

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Synthesis of 5,6-Dimethylglucose

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In the synthesis of the various partially methylated sugars investigators have attempted to use a number of blocking agents in what may be termed an indirect synthesis from the acetone sugars or related cyclic acetals, that is to say, reagents which will block certain hydroxyl groups while the acetone, etc., residues are removed and replaced by methyl or other substituents. The esters of the carboxylic acids are not satisfactory blocking agents for this type of synthesis because of their tendency to migrate and to be removed under the basic conditions of methylation, and the toluenesulfonates sometimes have the undesirable property of causing Walden inversions upon removal. While the acetates, benzoates and tosylates occasionally have been used for syntheses of this type, it seems desirable to have alternative procedures available for more general use.

Most promising of the blocking agents which have been proposed appear to be the nitro groups used by a number of English investigators,¹ and the benzyl groups of Freudenberg² and Zemlén³ and their co-workers, both of which lack the ability to migrate and may be removed readily by reduction. Since it is desirable to have several blocking agents with different properties available for use as occasion demands, we are presenting in this paper a study of the use of the benzyloxymethyl group in the synthesis of the previously unknown 5,6-dimethylglucose. This group appears to be somewhat more stable to alkali than the nitro group and to be introduced into the sugar molecule under somewhat less drastic conditions than the benzyl group, but like these groups is readily removable by reduction. This reduction could be performed either with sodium and alcohol or catalytically. By analogy with the results of other investigations on the reductive scission of compounds containing the O-benzyl group we would expect the primary reduction products of the benzyloxymethyl group to be toluene and formaldehyde, but our results indicate the produc-

tion of methyl alcohol rather than formaldehyde by reduction with sodium and alcohol.

Chloromethyl benzyl ether reacts with diacetoneglucose either with the method used by Freudenberg or that used by Zemlén for the introduction of benzyl groups, but in boiling ether instead of at the higher temperatures necessary with benzyl chloride. The resulting 3-benzyloxymethyl-diacetoneglucose (I) was hydrolyzed under the usual conditions to 3-benzyloxymethylmonoacetoneglucose (II) which was methylated to 5,6-dimethyl-3-benzyloxymethyl-monoacetoneglucose (III). Reduction of this compound with sodium and alcohol gave 5,6-dimethyl-monoacetoneglucose (IV) and acid hydrolysis gave 5,6-dimethylglucose (V). To verify the structures we have assigned to these compounds we have degraded 5,6-dimethylglucose to dimethylglyceric acid by a method similar to that used by Jackson and Hudson⁴ in the degradation of several glycosides. The dimethylglyceric acid was identified by a comparison of its derivatives with those of a sample of dimethylglyceric acid prepared by the methylation of glyceric acid.

It is interesting to compare 5,6-dimethylglucose with the 5-methylglucose described by von Vargha,⁵ since neither of these compounds can form the normal pyranose ring. Both sugars have a very low rotation, they rapidly reduce cold Fehling solution and cold neutral permanganate and color the Schiff aldehyde reagent; properties which have been taken by von Vargha to indicate the presence of a considerable amount of the open chain aldehyde form.

We found that phenyl isocyanate formed readily crystallizable, easily purified derivatives with two intermediates (II and IV) which failed to form crystalline acetates or tosylates. We were able to crystallize 5,6-dimethyl-monoacetoneglucose only by seeding with crystals obtained by the hydrolysis of the corresponding urethan. The preparation of polyurethans of some free sugars and glycosides with phenyl isocyanate has been described,⁶ but the products were amorphous and difficult to purify.

(1) Oldham, *J. Chem. Soc.*, **127**, 2840 (1925); Irvine and Rutherford, *THIS JOURNAL*, **54**, 1491 (1932); Bell, *J. Chem. Soc.*, 1553 (1936); Bell and Synge, *ibid.*, 1711 (1937); 833, 836 (1938).

