161. 2 : 6-*Dimethyl Glucose.*

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4 : 6-*Ethylidene* β-*methylglucoside* 3-*nitrate*, subjected to reactions described by Bell and Synge (J., 1937, 1711), yielded β-*methylglucoside* 3 : 4-*dinitrate*. This was methylated to give the 2 : 6-*dimethyl* derivative, from which crystalline 2 : 6-*dimethyl* β-*methylglucoside* was prepared. The constitution of this was proved by preparation of its known di-*p*-toluenesulphonate (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 1086). The free *sugar* was then prepared; as it did not crystallise, it was characterised by conversion into the corresponding *dimethyl gluconophenylhydrazide*. Eight new crystalline derivatives of β-methylglucoside are described.

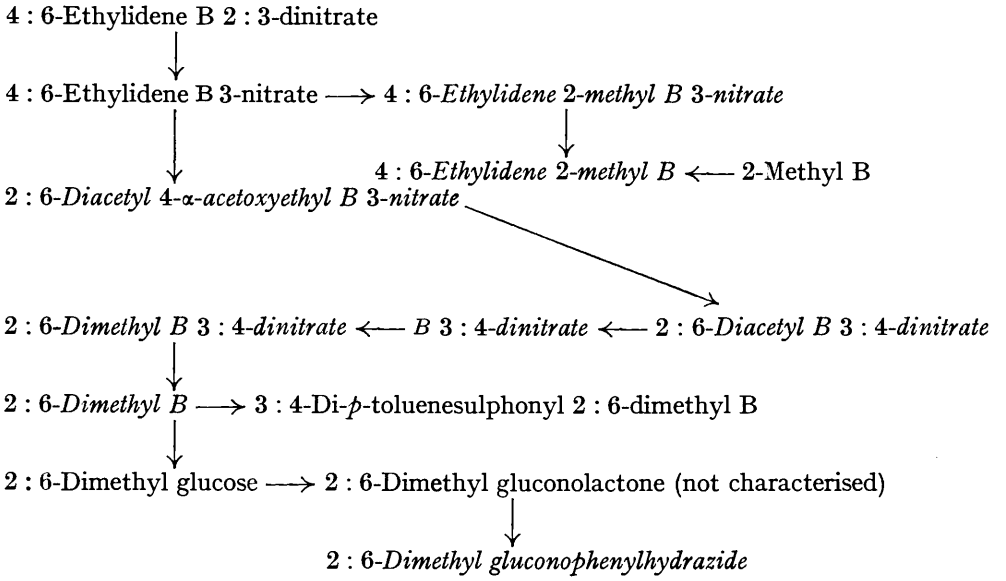
For a number of years one of us has made attempts to prepare 2 : 6-*dimethyl glucose*, with a view to its employment in polysaccharide chemistry. The two methods already described (Bell, J., 1935, 175; 1936, 186) gave the desired dimethyl sugar accompanied by so great a preponderance of isomers that its separation was impossible in any form other than 3 : 4-di-*p*-toluenesulphonyl 2 : 6-dimethyl β-methylglucoside (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 1086), a derivative from which it has not, so far, been regenerated.

Two circumstances have now combined to enable us to attain our end. First, in a private communication, Dr. J. W. H. Oldham has informed us that the action of sodium iodide in acetone on 4 : 6-ethylidene β-methylglucoside 2 : 3-dinitrate leads to the production of 4 : 6-*ethylidene* β-*methylglucoside* 3-*nitrate*. (A full description of the application of this reaction to other sugar nitrates is in course of preparation by Dr. Oldham. The present authors wish here to express their indebtedness to him; by his friendly co-operation this work was made possible.) Secondly, we have been able to show that acetic anhydride containing 0·1% of sulphuric acid can effect an opening at C_6 of the 1 : 3-dioxan ring of 4 : 6-ethylidene β-methylglucoside derivatives (Bell and Synge, J., 1937, 1711; following paper), leading to certain synthetically useful substitution reactions involving C_4 and C_6.

