

98. *Use of the Benzyl Radical in Syntheses of Methylated Sugars.*
Part I. 4 : 6-Dimethyl Glucose.

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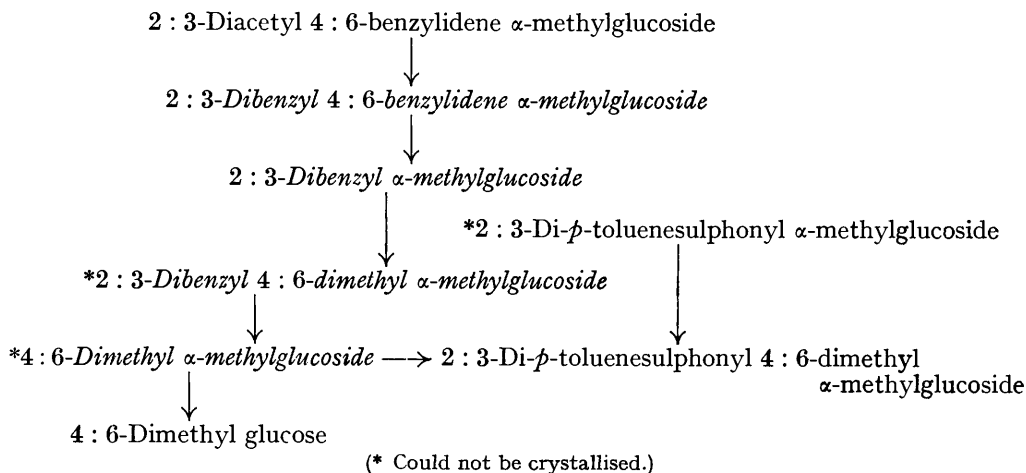
Temporary etherification of positions 2 and 3 in α -methylglucoside by the non-migratory radical benzyl affords an easy route to the synthetic preparation of 4 : 6-dimethyl glucose.

ETHERIFICATION by the non-migratory and comparatively stable benzyl radical of hydroxyl groups in sugars was first effected by Freudenberg, Hochstätter, and Engels (*Ber.*, 1925,

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58, 666) in the instance of diacetone glucose. 3-Benzyl glucose was obtained in this way. Later, Freudenberg and Plankenhorn (*Annalen*, 1938, 536, 260), by methylation of the glucoside of the latter substance, succeeded in a synthesis of 2 : 4 : 6-trimethyl glucose. Recently, Zemplén, Csürös and Angyal (*Ber.*, 1937, 70, 1848) have described a method of benzylation which has yielded excellent results in this laboratory. With a view to employing the benzyl radical to aid investigations at present in progress, as a test case we successfully benzylated 4 : 6-benzylidene α -methylglucoside and used the product as the starting point for an easy preparation of 4 : 6-dimethyl glucose.

The original synthesis of this sugar (Bell and Synge, J., 1937, 1711) necessitated working in the β -methylglucoside series and involved several rather delicate processes and the use of labile reagents. The present procedure, outlined below, is considerably less tedious :



The final product was identical with that of Bell and Synge (*loc. cit.*).

That no Walden inversion accompanies the removal of the benzyl groups by the method employed (sodium in alcohol) was proved : (a) by toluenesulphonation of our suspected 4 : 6-dimethyl α -methylglucoside ; we thus obtained a substance identical with the 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α -methylglucoside described by Mathers and Robertson (J., 1933, 1076) and prepared according to their directions, although we found m. p. 113° in place of 116—117° ; and (b) by the purity of the free sugar obtained on hydrolysis of the glucoside.

EXPERIMENTAL.

Polarimetric observations were made on chloroform solutions in a 2 dm. tube, unless stated otherwise. Solvents were evaporated under reduced pressure.

2 : 3-Dibenzyl 4 : 6-Benzylidene α -Methylglucoside (I).—18 G. of 2 : 3-diacetyl 4 : 6-benzylidene α -methylglucoside (Mathers and Robertson, J., 1933, 696) were treated by the following slight modification of the procedure of Zemplén *et al.* (*loc. cit.*). The substance was powdered, and mixed with 130 g. of powdered potassium hydroxide, 27 ml. of benzyl chloride, and 250 ml. of xylene (the last to maintain fluidity). The whole was stirred vigorously for 4 hours at 95—100° in a closed vessel fitted with a calcium chloride outlet-trap. The product was mixed with water and distilled in a vacuum until all volatile substances were eliminated. The residue, which crystallised, was collected, washed with water, dried, and recrystallised from aqueous alcohol. From two such preparations, 35 g. (75%) of fine needles, m. p. 93°, were obtained. $[\alpha]_D^{20} - 31.2^\circ$ ($c = 5$) (Found: C, 72.4; H, 6.4; OMe, 7.3. $C_{28}H_{30}O_8$ requires C, 72.7; H, 6.5; OMe, 6.7%).

