[CONTRIBUTION FROM THE UNIVERSITY OF ST. ANDREWS, SCOTLAND]

A NEW METHOD OF PREPARING 2-MONOMETHYLGLUCOSE SYNTHESIS OF 2,6-DIMETHYLGLUCOSE

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During the course of a recent research conducted in this Laboratory[1] it became necessary to examine the mixture of dimethylglucoses obtained from partially methylated starch by hydrolysis. One of the methods employed consisted in treating the mixed dimethyl methylglucosides with *p*-toluenesulfonyl chloride in order to determine the proportion of sugar unsubstituted in the 6-group. The results obtained are described elsewhere but it may be mentioned here that a crystalline product was isolated which had the composition of a dimethyl methylglucoside di-*p*-toluenesulfonate, and from its small levorotation was evidently the β-form. The compound failed to react with sodium iodide when heated in acetone solution at 100°, showing that group 6 was methylated and, from evidence which has been accumulated in this Laboratory on the chemistry of starch, it was thought most likely that the methyl groups were in positions 2 and 6.

In order to test the correctness of this view it was necessary to compare the above compound with a synthetic specimen of 2,6-dimethyl-3,4-di-*p*-

STAGE A

PREPARATION OF 2-MONOMETHYLGLUCOSE

Glucosemonoacetone → 3,5,6-Tribenzoylglucosemonoacetone → 3,5,6-Tribenzoylglucose → *3,5,6-Tribenzoyl-γ-methylglucoside → *2-Monomethyl-3,5,6-tribenzoyl-γ-methylglucoside → *2-Monomethyl-γ-methylglucoside → 2-Monomethylglucose

STAGE B

CONVERSION INTO THE 2,6-DIMETHYL SERIES

2 Monomethyl glucose

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*2-Monomethyl-β-methylglucoside

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*2-Monomethyl-3,4,6-tri-*p*-toluenesulfonyl-β-methylglucoside

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*6-Iodo-2-methyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside

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*2-Monomethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside-6-mononitrate

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*2-Monomethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside

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*2,6-Dimethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside

* Compounds now described for the first time.

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[1] Irvine and Rutherford, forthcoming paper.

toluenesulfonyl-β-methylglucoside. For this purpose the scheme of reactions outlined was selected.

The starting material, *viz.*, 2-monomethylglucose, has until recently been known somewhat vaguely as an uncrystallizable sirup but, after the present work had been begun, Brigl[2] prepared the crystalline sugar from the tetrabenzoate of glucose ethyl mercaptal. Levene, Meyer and Raymond[3] have further examined the compound and identified it with the sugar which was described incorrectly as 4-monomethylglucose by Pacsu.[4] None of the methods hitherto employed for its preparation seem so suitable as the one actually adopted in the present research. The most convenient initial material for the preparation of this substance is the crystalline carbon tetrachloride addition compound of 3,5,6-tribenzoylglucose first described by Fischer[5] and the starting point of the present research was therefore glucosediacetone. Slight modifications were introduced into the preparation of this substance and its conversion into glucosemonoacetone was profoundly modified, the yields being improved to the order of 85% of the theoretical amount. Freudenberg[6] describes an improved method of preparing this substance but he does not state his yields and the length of treatment (four days) is a disadvantage. The removal of the acetone group from tribenzoylglucosemonoacetone was also modified from the method originally described by Fischer. Subsequently the tribenzoylglucose thus obtained was treated with acid methyl alcohol at ordinary temperature until the action on Fehling's solution vanished, the product being thereafter methylated by the silver oxide reaction in the usual manner. The preliminary treatment with acid methyl alcohol appears to be necessary since inferior yields of the methylated sugar are obtained by the direct methylation of tribenzoylglucose. On alkaline saponification followed by acid hydrolysis crystalline 2-monomethylglucose was obtained in good yield. The corresponding β-methylglucoside was in turn converted into the tri-*p*-toluenesulfonyl derivative which, after successive treatment with sodium iodide and silver nitrate followed by removal of the nitrate group and methylation, yielded a crystalline compound, *viz.*, 2,6-dimethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside, identical with that already isolated from the dimethylglucoses obtained from starch. The constitution of 2-monomethylglucose is practically settled by its method of preparation and by its conversion into glucosazone through the loss of a methoxyl group. It was, however, further confirmed by the conversion of the corresponding β-methylglucoside into a benzylidene derivative which

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[2] Brigl, *Ber.*, **63**, 1551 and 2884 (1930).

[3] Levene, Meyer and Raymond, *J. Biol. Chem.*, **91**, 497 (1931).