The reactions studied in the course of this work are summarised below, where B signifies β-methylglucoside.

The constitution of the new sugar is evident from the following considerations: (1) Non-migration of nitrate groups being assumed, one methyl group must be in position 2, since authentic 2-methyl β-methylglucoside yields the same ethylidene derivative as was obtained by methylating the mononitrate of 4 : 6-ethylidene β-methylglucoside used as starting material. This confirms the position of esterification in the latter as C_3. (2) The 3 : 4-di-*p*-toluenesulphonyl 2 : 6-dimethyl β-methylglucoside obtained in this research is identical with the synthetic product of Oldham and Rutherford (*loc. cit.*), which was

obtained from 2-methyl β-methylglucoside by introduction of methyl into position 6 by a generally applicable method.



Sodium methoxide is used to remove catalytically the two acetyl groups from 2 : 6-diacetyl β-methylglucoside 3 : 4-dinitrate, readily converting it into β-methylglucoside 3 : 4-dinitrate. It is noteworthy that the same treatment applied to 6-acetyl β-methylglucoside 2 : 3 : 4-trinitrate is without effect (Bell and Synge, 1937, *loc. cit.*). Possibly in each case an equilibrium is reached, but in the latter the free energy of "*Umesterung*" is such that the reaction does not proceed far. This view is supported by the fact that the mother-liquors from the crystallisation of β-methylglucoside 3 : 4-dinitrate yield on evaporation an uncrystallisable residue, from which by repeated treatment with sodium methoxide a further crop of crystalline β-methylglucoside 3 : 4-dinitrate can be obtained. This behaviour is intermediate between that of 6-acetyl β-methylglucoside 2 : 3 : 4-trinitrate and that of 4 : 6-diacetyl β-methylglucoside 2 : 3-dinitrate (Bell and Synge, 1937, *loc. cit.*), which is converted quantitatively into the corresponding dinitrate on treatment with sodium methoxide under the same conditions.

Experimental.

Unless otherwise stated, all evaporations were carried out under reduced pressure and below 50°. Substances were recrystallised until a constant m. p. was attained.

4 : 6-*Ethylidene* β-*Methylglucoside* 3-*Nitrate* (I).—Despite various experimental modifications, this reaction gave uncertain results. The best yield was obtained thus: 2 g. of 4 : 6-ethylidene β-methylglucoside 2 : 3-dinitrate (Oldham, unpublished work; Bell and Synge, J., 1937, 1711) were heated for 1 hr. in a sealed tube with 1 g. of sodium iodide and 20 ml. of acetone at 100°. After cooling, the product was mixed with chloroform, and washed first with sodium thiosulphate solution and then with concentrated potassium bicarbonate solution; after drying (sodium sulphate), the colourless chloroform solution was evaporated to dryness, and the crystalline residue was recrystallised first from a small quantity of ether and then from ethyl alcohol. Yield, 1·2 g. (needles), m. p. 135—140°. The pure *nitrate*, obtained by recrystallisation from methyl alcohol, had m. p. 146—148°, $[\alpha]_D^{18°}$ −30·8° (l = 2, c = 1·8 in chloroform) (Found: C, 41·1; H, 5·5; N, 5·0; OMe, 11·7. $C_9H_{15}O_8N$ requires C, 40·8; H, 5·7; N, 5·3; OMe, 11·7%).

4 : 6-*Ethylidene* 2-*Methyl* β-*Methylglucoside* 3-*Nitrate* (II).—2·7 G. of (I), treated with Purdie's reagents, gave 2·7 g. of pure *product*, which, recrystallised from light petroleum (b. p. 60—80°), formed prisms, m. p. 104·5—105·5° after softening at 101°, $[\alpha]_D^{16°}$ −28·7° (l = 2, c = 3·3

in chloroform) (Found: C, 43·9; H, 6·4; N, 4·9; OMe, 22·0. $C_{10}H_{17}O_8N$ requires C, 43·0; H, 6·1; N, 5·0; OMe, 22·2%).

