

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

Preparation of Methyl Glucosides of Methylated Glucoses

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The lack of crystalline derivatives suitable for the identification of partially methylated glucoses has long been apparent, especially as the phenyl-osazone reaction is in many cases of little service. For many reasons the most suitable type of reference compound is to be found in the corresponding α - or β -methylglucoside, the latter being superior from a practical point of view as they are generally more readily crystalline and have higher melting points than the α -isomerides. Accordingly a survey has been made of the methods of preparing β -methylglucosides of typical partially methylated glucoses.

It was found that processes based on the conversion of such sugars into the acetobromo derivatives according to the original method described by Fischer¹ are unsatisfactory and recourse was had to the formation and subsequent reaction with methyl alcohol of the corresponding bromobenzoyl derivatives. As discovered by Fischer² pentabenzoylglucose is smoothly converted into tetrabenzoylbromoglucose and thereafter into tetrabenzoyl- β -methylglucoside. This method, modified to accommodate the different solubilities involved, has been found to be applicable to all types of partially methylated glucoses. The processes involved are somewhat tedious, and practice is necessary before the best results can be obtained, but as the yields can be as high as 85% and rarely fall below 45% of the theoretical amount, the method is a substantial improvement on any hitherto described in the literature. The examples now quoted include the preparation of the β -methylglucosides of (a) 2-monomethylglucose, (b) 3-monomethylglucose, (c) 2,3-dimethylglucose, (d) 2,4,6-trimethylglucose, (e) 2,3,6-trimethylglucose. The first mentioned compound has been described for the first time; the second has recently been prepared by Helferich,³ who obtained it by the acetobromo method in greatly inferior yield; the 2,3-dimethyl- β -methylglucoside, which was formerly described by Oldham and Rutherford⁴ as a sirup has now been obtained in the crystalline condition; the 2,3,6-

trimethyl- β -methylglucoside has already been described by Schlubach and Moog⁵ and by Irvine and McDonald,⁶ while the 2,4,6-isomeride was apparently encountered by Haworth⁷ in an impure state. As 3,4,6-trimethyl- β -methylglucoside has been synthesized recently in this Laboratory and as the 2,3,4-trimethyl derivative is already known,⁸ the four possible isomeric trimethyl- β -methylglucosides of the normal type have now been characterized. As these compounds are of special importance in constitutional studies, their properties are tabulated for comparison.

β -Methylglucosides of trimethylglucose	M. p., °C.	Specific rotation for c		
		in H ₂ O	approx. 5% in MeOH	in CHCl ₃
2,3,4	93-94	-19.6	-22.9	-20.2
2,3,6	59-60	-29.9	-35.1	-47.5
2,4,6	70-71	-25.1	-23.4	-27.4
3,4,6	52-53	-7.3	-9.1	-15.2

The optical values emphasize the importance for identification work of determining the specific rotations of such compounds in more than one solvent.

In the work now described, when inferior yields of β -glucosides are obtained, this is invariably due to a portion of the sugar undergoing benzoylation where possible in the γ -form, giving benzoyl derivatives from which the parent sugar can only be partially regenerated owing to the formation of obscure by-products.⁹

Experimental

General Directions

Benzoylation.—A 20-30% excess of benzoyl chloride is added with cooling to a solution of the sugar in about 1.5 times the theoretical amount of pyridine. After standing overnight the mass is rubbed with water to destroy excess benzoyl chloride, and benzene and water are added to dissolve the reaction products. The water layer is separated and extracted once with benzene, the total benzene is then washed twice with 15-20% aqueous hydro-

(5) Schlubach and Moog, *Ber.*, **56**, 1957 (1923).(6) Irvine and McDonald, *J. Chem. Soc.*, 1502 (1926).(7) Haworth, *ibid.*, 273 (1926).(8) Irvine and Oldham, *J. Chem. Soc.*, 119, 1744 (1921).(9) 2,4,6-Trimethylglucose: The fact that the other three compounds in the table have been definitely synthesized is sufficient proof of the correctness of the tentative formula proposed by Haworth (*loc. cit.*) for this substance but it may be recorded here that it has also been synthesized by a method that leaves no doubt as to its constitution. The description of this work is withheld until a forthcoming paper.(1) Fischer, *Ber.*, **49**, 584 (1916).(2) Fischer, *Ann.*, **383**, 68 (1911).(3) Helferich, *J. prakt. Chem.*, **11**, 132, 321 (1932).(4) Oldham and Rutherford, *This Journal*, **54**, 366 (1932).