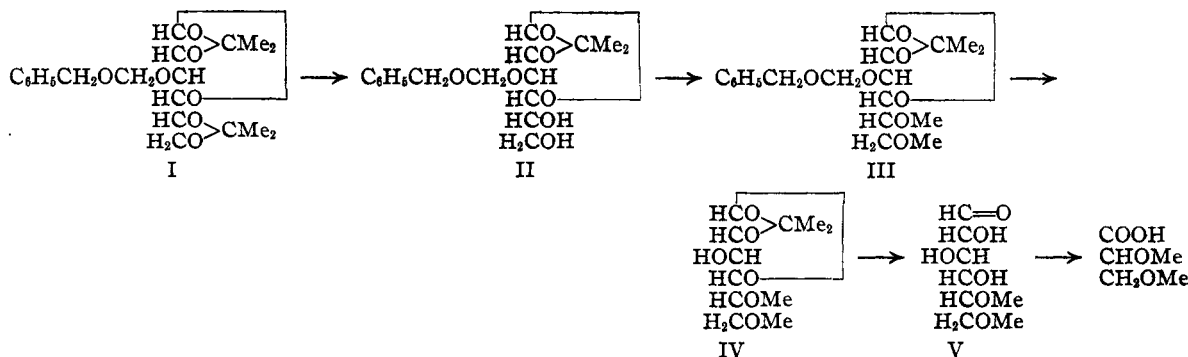
(2) Freudenberg, Hochstetter and Engels, *Ber.*, **58**, 666 (1925); Freudenberg, Dürr and Hochstetter, *ibid.*, **61**, 1735 (1928); Freudenberg and Plankenhorn, *Ann.*, **536**, 257 (1938).

(3) Zemlén, Csűrös and Augyal, *Ber.*, **70**, 1848 (1937).

(4) Jackson and Hudson, *THIS JOURNAL*, **59**, 994 (1937).

(5) Von Vargha, *Ber.*, **69**, 2098 (1936).

(6) Maquenne and Goodwin, *Bull. soc. chim.*, (3) **81**, 430 (1904); Jolles and Botrini, *Gazz. chim. ital.*, **65**, 1217 (1935).



Experimental

Chloromethyl benzyl ether was prepared by the method of Hill and Keach.⁷ This method is known to give variable results^{7,8} and we obtained a large percentage of failures. By the addition of an equal volume of petroleum ether to the chloromethyl benzyl ether after separation of the water layer, the danger of decomposition on distillation was diminished and a good yield was obtained in the great majority of attempts at preparation.

3-Benzoxymethyl-diacetoneglucose. Method A.—Fifteen grams of diacetoneglucose was dissolved in 40 cc. of dry ether and allowed to react with the theoretical amount of sodium. The reaction took about two days at room temperature. When the reaction was complete traces of unreacted sodium were removed with a spatula and the theoretical amount of chloromethyl benzyl ether was added slowly. Considerable heat was evolved. When the reaction slowed down the ether was refluxed for a few hours and allowed to stand overnight. The ether solution was washed with aqueous sodium carbonate and then with water, dried over potassium carbonate and after removing the solvent the residue was distilled in vacuum. After a fore-run of diacetoneglucose the main fraction distilled at 163–177° at 0.2 mm. with a bath temperature of 214–245°; yield 12 g. or 55%.

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{O}_7$: C, 63.2; H, 7.4. Found: C, 63.3; H, 7.3.

In other preparations of this material the product was subjected to a careful fractionation in an unsuccessful attempt to obtain a crystalline product. The course of one of these fractionations was followed by analysis and it was found that the lower boiling fractions were several per cent. too high and the higher boiling fractions about 1% too low in carbon content. Diacetoneglucose is not the principal impurity. We believe the analysis quoted is in good agreement with theory only because of the accidental compensation of incidental impurities of higher and lower carbon contents.

All distillations recorded in this paper were carried out in flasks with wide, low side arms. Bumping was prevented by packing the boiling chamber with glass wool.