[4] Pacsu, *Ber.*, **58**, 1455 (1925).

[5] Fischer, *ibid.*, **49**, 100 (1916).

[6] Freudenberg, *ibid.*, **61**, 1741 (1928).

on methylation gave the 2,3-dimethyl benzylidene-β-methylglucoside already obtained by Freudenberg[7] from 3-monomethylglucose. It may be mentioned that both 2-monomethylglucose and its benzylidene-β-methylglucoside showed marked depressions of melting point when mixed with 3-monomethylglucose and its benzylidene-β-methylglucoside.

Experimental

Ninety grams of β-glucose was shaken for sixty hours with 1.5 liters of acetone containing 15–18 g. of hydrogen chloride. The solution was then filtered from unchanged glucose, the amount of which varies greatly, and the filtrate neutralized with excess of a 30–35% solution of sodium hydroxide in the manner described by Minsaas.[8] The upper acetone layer was thereafter decanted, the lower layer washed several times with acetone and the whole taken to dryness at 100° in a flask containing a further small quantity of the soda solution. When all the acetone had been removed, water was added and the aqueous solution extracted three or four times with chloroform. The chloroform extract was shaken with sodium sulfate and charcoal, taken to dryness and dried at 100°. The aqueous layer contained any glucosemonoacetone present, and if this compound be required, the water can be saturated with carbon dioxide, the solution taken to dryness and the dry residue extracted with ethyl acetate. The glucosediacetone obtained from the chloroform is sufficiently pure for conversion into the monoacetone or other easily crystallized derivatives. For conversion to the monoacetone derivative, the diacetone compound was dissolved in 5–8% concentration in 50% aqueous acetone and sufficient aqueous hydrochloric acid added to make the acid concentration in the whole system $N/1000$. The solution was then boiled for thirty to forty-five minutes, the reaction being interrupted as soon as the action on Fehling's solution became at all marked. About three or four times the amount of ammonia solution necessary to neutralize the acid present was then added, and the acetone removed at 100°. The residual aqueous solution was cooled and extracted with chloroform until the extracts were no longer colored. This process removes unaltered glucosediacetone, leaving only glucosemonoacetone, together with any glucose that may have been formed, in the aqueous portion. More ammonia solution was added, the water removed and the well-dried residue repeatedly extracted with ethyl acetate. A typical experiment gave the following yields: 90 g. of β-glucose gave 47 g. of unchanged sugar, and 50 g. of material soluble in chloroform, 8 g. of glucosemonoacetone being recovered from the aqueous layer; 38.8 g. of the material soluble in chloroform gave, after hydrolysis extending for one hour, 5.3 g. of impure glucosediacetone and 6.2 g. of residue insoluble in ethyl acetate. The ethyl acetate extracts gave 18.5 g. of glucosemonoacetone in the first crop and 3 g. in the second. The yield is thus about the theoretical amount if the glucose formed is taken into account. The formation of glucose can be diminished if the time of hydrolysis is shortened but in this case increased quantities of glucosediacetone are recovered unchanged. The material so recovered can be hydrolyzed again but the yields are inferior as they contain all the impurities originally present.

3,5,6-Tribenzoylglucose.—Tribenzoylglucosemonoacetone prepared as described by Fischer[5] was boiled for two hours with glacial acetic acid containing 30% of water by volume. After taking to dryness and crystallizing from carbon tetrachloride, in which the addition compound is almost insoluble, 13.1 g. of product was obtained from 16 g. of the starting material, 1.2 g. of unaltered substance being recovered from the mother

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[7] Ref. 6, p. 1750.

[8] Minsaas, *Kgl. Norske Videnskab. Selskabs. Forh.*, 1926–1928, I, *Medd.*, No. 2, 113–114 (1929).

liquors. A further small quantity of this material can be obtained if the residue is treated with acid acetone. The yield is thus of the order of 70%.