chloric acid, and once with dilute sodium hydroxide solution. The benzene solution is then dried over sodium sulfate and taken to dryness at 100°. When working with monomethylglucoses the benzoate is crystallized at this stage from methyl alcohol and well washed with the same solvent. In other cases the product is converted directly to the glucoside. The methyl alcoholic mother liquors contain benzoylated derivatives of the γ -form of the sugar from which the latter can be partially recovered as described in the case of 3-monomethylglucose.

Conversion to the Glucoside.—The benzoyl derivative is dissolved in 10% total concentration, in a system containing (by volume) 55% of benzene, 20% of a saturated solution of hydrogen bromide in glacial acetic acid and 15% of dry ether. After standing until the optical rotation reaches a maximum (6 hours for monomethyl, 4.5 hours for dimethyl and 2 hours for trimethyl, derivatives), the solution is washed with benzene into a separating funnel, shaken twice with water and then with a concentrated solution of potassium bicarbonate until no more effervescence takes place. The benzene solution after drying over sodium sulfate and filtration is mixed with about half its own volume of methyl alcohol, and a weight of silver carbonate is added equal to that of the sugar originally used. This mixture is shaken until the supernatant liquid is free from bromine, more silver carbonate being added if necessary, and after filtration is taken to dryness. The product should not reduce Fehling's solution but if it does so it should be methylated with silver oxide and methyl iodide. Crystallization at this stage need be carried out only in the case of the monomethyl glucoses.

Debenzoylation. For monomethyl and dimethyl derivatives the benzoylated glucoside is dissolved in a little hot methyl or ethyl alcohol, and to this is added a weight of potassium equal to one-fiftieth of the weight of material taken (but less than 0.2–0.3 g. of potassium should never be employed) previously dissolved in the same solvent. The solution is then boiled for half a minute, water added and the system concentrated *in vacuo* at 100° until no more oily drops of methyl or ethyl benzoate distil. If more than a trace of insoluble material remains in the solution it should be extracted three times with chloroform, the chloroform removed and the whole process of debenzoylation repeated on the residue. The combined aqueous solutions are then treated with slightly less than the requisite amount of tartaric acid to convert the potassium to the acid salt, filtered, and repeatedly extracted with chloroform to remove benzoic acid and color. The subsequent isolation from the clear aqueous solution so obtained varies according to the number of methyl groups in the sugar, and in the case of the trimethylglucoses the procedure is different throughout as described later.

Application to 2-Monomethylglucose

The crude crystals of tetrabenzoylmonomethylglucose obtained as described in the general account amount to 72% of the theoretical yield and consist of a mixture of α and β forms from which the pure β compound can be obtained by recrystallizing from glacial acetic acid, and amounts to about 90% of the total crystals. The pure compound consists of broken prisms insoluble in water and petroleum ether, very sparingly soluble in cold alcohols,

ether or acetic acid, readily soluble in other solvents; m. p. 169–170°. Calcd. for $C_{22}H_{30}O_{10}$: OMe, 5.08. Found: OMe, 5.11. $[\alpha]_D$ in chloroform -6.2° for $c = 5.112\%$.

For conversion to the glucoside the crude crystals can be used. During this process the rotation of the solution rose to $[\alpha]_D +182.4^\circ$ and the crude glucoside was obtained in quantitative yield. On crystallization from absolute alcohol pure tribenzoyl-2-monomethyl- β -methylglucoside was isolated as broken prisms melting at 119–120°, insoluble in water, ether and petroleum ether, sparingly soluble in cold alcohols and acetic acid, soluble in other solvents. Calcd. for $C_{23}H_{30}O_9$: OMe, 11.9. Found: OMe, 11.3. $[\alpha]_D$ in chloroform -40.4° for $c = 5.182\%$.