3-Benzoxymethyl-diacetoneglucose prepared in this way is a yellowish, slightly viscous oil. On reduction by the method described later in the preparation of 5,6-di-

methyl-monoacetoneglucose we obtained diacetoneglucose in 78% yield based on the crude product. Reduction in hydrogen with palladium black in acid solution also gave diacetoneglucose. Colorless 3-benzoxymethyl-diacetoneglucose can be obtained by refluxing with aqueous alcoholic potassium hydroxide and redistilling.

Method B.—Ten grams of 3-acetyl-diacetoneglucose⁹ was dissolved in 100 cc. of ether and 21 g. of chloromethyl benzyl ether was added. Eighty-five grams of powdered potassium hydroxide was added over the course of an hour while the mixture was stirred vigorously with a mechanical stirrer. The ether was refluxed for an hour and a half after the addition of the potassium hydroxide. Water sufficient to dissolve the inorganic materials was added and the two layers separated. The water layer was washed with a little ether, the combined ether extracts washed with a little water and dried over potassium carbonate. The residue after evaporation of the ether was distilled and the fraction boiling at 150–160° at 0.14 mm. was collected. This was redistilled and 4.5 g. was collected at 157–160° at 0.15 mm., bath temperature 210–230°. Hydrolysis with aqueous alcoholic hydrochloric acid gave 70% of the theoretical amount of formaldehyde, isolated as the dimethyldihydroresorcinol condensation product.¹⁰

3-Benzoxymethyl-monoacetoneglucose.—Ninety - six grams of 3-benzoxymethyl-diacetoneglucose (Method A, b. p. 150–170° at 0.1 mm.) was dissolved in 300 cc. of glacial acetic acid and 30 cc. of water was added. After standing for fourteen hours at room temperature the solvent was distilled off in vacuum and the residue dissolved in an additional 300 cc. of glacial acetic acid to which was added 50 cc. of water. This was allowed to stand for nine hours at room temperature, the solvents distilled off in vacuum, the residue mixed with water and sodium carbonate added in the amount necessary to neutralize the remaining acetic acid. The two layers were separated and the water layer extracted with 90 cc. of chloroform. A small amount of the chloroform solution was dried with sodium carbonate, the chloroform distilled off and the oily residue dried at 56° in vacuum for two hours.

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_7$: C, 60.0; H, 7.1. Found: C, 58.2; H, 6.9.

3-Benzoxymethyl-monoacetoneglucose (1.23 g.) was reduced with sodium and absolute alcohol under the conditions described later in the preparation of 5,6-dimethyl-

(7) Hill and Keach, *THIS JOURNAL*, **48**, 257 (1926).

(8) Carré, *Compt. rend.*, **186**, 1629 (1928); *Bull. soc. chim.*, **43**, 767 (1928).

(9) Fischer, *Ber.*, **51**, 321 (1918).

(10) Vorländer, *Z. anal. Chem.*, **77**, 241, 321 (1929).

monoacetoneglucose. Monoacetoneglucose was isolated from the product in a yield of 68% calculated on the crude product. 3-Benzoxymethyl-monoacetoneglucose (0.9 g.) was dissolved in 2 cc. of dry benzene and 0.75 g. of phenyl isocyanate was added. The solution was warmed in a bath at 85° for three hours. A few drops of absolute alcohol were added and the solution again warmed for a few minutes. The benzene was evaporated and the residue crystallized from aqueous alcohol. The crystals so obtained were dissolved in chloroform and filtered from a small amount of diphenylurea which was obtained as a by-product. After recrystallization from aqueous alcohol or benzene the product melted at 148–148.5° (corr.); yield about 0.7 g. crude or 0.4 g. of pure product. The same 5,6-dicarbanilyl-3-benzoxymethyl-monoacetoneglucose was obtained from 3-benzoxymethyl-diacetoneglucose prepared by either method A or B. For analysis the preparation was dried at 100° in a vacuum for two hours.

