied by Irvine and McGlynn,² who showed that this particular trimethylglucose could react equally as a normal or as a γ -sugar, from which it follows that groups 1, 4 and 5 must be unmethylated.

¹ Denham and Woodhouse, *J. Chem. Soc.*, 105, 2357 (1914).

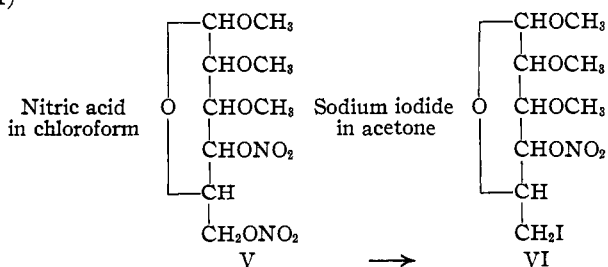
² Irvine and McGlynn, *THIS JOURNAL*, 54, 356 (1932).

³ Irvine and Hirst, *J. Chem. Soc.*, 121, 1213 (1922).

Although there seemed no reason to doubt the validity of these arguments it was advisable to confirm, by synthetical methods, a constitutional formula upon which so much depends and this we have succeeded in doing. The starting point was α -methylglucoside which was converted by improved methods into the 2,3-dimethylmethylglucoside (formula IV) described by Irvine and Scott⁴



The constitution of compound IV is known as the parent sugar can be oxidized to di-methoxysuccinic acid $\begin{array}{c} \text{CHOCH}_3-\text{COOH} \\ | \\ \text{CHOCH}_3-\text{COOH} \end{array}$ which was identified by conversion into the corresponding dimethoxysuccinamide.⁵ There was every assurance, therefore, that the subsequent synthetical reactions were carried out on a substituted methylglucoside containing methyl groups in positions 2 and 3. Advantage was then taken of the reaction discovered by Oldham,⁶ who showed that when position 6 of the glucose molecule is nitrated the nitrate group can be replaced by iodine. Dimethylmethylglucoside (IV) was accordingly converted into 2,3-dimethylmethylglucoside-4,6-dinitrate (V) and thereafter into 2,3-dimethyl-6-iodomethylglucoside-4-nitrate (VI)

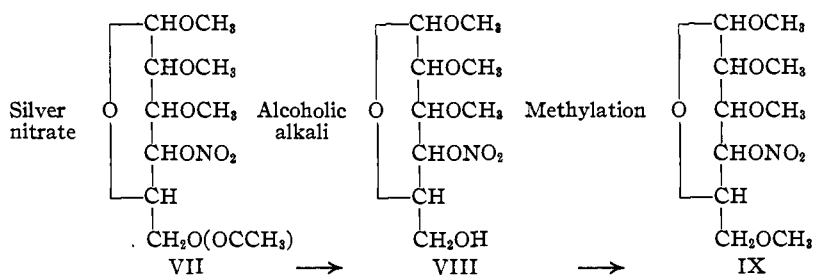


By acting on the iodo derivative with silver acetate and hydrolyzing the product (VII) with alcoholic alkali, 2,3-dimethylmethylglucoside-4-mononitrate (VIII) was obtained and the free hydroxyl group generated in position 6 was thereafter methylated to give 2,3,6-trimethylmethylglucoside-4-mononitrate (IX).

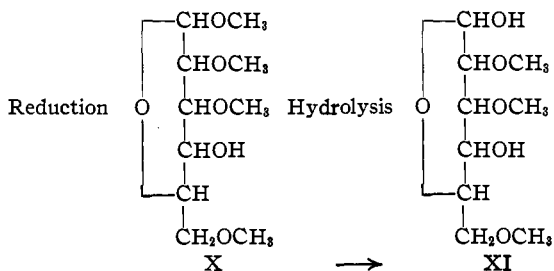
⁴ Irvine and Scott, *J. Chem. Soc.*, 103, 575 (1913).

⁵ Purdie and Irvine, *ibid.*, 79, 957 (1901).

⁶ Oldham, *ibid.*, 127, 2840 (1925).



Finally, the nitrate group was eliminated from position 4 by reduction and the trimethylmethylglucoside (X) thus produced was hydrolyzed to give 2,3,6-trimethylglucose (XI).



The product crystallized readily on nucleation and proved to be identical in every respect with the trimethylglucose obtained from methylated lactose, cellobiose, cellulose, starch and glycogen. On the whole, the synthesis proceeded smoothly although the intermediate compounds were uncrystallizable sirups which could not be further purified by distillation owing to the instability of the nitrate groups. Poor yields were obtained in replacing iodine by acetyl and a complication was introduced by the formation of some trimethylanhydroglucose during the reduction of the nitrate group in position 4. This tendency for nitrogen to be eliminated along with a methyl group is, of course, already well recognized.

Experimental

The account of the experimental methods is confined to compounds prepared for the first time in the course of the synthesis.

Nitration of 2,3-Dimethylmethylglucoside.—Two optional methods were employed, that of Gibson⁷ and the simpler process described by Oldham,⁸ the latter gives better yields and a purer product. A 5% solution of dimethylmethylglucoside (12 g.) in chloroform containing 30% of nitric acid was kept at room temperature for five minutes and poured into a separating funnel containing ice. After shaking, the chloroform layer was run off and dried over sodium sulfate, the solvent being then removed at 60°. The residue was dissolved in methyl alcohol so as to make a 10% solution and boiled under a reflux condenser for three hours with barium carbonate. On removing

⁷ Gibson, *Proc. Roy. Soc. Edinburgh*, **28**, 705 (1908).

the solvent and extracting with ether the product was finally isolated as a sirup which was dried at 100° in a vacuum; yield (13.8 g.) or 89%.