After debenzoylation the clear aqueous solution obtained as already described in the general account was taken to dryness and the solid residue extracted with acetone, the glucoside being isolated in 97% yield. After two recrystallizations from propyl acetate it was obtained as minute prisms melting at 97–98°, insoluble in ether, benzene and petroleum ether, soluble in other solvents. Calcd. for $C_{14}H_{18}O_6$: OMe, 29.8. Found: OMe, 29.8. The rotation in water and methyl alcohol was $[\alpha]_D -37.5^\circ$, -41.9° for $c = 5.043$ and 5.034%, respectively.

Application to 3-Monomethylglucose. In this case also the crude crystalline tetrabenzoate is obtained in 72% yield. The pure β form (from glacial acetic acid) melted at 198–199° and consisted of broken prisms with the same solubilities as the corresponding 2-monomethyl derivative. Calcd. for $C_{24}H_{30}O_9$: OMe, 5.08. Found: OMe, 5.05. $[\alpha]_D$ in chloroform was 3.6° for $c = 4.94\%$.

In this case also the crude crystals can be used for conversion to the glucoside. The rotation of the solution rose to $+128.8^\circ$ in six hours and after the usual procedure the yield of crude tribenzoyl-3-monomethyl- β -methylglucoside was quantitative. After several recrystallizations from absolute alcohol the melting point was 125–126°, but this figure is somewhat uncertain as the value appeared to rise to about 130°, and then on further recrystallization to fall to the figure quoted. The pure glucoside (yield about 90%) consisted of long narrow prisms insoluble in water, ether and petroleum ether, sparingly soluble in cold alcohols and acetic acid, soluble in other solvents. Calcd. for $C_{25}H_{32}O_9$: OMe, 11.9. Found: OMe, 12.0. The rotation was irregular in chloroform, being 14.7° for $c = 5.016\%$.

Debenzoylation was quantitative but 3-monomethyl- β -methylglucoside is a sirup, though on dissolving in chloroform and cooling a crystalline substance separated which appears to be a chloroform addition compound since it at once becomes sirupy in contact with any other solvent. Further, the crystals after drying overnight in a vacuum desiccator contained combined chlorine and reduced Fehling's solution, although the material as isolated from acetone did not do so, and on drying in a vacuum at 100° lost approximately the weight required for one molecular proportion of chloroform. This compound although it cannot be isolated and preserved can be used nevertheless to purify the glucoside since it is sufficiently stable to be filtered and washed after which it can be dried at 100° when it reverts to the sirupy glucoside. The yield of purified material obtained by this process is of the order

of 90%. The sirupy glucoside is insoluble in ether, petroleum ether and cold chloroform, soluble in other solvents. Calcd. for $C_8H_{16}O_8$: OMe, 29.8. Found: OMe, 28.7%. The $[\alpha]_D$ in water was -26.6° and in methyl alcohol -30.2° for $c = 5.507$ and 5.017% , respectively. The methyl alcoholic mother liquors from the preparation of the tetrabenzoate contain γ forms which are recoverable. The solution is taken to dryness and then treated in the usual manner with hydrogen bromide, etc., left overnight in 1% acid methyl alcohol in the cold, methylated with methyl iodide and silver oxide until the action on Fehling's solution vanishes, and finally debenzoylated and isolated in the usual manner. All these processes are practically quantitative. After hydrolysis with 8% aqueous hydrochloric acid the original sugar is recovered in good yield and crystallizes to the extent of about 50%. The residue does not crystallize on further standing nor does it yield on benzoxylation any appreciable quantity of the crystalline tetrabenzoate. The total yield of methylglucoside obtainable is of the order of 84%. This method of recovering γ forms applies equally, as already stated, to 2-monomethylglucose.