2 : 3-Dibenzyl α -Methylglucoside (II).—35 G. of (I) were dissolved in a mixture of 450 ml. of acetone, 100 ml. of water, and 30 ml. of *n*-hydrochloric acid and boiled under reflux until the rotation of the solution was constant. After neutralisation of the acid with barium carbonate and the addition of more water the solution was evaporated to dryness. The residual syrup crystallised on keeping ; the yield was theoretical. The substance crystallised

in needles, m. p. 75—76°, from light petroleum (b. p. 60—80°). $[\alpha]_D^{18^\circ} + 18.8^\circ$ ($c = 4.9$) (Found : C, 66.6; H, 6.8; OMe, 8.6. $C_{21}H_{26}O_6$ requires C, 67.3; H, 6.95; OMe, 8.2%).

2 : 3-Dibenzyl 4 : 6-Dimethyl α -Methylglucoside (III).—(A) 6.2 G. of (II) were methylated twice with Purdie's reagents, and the product distilled in a high vacuum. The main fraction, b. p. 215—220°/0.03 mm. (bath temp.), had $n_D^{18^\circ} 1.5291$ and $[\alpha]_D^{18^\circ} + 32.9^\circ$ ($c = 5$) (Found : OMe, 23.3. $C_{23}H_{30}O_6$ requires OMe, 23.1%).

(B) (II) may also be methylated, in acetone solution, with methyl sulphate and alkali, but a final treatment with Purdie's reagents is necessary. After three methylations with methyl sulphate the distilled product had $n_D^{19^\circ} 1.5305$ and OMe, 21.8%; after a further treatment with methyl iodide and silver iodide, $n_D^{21^\circ}$ was 1.5273 and $[\alpha]_D^{21^\circ} + 31.8^\circ$ ($c = 5$) (Found : OMe, 22.1%).

4 : 6-Dimethyl α -Methylglucoside (IV).—The only method for the removal of the benzyl groups from (III) which gave satisfactory results was the following modification of the procedure of Freudenberg and Plankenhorn (*loc. cit.*). 8.2 G. of (III) were dissolved in 80 ml. of 97% alcohol, and 12.5 g. of metallic sodium added fairly rapidly in small portions. When found necessary, small amounts of alcohol (40 ml. in all) were added, and the reaction mixture warmed to complete the solution of the sodium. Some water was then added to give a clear solution; from this the bulk of the sodium was precipitated as the bicarbonate by saturation with carbon dioxide. The filtered solution was evaporated to dryness, and the residue extracted with ether. The ethereal solution was evaporated to dryness and the syrup which remained was subjected to partition between benzene and water. The benzene layer contained 0.4 g. of material and the water layer on evaporation yielded 3.6 g. of a colourless syrup. 4.2 G. of such material were distilled in a high vacuum; the first fraction (bath temp. up to 160°/0.5 mm.) amounted to 3.0 g. of a syrup which could not be crystallised and had $n_D^{21^\circ} 1.4698$ (Found : OMe, 40.7. $C_9H_{18}O_6$ requires OMe, 41.8%). On continuing the distillation up to 185°, about 1 g. of a very viscous syrup distilled; this apparently contained material of low methoxyl content.

Another preparation, distilled at 140—142°/0.05 mm., had $n_D^{21^\circ} 1.4710$. Redistilled, it had $n_D^{18.5^\circ} 1.4715$ and $[\alpha]_D^{20^\circ} + 156.8^\circ$ (Found : OMe, 40.2%). The substance could not be crystallised, but subsequent investigation showed that it must be essentially 4 : 6-dimethyl α -methylglucoside.

2 : 3-Di-*p*-toluenesulphonyl 4 : 6-Dimethyl α -Methylglucoside (V).—(A) From 2 : 3-di-*p*-toluenesulphonyl α -methylglucoside. This substance was prepared and methylated according to Mathers and Robertson (J., 1933, 1076). Our product melted at 113° despite recrystallisation from a number of different solvents, and had $[\alpha]_D^{18^\circ} + 55.5^\circ$. The original authors give 116° as the m. p. of their product; in view of this, and the fact that they do not record an elementary analysis, we do so here (Found : C, 52.1; H, 5.6; S, 11.2; OMe, 17.6. Calc. for $C_{23}H_{30}O_{10}S_2$: C, 52.1; H, 5.7; S, 12.0; OMe, 17.6%).

(B) From (IV). 0.4 G. of distilled material was twice treated with *p*-toluenesulphonyl chloride in dry pyridine at 38° and worked up in the usual way, 0.8 g. of crude product being obtained. Repeated crystallisation from methyl alcohol failed to raise the m. p. above 113°. $[\alpha]_D^{18^\circ}$ was 55.0° ($c = 2.4$) (Found : C, 52.2; H, 5.5; S, 11.4; OMe, 18.0%). The mixed m. p. with the product from (A) was 113°; the two substances are therefore identical and the structure assigned to (IV) is thus confirmed.

4 : 6-Dimethyl α -Glucose.—3.6 G. of (IV) were heated at 100° with 50 ml. of *N*-hydrochloric acid, the course of the hydrolysis being followed polarimetrically. The product, isolated as described by Bell and Syngé (*loc. cit.*), crystallised in needles from ethyl acetate in good yield. It melted at 156—157°, alone or mixed with authentic 4 : 6-dimethyl α -glucose. The mutarotation of the sugar, determined in water, compared well with the original observations ($c, 4; l, 2$):

Time (mins.)	3	23	29	60	1140
$[\alpha]_D^{18^\circ}$	+108.4°	+102.3°	+100.6°	+87.9°	+65.7° (const.)

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