Anal. Calcd. for $C_{31}H_{34}N_2O_9$: C, 64.3; H, 5.9; N, 4.84. Found: C, 64.3; H, 5.8; N, 4.95.

5,6-Dimethyl-3-benzoxymethyl-monoacetoneglucose.—Eighty-six grams of 3-benzoxymethyl-monoacetoneglucose was methylated twice with 300 cc. of dimethyl sulfate and 288 g. of sodium hydroxide each time, using the general conditions described by West and Holden.¹¹ The product from these methylations was methylated twice with silver oxide and 170 g. of methyl iodide each time. We are unable to account for the extreme difficulty of methylating this compound. The product was distilled twice in vacuum, the second time it was collected at 155–163° at 0.12 mm. with a bath temperature of 185–200°; yield 49 g.

Anal. Calcd. for $C_{17}H_{22}O_8(OCH_3)_2$: C, 62.0; H, 7.7; OCH_3 , 16.85. Found: C, 62.6; H, 7.6; OCH_3 , 13.85.

5,6-Dimethyl-monoacetoneglucose.—To 42 g. of 5,6-dimethyl-3-benzoxymethyl-monoacetoneglucose was added 57 g. of sodium. The flask was heated on the steam-bath under a reflux condenser and absolute alcohol was added over a period of six hours until all the sodium had been decomposed. Several hundred cc. of water was added and the solution almost neutralized with acetic acid. Most of the alcohol was distilled off on a steam-bath and the aqueous solution was extracted six times with 100 cc. of chloroform each time. The chloroform was distilled off and the residue was dissolved in 300 cc. of 90% acetic acid and allowed to hydrolyze for eighteen hours at room temperature to remove traces of diacetoneglucose which might still be present. The solvents were removed in vacuum, the residue taken up in water, neutralized with sodium carbonate and extracted with chloroform. The product distilled at 105–110° at 0.15 mm. with a bath temperature of 145–160°; yield 20 g. or 71%. When seeded with crystalline material obtained as described below it crystallized in rods completely and immediately with a rise in temperature. After recrystallization from low boiling ligroin it melted at 56–56.5° (corr.); $[\alpha]^{20}_D -12.8$ (water, $c = 4.18$).

Anal. Calcd. for $C_9H_{14}O_4(OCH_3)_2$: C, 53.2; H, 8.1; OCH_3 , 25.0. Found: C, 53.2; H, 8.2; OCH_3 , 23.2.

Crystallization of 5,6-Dimethyl-monoacetoneglucose.—One gram of non-crystalline 5,6-dimethyl-monoacetone-

glucose was dissolved in 2 cc. of dry benzene and 0.5 g. of phenyl isocyanate added. The mixture was held in a water-bath at 85° for three hours. A few drops of absolute alcohol were added and the solution warmed for a few minutes. The benzene was evaporated and the product crystallized from aqueous alcohol; yield 0.7 g. of crude material. It was purified with very little loss by digesting with a few cc. of 20–40° petroleum ether. After two treatments it melted at 88–89° (corr.) and this value was unchanged by further treatment. The compound crystallized in flat plates or prisms from petroleum ether, in buttons from a mixture of benzene and petroleum ether, and from aqueous alcohol in long needles which melted several degrees lower; $[\alpha]^{20}_D -12.3$ (95% alcohol, $c = 3.25$).

Anal. Calcd. for $C_{16}H_{19}NO_5(OCH_3)_2$: C, 58.9; H, 6.9; N, 3.8; OCH_3 , 16.9. Found: C, 59.5; H, 7.2; N, 3.9; OCH_3 , 16.2.

In one preparation in which we used a drop of pyridine as a catalyst, we obtained another derivative which melted at 241–242° after recrystallization from acetone-alcohol, and gave an analysis corresponding approximately to the N,N'-diphenylallophanate of 5,6-dimethyl-monoacetoneglucose.