2-Monomethyl-3,5,6-tribenzoyl-γ-methylglucoside and 2-Monomethyl-γ-methylglucoside.—The carbon tetrachloride compound is unsuitable for direct methylation by the silver oxide method as poor yields of final product are obtained. It was therefore first condensed in the cold with 1% acid methyl alcohol until the action on Fehling's solution had completely vanished, and the glucoside isolated by neutralizing with lead carbonate at the boiling point. The product which required no further purification was then methylated two or three times with methyl iodide in the usual manner and the methoxyl content determined. When this approximated to 11.9% the substance was ready for debenzoylation, which was carried out by a method essentially similar to that described by Zemplén.[9] The glucoside was dissolved in methyl alcohol and treated with a small quantity of potassium methylate also dissolved in methyl alcohol, the solution being then boiled for about one minute and a slight deficiency of tartaric acid added after cooling. After adding much water, and filtering if necessary, the solution was extracted with chloroform until the extracts were colorless. A little potassium carbonate solution was then added and the solution taken to dryness at 100°. The well-dried residue was extracted with acetone, filtered and the acetone removed. In this way 2-monomethyl-γ-methylglucoside was obtained as a fairly mobile sirup having n_D 1.4860. No analysis was carried out at this stage. A typical experiment was as follows. The glucoside obtained from 30 g. of the carbon tetrachloride compound was treated with 0.5 g. of potassium methylate followed by 1.5 g. of tartaric acid, 9.4 g. of debenzoylated glucoside being obtained, a yield of 97%, calculating from the carbon tetrachloride compound. This was hydrolyzed with 0.24% aqueous sulfuric acid, the solution being boiled until the rotation became constant, usually after one or two hours. The final specific rotation of the solution varied from +54 to +62°. After neutralizing with barium carbonate the filtrate was taken to dryness at 100°. The crude sugar (yield 94%) crystallized when boiled with absolute alcohol but the yields of crystalline product varied from 58 to 87% of the total product. The reasons for this irregularity are still under investigation. After several recrystallizations from absolute alcohol the sugar, which consists of small prisms, melted after slight sintering at 157–158°. The compound is soluble in water, fairly soluble in methyl alcohol, very slightly so in hot ethyl alcohol, insoluble in other solvents. Calcd. for $C_7H_{14}O_6$: OCH_3, 15.9. Found: 16.0. The specific rotation was determined in water and methyl alcohol, in both of which solvents it showed upward mutarotation.

Time from contact of solvent	Water c = 3.855%	Time from contact of solvent	Methyl alcohol c = 1.88%
4 minutes	$[\alpha]_D$ + 36.4°	9 minutes	$[\alpha]_D$ + 25.8°
45 minutes (catalyzed)	+ 55.5°	90 minutes	+ 28.0°
15 hours	+ 66.0°	4 hours (catalyzed)	+ 32.3°
		50 hours	+ 59.2°
		74 hours	+ 59.7°

The permanent specific rotations now determined for this sugar in water show good agreement.

Oldham and Rutherford	Levene and co-workers	Brigl and Schinle
+66.0°	+62.1°	+65.6°

The action of acid methyl alcohol in the cold on the sugar was also investigated. For this purpose 15 cc. of the above solution was made up to 20 cc., sufficient hydrogen

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[9] Zemplén, *Ber.*, **62**, 1613 (1929).

chloride in methyl alcohol being added to make the total concentration of acid 1%. The reaction was then followed polarimetrically, the following changes being observed

Time	$[\alpha]_D$ for c = 1.4045%
5 minutes	+66.2°
2.5 hours	+40.5°
6.5 hours	+ 9.6°
24.5 hours	−17.9° (The solution no longer reduced
48.5 hours	−15.3° Fehling's solution.)

On treatment of the sugar with phenylhydrazine acetate in the usual manner for osazone formation, 0.6 g. of the sugar gave 0.4 g. of glucosazone, as shown by absence of methoxyl, by the melting point, and mixed melting point with authentic glucosazone. This result alone is sufficient to prove that the methoxyl group is in position 2 of the glucose chain. The phenylhydrazone of the sugar, previously described by Brigl,[2] was prepared, giving crystals which melted at 176°.

2-Monomethyl-3,4,6-tri-*p*-toluenesulfonyl-β-methylglucoside.—2-Monomethylglucose was converted into its β-glucoside by a method which will be described in a forthcoming paper, together with the properties of the glucoside. One and six-tenths grams of crude glucoside was treated with *p*-toluenesulfonyl chloride in the usual manner, giving 3.0 g. of crystalline and 1.5 g. of sirupy product. The yield of crystals was thus about 60% of the theoretical amount but the over-all yield was about 90%. The product crystallized from a mixture of alcohol and glacial acetic acid in fine needles of m. p. 168–169°, with decomposition, after sintering at 167°. It is sparingly soluble or insoluble in most solvents except chloroform and acetone. Calcd. for $C_{29}H_{34}O_{12}S_3$: OCH_3, 9.25. Found: OCH_3, 9.41. The rotation in chloroform was $[\alpha]_D$ +13.8° for c = 4.110%.