Anal. Calcd. for $C_9H_{16}O_{10}N_2$: OCH_3 , 29.8. Found: OCH_3 , 30.0.

Treatment with Sodium Iodide.—As this reaction is liable to be accompanied by the development of excessive pressures, it is advisable to use only small quantities of the above dimethylmethylglucoside dinitrate in each operation. The dinitrate, in lots of 2.5 g., was dissolved in acetone (10 cc.) and 5 g. of sodium iodide was added, the mixture being thereafter heated in a sealed tube at 100° for six hours. Care has to be exercised in opening the tubes. The product was washed into a flask with acetone, the solvent evaporated and the residue shaken with a mixture of benzene and water. Free iodine was removed by washing the benzene layer with sodium thiosulfate and, after drying, the solvent was evaporated. Only a small proportion of the product was retained by the aqueous layer and this was recovered by extraction with chloroform. The average yield was 2.1 g. in each operation. The product was a sirup which on the evidence of methoxyl and iodine determinations contained some mono-nitrate but the mixture was employed directly in the succeeding reaction.

Replacement of Iodine by Methoxyl.—Three series of consecutive reactions were involved. (a) A 10% solution of the above sirup was prepared in acetonitrile and three times the theoretical amount of silver acetate added together with sufficient pyridine to obtain complete solution. On boiling for four hours the whole of the iodine was precipitated as silver iodide and much colloidal silver was formed, the liquid being afterward filtered and evaporated under reduced pressure at 60°. On extracting the residue with ether, the acetate of 2,3-dimethylmethylglucoside mono-nitrate passed into solution and was isolated as usual.

(b) The sirup was dissolved in absolute alcohol so as to form a 5% solution and the theoretical amount of 2 *N* sodium hydroxide added. After thirty minutes the liquid was filtered to remove silver oxide, diluted largely with water and the solution extracted repeatedly with chloroform. Removal of the solvent gave 6.2 g. of a sirup (n_D 1.464) giving analytical figures showing that it consisted essentially of dimethylmethylglucoside mono-nitrate.

(c) Three methylations by means of the silver oxide reaction converted the above sirup into trimethylmethylglucoside mono-nitrate; yield, 6 g.; n_D 1.4595.

Anal. Calcd. for $C_{10}H_{19}O_8N$: OCH_3 , 44.1. Found: OCH_3 , 43.0.

Up to this stage it was impossible to purify the compounds by distillation owing to the presence of the nitrate group.

Reduction of the Nitrate Group.—A 10% solution of the above mono-nitrate in glacial acetic acid was warmed on a water-bath with finely divided iron. Nitrous fumes were evolved and as after forty-five minutes a test sample gave no further reaction with diphenylamine; the reduction was then arrested. The mixture was filtered and largely diluted with water, the total liquid and also the solid residues being repeatedly extracted with chloroform, from which the product was isolated as usual. Impurities were removed by taking up in ether and finally the resulting mobile sirup was distilled at 130–140° (0.2 mm.); yield, 3.6 g.; n_D 1.4595; OCH_3 , 48.1%. The sirup reacted sharply as a glucoside toward Fehling's solution but the low value for the Zeisel estimation indicates that, as is usually the case, the elimination of nitrogen was accompanied to some extent by anhydro-formation.

Hydrolysis of the Trimethylmethylglucoside.—This was carried out according to standard methods and gave a sirup which crystallized readily. After draining on a tile the sugar melted at 108–110° and when recrystallized this value remained unaffected at 114° when the synthetic sugar was mixed with an authentic specimen of

2,3,6-trimethylglucose. In every respect the two specimens were identical in composition and properties; yield 1.8 g.

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Summary

1. The constitution of 2,3-dimethylglucose has been verified and the sugar has been converted by a sequence of synthetical reactions into 2,3,6-trimethylglucose.

2. These reactions are based on the fact that while 2,3-dimethylglucose gives a di-nitrate, only the nitrate group in position 6 is replaceable by iodine. It was therefore possible to restrict the introduction of the third methyl group to position 6 as positions 4 and 5 were masked.

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

THE REDUCING ACTION OF THE GRIGNARD REAGENT AND THE SYNTHESIS OF TERTIARY ALIPHATIC CARBINOLS

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It was recently shown¹ that a few aliphatic aldehydes and a number of aliphatic ketones were more or less completely reduced to the corresponding primary and secondary alcohols by treatment with certain Grignard reagents. These reductions were roughly correlated with the size and complexity of the alkyl groups present in the carbonyl compound and the reagent and the limits of usefulness of the Grignard reagent in synthesizing aliphatic carbinols were pointed out.

The present work was undertaken in order to secure additional information about the effect of branched chain alkyl groups on the reaction between aliphatic ketones and the Grignard reagent. By the use of a properly chosen series of isomeric ketones and reagents we hoped to learn not only the exact effect of branching the alkyl groups but also, using substances of equal complexity, to learn the effect of the location of the branched groups. We have, therefore, treated each of the three ketones, di-propyl ketone, propyl isopropyl ketone and di-isopropyl ketone, with propyl- and isopropylmagnesium bromides. Some of these reactions had been done before but we found it necessary to repeat certain of them because the reported results were either contradictory or incomplete. We followed in our Grignard reactions what we prefer to term the normal procedure: the addition of the carbonyl compound to an excess of reagent free from excess magnesium. Using this procedure completeness of reaction is as-

¹ Conant and Blatt, *THIS JOURNAL*, **51**, 1227 (1929).