Anal. Calcd. for $C_{26}H_{30}N_2O_8$: C, 61.7; H, 6.2; N, 5.75. Found: C, 61.1; H, 6.2; N, 6.24.

One hundred and thirty mg. of sodium was dissolved in 5 cc. of absolute methyl alcohol and to this was added 750 mg. of 3-carbanilyl-5,6-dimethyl-monoacetoneglucose described above. The mixture was refluxed for one hour, water added to the appearance of a slight turbidity, the mixture seeded with phenyl methyl urethan and placed in the ice box. The next day phenyl methyl urethan had crystallized out in 50% of the theoretical quantity. The alcohol was evaporated off and the residue taken up with water and placed in the ice box to remove a further small crop of phenyl methyl urethan. This was filtered off and the filtrate extracted ten times with a third of its volume of petroleum ether to remove the last traces of phenyl methyl urethan. The water layer was treated with norite, filtered, and the sugar extracted with chloroform. The chloroform was distilled off in vacuum and the last traces of water were removed by distilling with a mixture of absolute alcohol and benzene. The residue crystallized on cooling and scratching with a glass rod. These crystals were used to seed the main crop of 5,6-dimethyl-monoacetoneglucose.

5,6-Dimethylglucose.—Two grams of 5,6-dimethyl-monoacetoneglucose was dissolved in 10 cc. of N hydrochloric acid and held in a bath at 80° for thirty minutes. The solution was cooled and the acid neutralized with silver carbonate. The filtrate was treated with hydrogen sulfide to remove the last traces of silver, shaken with carbon, filtered and evaporated to dryness in vacuum. The sugar is a colorless or light greenish-yellow oil which so far has failed to crystallize. When treated with Fehling solution at room temperature the solution becomes cloudy almost immediately and yellow copper oxide settles in about half an hour. Neutral potassium permanganate is decolorized instantly at room temperature. The sugar redens fuchsin-sulfurous acid but the color does not develop as rapidly nor is it as deep as is typical of true aldehydes.

(11) West and Holden, THIS JOURNAL, 56, 930 (1934).

After drying for one week in a vacuum desiccator over phosphorus pentoxide it showed $[\alpha]^{25}_D +4.0 \pm 0.3^\circ$ (water, $c = 2.4$). No mutarotation was observed.

5,6-Dimethylglucose retains water so tenaciously that we were unable to get a satisfactory analysis. After two weeks in a vacuum desiccator over phosphorus pentoxide, the carbon and hydrogen analysis corresponded to a little more than half a mole of water per mole of sugar. The osazone was oily. The *p*-bromophenyl osazone was treated with carbon and recrystallized in poor yield from 95% alcohol. It formed very fine yellow needles melting at 155.5–156° dec. (corr.). It was dried for one hour in vacuum at 100° for analysis.

Anal. Calcd. for $C_{18}H_{18}Br_2N_4O_2(OCH_3)_2$: C, 44.1; H, 4.5; N, 10.3. Found: C, 44.3; H, 4.8; N, 10.4.

Glyceric acid was prepared by the method of Debus.¹²

We failed to resolve it with brucine by the method reported in the literature to have given resolution.¹³ The *d,l* mixture was methylated with silver oxide and methyl iodide and the product distilled in a vacuum.

Anal. Calcd. for $C_3H_5O(OCH_3)_2$: OCH_3 , 62.8. Found: OCH_3 , 55.2.

The ester was hydrolyzed with barium hydroxide, the excess barium removed with carbon dioxide, the solution of the barium salt of dimethylglyceric acid acidified with an excess of concentrated hydrochloric acid and extracted with chloroform for four hours in a continuous extraction apparatus. The chloroform extract was covered with a layer of water, the water layer made slightly basic to litmus with sodium hydroxide and then just acid to litmus with hydrochloric acid. The solution was evaporated to dryness in a vacuum but the sodium salt of dimethylglyceric acid failed to crystallize.