6-Iodo-2-monomethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside.—One and three-tenths grams of the crude *p*-toluenesulfonyl derivative was treated with sodium iodide in the usual manner, giving 1.1 g. of product which gave 0.6 g. on recrystallization in the first crop. This consisted of tufts of fine needles melting at 184-185° with much the same solubilities as the last compound. Calcd. for $C_{22}H_{28}O_9S_2I$: OCH_3, 9.9; I, 20.2. Found: OCH_3, 9.4; I, 20.4. The rotation in chloroform was $[\alpha]_D$ +26.6° for c = 4.300%.

2-Monomethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside-6-nitrate.—This derivative was prepared from the above compound in the usual way, 0.429 g. giving 0.25 g. of pure material. Although the yields in this series of compounds are individually poor, they can be greatly improved by using the iodo compound in the form of a sirup. In this way 2.0 g. of the crude tri-*p*-toluenesulfonyl compound gave 1.5 g. of crude crystals which in turn yielded 1.2 g. of pure product. The crude yield was thus almost 90% of the theoretical amount. The product, which had much the same solubilities as the two previous compounds, crystallized from a mixture of alcohol and glacial acetic acid in fine needles melting at 157–158° and having $[\alpha]_D$ in chloroform −3.4° for c = 2.449%. Calcd. for $C_{22}H_{28}O_{12}S_2N$: OCH_3, 11.03; N, 2.49. Found: OCH_3, 11.0; N, 2.24.

2-Monomethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside.—One and two-tenths grams of the nitrate compound was reduced, as described in other papers, giving 1.1 g. of crude product. This crystallized with difficulty from butyl alcohol in short needles, insoluble in water and petroleum ether but soluble in other solvents. It melted after several recrystallizations at 137–140°, attempts to improve this value being unsuccessful. From 1.1 g. a first crop of 0.35 g. was obtained, 0.4 in the second and 0.1 in the third crop. Calcd. for $C_{22}H_{29}O_{10}S_2$: OCH_3, 11.99. Found: OCH_3, 11.53. The rotation in chloroform was $[\alpha]_D$ −17.8° for c = 3.535.

2,6-Dimethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside.—0.647 g. of crude material was methylated twice in the usual manner with silver oxide and methyl iodide, giving 0.666 g. of product. On treatment with absolute alcohol this gave 0.504 g. in the first crop, m. p. 155–157°. A further very small crop was obtained of about 0.02 g. The properties of this substance are described elsewhere.[10]

2-Monomethylbenzylidene-β-methylglucoside.—This was made by the method of Freudenberg.[6] The glucoside was dissolved in benzaldehyde (1 in 3) and shaken with half its weight of zinc chloride. As the mixture went solid almost at once it was warmed at 70° for about three hours, but this was probably unnecessary for completion of the reaction. The mixture was thereafter poured into water after being mixed with benzene. At this stage a large amount of crystalline material separated which was filtered off and proved to be the desired compound. The benzene was taken to dryness after separation from the water and the benzaldehyde removed in a vacuum at 100°. The crystalline material weighed 4.7 g. and 4.4 g. was recovered from the benzene. This latter was treated with a mixture of propyl alcohol and petroleum ether, when a further quantity was isolated. On recrystallization from absolute alcohol, 6.1 g. in all was obtained, representing a yield of about 67% of the theoretical amount.

The material when pure consisted of needles melting at 170–171°, a value which was greatly depressed on mixing with the corresponding compound from 3-monomethylglucose. The product was fairly soluble in chloroform and acetone and sparingly soluble or insoluble in other solvents. Calcd. for $C_{15}H_{20}O_6$: OCH_3, 20.9. Found: OCH_3, 21.3. The rotation in chloroform was $[\alpha]_D$ −69.2° for $c = 4.2$.

2,3-Dimethylbenzylidene-β-methylglucoside.—The benzylidene compound was methylated twice with silver oxide and methyl iodide in the usual manner, when 0.6 g. of starting material gave 0.4 g. of product after crystallization from absolute alcohol. This melted at 132–135°, a value which was unaltered on admixture with an authentic specimen of 2,3-dimethylbenzylidene-β-methylglucoside, thus further proving the constitution of both 2-monomethyl and of 2,3-dimethylglucose.

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Summary

1. The preparation of glucosemonoacetone has been greatly facilitated.

2. 2-Monomethylglucose has been prepared by an improved method.

3. 2,6-Dimethyl-3,4-di-*p*-toluenesulfonyl-β-methylglucoside has been synthesized and found to be identical with the product (m. p. 155–157°) of the same composition isolated from starch.

4. 2-Monomethylglucose has been converted through its β-methylglucoside into the benzylidene derivative of 2,3-dimethyl-β-methylglucoside, thereby confirming the constitution of the compounds involved.

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[10] Irvine and Rutherford, forthcoming paper.