Application to 2,3-Dimethylglucose.—From the crude benzoxyated product the α form of the tribenzoate can be obtained in poor yield by crystallization from alcohol, but it is better to convert the unpurified product into the glucoside. The latter can likewise be crystallized at this stage, but it is more convenient to debenzoylate it without purification. To the clear aqueous solution ultimately obtained is added much potassium carbonate and the system is then extracted three times with chloroform, which removes 70% of the dissolved product. On rebenzoxylation, followed by crystallization from butyl alcohol and petroleum ether about 27% of the sugar is obtained as the benzoxyated glucoside. This consists of fine felted needles of m. p. $99-101^\circ$, soluble in all solvents except water and petroleum ether. Calcd. for $C_{28}H_{28}O_8$: OMe, 21.6. Found: OMe, 20.9. The rotation in chloroform was $[\alpha]_D -8.2^\circ$ for $c = 5.238\%$. On debenzoylation this material gave a 92% yield of crude product, falling to 80% on recrystallization from carbon tetrachloride. The 2,3-dimethylmethylglucoside thus obtained consists of prisms melting at $62-64^\circ$, soluble in all solvents except petroleum ether. Calcd. for $C_9H_{18}O_8$: OMe, 41.9. Found: OMe, 41.3. The rotation was determined in a number of solvents: $[\alpha]_D$ in chloroform -47.8° for $c = 4.364\%$; in acetone, -38.7° for $c = 5.021\%$; in water, -36.6° for $c = 5.057\%$. The material remaining in the potassium carbonate solution from the original conversion to the glucoside appears to consist of obscure by-products, deficient in methoxyl, and giving only a 15% yield of the glucoside on hydrolysis followed by benzoxylation, etc. The mother liquors from the crystallization of the benzoxyated glucoside described above consisted of the γ form of the glucoside from which the parent sugar can be recovered in fairly good yield on debenzoylation and hydrolysis. This can if necessary be again converted to the glucoside. The over-all yield of the glucoside obtainable by all these operations is of the order of 54% of the theoretical.

Application to 2,4,6-Trimethylglucose.—The benzoxyated sugar was converted into the corresponding glucoside in the usual manner. For debenzoylation the initial stages were the same as already described, except that sodium was used instead of potassium and the concentrated aqueous solution obtained after the removal of the methyl benzoate was boiled for half an hour with a further quantity of dilute sodium hydroxide and then extracted five or six times with chloroform. A 92% yield of the glucoside was thus obtained. This crystallized well from light petroleum ether, giving after several recrystallizations prisms of m. p. $70-71^\circ$, sparingly soluble in petroleum ether, soluble in all other solvents. Calcd. for $C_{10}H_{20}O_8$: OMe, 52.5. Found: OMe, 51.7. $[\alpha]_D$ in chloroform, -27.4° for $c = 5.021\%$; in methyl alcohol, -23.4° for $c = 5.015\%$; in water, -25.1° for $c = 5.038\%$.

Application to 2,3,6-Trimethylglucose.—The isolation of the glucoside was carried out as described for 2,4,6-trimethylglucose but boiling with alkali after debenzoylation unexpectedly caused much decomposition, although the product was without action on Fehling's solution. A 71% yield of the glucoside was obtained on removing the chloroform and this when distilled in a vacuum left no residue. The distillate which consisted of a mixture of the normal and γ forms was boiled for four hours with *N*/70 aqueous hydrochloric acid, a reagent which hydrolyzes the γ -glucoside but has no effect on the normal form. The solution on extraction with chloroform gave the normal glucoside (80% of the total present) while the aqueous solution contained free 2,3,6-trimethylglucose which was isolated by saturating the solution with potassium carbonate and extracting with chloroform. The product was crystallized from light petroleum ether, giving an 80% yield of pure 2,3,6-trimethyl- β -methylglucoside and the residue was still largely crystalline. By hydrolyzing the above residue and utilizing the free sugar so obtained together with that from the γ -glucoside the over-all yield of pure glucoside amounted to 60%. The pure β -glucoside consisted of prisms m. p. $59-60^\circ$ soluble in all solvents except petroleum ether. Calcd. for $C_{10}H_{20}O_8$: OMe, 52.5. Found: OMe, 51.4. The rotation was as follows: $[\alpha]_D$ in methyl alcohol, -35.1° for $c = 5.026\%$; in chloroform, -47.5° for $c = 5.006\%$; in water, -29.9° for $c = 5.018\%$.

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Summary

An improved general method of preparing β -methylglucosides of partially methylated glucoses is described, specific directions being given in the cases of: (a) 2-monomethylglucose, (b) 3-monomethylglucose, (c) 2,3-dimethylglucose, (d) 2,3,6-trimethylglucose and (e) 2,4,6-trimethylglucose.

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