Sodium dimethylglycerate was converted to the *p*-bromophenacyl ester by warming with slightly less than the theoretical quantity of *p*-bromophenacyl bromide in alcohol for three hours. The ester was recrystallized to constant melting point by crystallizing alternately from 80% alcohol and from petroleum ether containing about 20% of benzene. It melted at 66.5–67.5° (corr.). The *p*-phenylphenacyl ester, prepared in the same way, was treated with carbon and recrystallized from alcohol by the very slow addition of water at 0°, m. p. 62.5–63° (corr.). Both esters were dried for analysis at 35° in vacuum for two hours.

Anal. Calcd. for $C_{13}H_{15}BrO_5$: C, 47.1; H, 4.6. Found: C, 47.4; H, 4.6. Calcd. for $C_{17}H_{19}O_5(OCH_3)_2$: C, 69.5; H, 6.1; OCH_3 , 18.9. Found: C, 69.3; H, 5.9; OCH_3 , 18.9.

Degradation of 5,6-dimethylglucose was carried out in a manner similar to that used by Jackson and Hudson⁴ with several glycosides. When the degradation is carried

out with large amounts of materials or in concentrated solutions, there is a tendency for the reaction mixture to become warm with the separation of iodine. This happened to some extent in one run using 1.5 g. of the sugar and 7 g. of periodic acid, but it apparently did not affect the course of the reaction. After standing overnight at room temperature, the oxidation mixture was filtered from the iodine which had separated and extracted with chloroform for twelve hours in a continuous extractor. The chloroform extract was covered with a layer of water, the chloroform evaporated on the steam-bath and the water solution filtered from more iodine which had separated. Excess bromine was added and the solution allowed to stand overnight at room temperature. The water was distilled down to a volume of 10–15 cc. in vacuum, 5 g. of hydrated barium hydroxide was added, the solution protected from the air with a tube of soda lime and heated on the steam-bath for a total period of ten hours to racemize the *d*-dimethylglyceric acid to the *d,l* mixture. The solution was diluted to a volume of several hundred cc. and the excess barium was removed with carbon dioxide. The filtrate from the barium carbonate was evaporated in a vacuum, acidified with concentrated hydrochloric acid, and extracted with chloroform in a continuous extractor. The chloroform extract was covered with a layer of water, the water solution made faintly alkaline to litmus with sodium hydroxide and then just acid with hydrochloric acid. The solvents were removed in vacuum and the product converted to the *p*-bromophenacyl ester and the *p*-phenylphenacyl ester. The *p*-bromophenacyl ester melted at 65.5–66.5° (corr.) after recrystallization and the mixed melting point with the *p*-bromophenacyl ester of dimethylglyceric acid was 66–67° (corr.). The *p*-phenylphenacyl ester melted at 62.5–63° (corr.) after recrystallization and the mixed melting point with the *p*-phenylphenacyl ester of dimethylglyceric acid was also 62.5–63° (corr.).

Anal. Calcd. for $C_{13}H_{15}BrO_5$: C, 47.1; H, 4.6. Found: C, 47.2; H, 4.6. Calcd. for $C_{17}H_{19}O_5(OCH_3)_2$: C, 69.5; H, 6.1; OCH_3 , 18.9. Found: C, 69.8; H, 6.3; OCH_3 , 18.2.

We wish to thank Mr. Saul Gottlieb for the microanalyses reported in this paper.

Summary

5,6-Dimethylglucose has been synthesized from diacetoneglucose using the benzoxymethyl group as a substituent for blocking the third hydroxyl group.

Urethans prepared with phenyl isocyanate were found to have many desirable properties as crystalline derivatives of some of our intermediates.

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(12) Debus, *Ann.*, **106**, 79 (1858).

(13) Neuberg and Silbermann, *Ber.*, **37**, 339 (1904); Frankland and Done, *J. Chem. Soc.*, **87**, 618 (1905).