4 : 6-*Ethylidene* 2-*Methyl* β-*Methylglucoside* (III).—(a) *From* (II). Reduction of (II) by alcoholic sodium sulphide, followed by extraction of the reaction mixture by chloroform in the usual way, gave a 97% yield of nitrate-free, fine needles. After recrystallisation from ether, these had m. p. 122—123°, $[\alpha]_D$ −66·0° ($l = 2$, $c = 2$ in chloroform) (Found: C, 51·2; H, 7·5; OMe, 26·2. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7; OMe, 26·5%).

(b) *From pure 2-methyl* β-*methylglucoside* (Oldham, *J. Amer. Chem. Soc.*, 1934, **56**, 1360), m. p. 94—96°. The glucoside, added to 10 parts of paraldehyde (dried over calcium chloride) containing 1% of sulphuric acid, dissolved immediately. After keeping at 0° for 12 hrs., excess of sodium bicarbonate solution was added, and the whole evaporated to dryness. The residue was dissolved in water, and the solution extracted six times with chloroform. The product crystallised from the extract and on recrystallisation from ether formed fine needles, having m. p. 122°, not depressed by the specimen obtained in (a), $[\alpha]_D^{17°}$ −64·0° ($l = 2$, $c = 2$ in chloroform).

2 : 6-*Diacetyl* 4-α-*Acetoxyethyl* β-*Methylglucoside* 3-*Nitrate* (IV).—A solution of 2·5 g. of (I) in 50 ml. of acetic anhydride containing 0·05 ml. of sulphuric acid was observed polarimetrically until the rotation reached a steady value (30 mins.). It was then poured into 250 ml. of water containing some sodium acetate, and was stirred until the acetic anhydride had decomposed, crystals being meanwhile deposited. The whole was extracted thrice with benzene, and the extract, after drying (sodium sulphate), evaporated. A solution of the residue in hot alcohol deposited crystals on cooling. The mother-liquor from these was evaporated, and the syrupy residue subjected again to acetolytic treatment. A further small quantity of crystals was obtained on working up as before. Recrystallised from alcohol, the *substance* (1·85 g.) had m. p. 125—126° after softening at 124°, $[\alpha]_D^{20°}$ + 13·4° ($l = 2$, $c = 4·8$ in chloroform) (Found: C, 44·3; H, 5·7; N, 3·6. $C_{15}H_{23}O_{12}N$ requires C, 44·0; H, 5·6; N, 3·4%).

2 : 6-*Diacetyl* β-*Methylglucoside* 3 : 4-*Dinitrate* (V).—5·9 G. of (IV) were treated with fuming nitric acid in chloroform and worked up in the usual manner (Bell and Synge, 1937, *loc. cit.*). The syrup obtained deposited crystals from alcohol, giving 3·7 g. in the first crop. The mother-liquors on concentration yielded no more crystals, but on repetition of the treatment with nitric acid on the evaporated residue a further 0·3 g. of crystals was obtained. The *substance* formed needles, m. p. 90—91°, $[\alpha]_D^{20°}$ −27·3° ($l = 2$, $c = 2·9$ in chloroform) (Found: C, 36·95; H, 4·3; N, 8·2; OMe, 8·3. $C_{11}H_{16}O_{12}N_2$ requires C, 35·85; H, 4·35; N, 7·6; OMe, 8·4%).

β-*Methylglucoside* 3 : 4-*Dinitrate* (VI).—4·0 G. of (V) were treated for 1 hr. at room temperature in 10 ml. of chloroform with a freshly prepared solution of 3 mg. of sodium in 10 ml. of methyl alcohol. After neutralisation with acetic acid the solution was evaporated to dryness, and the product extracted with ether. Addition of chloroform to the residue from the evaporation of the ether produced an immediate crop of fine needles, which, after recrystallisation from hexane–chloroform (1 : 1), gave 2·6 g., m. p. 116—118°. A second treatment with sodium methoxide of the uncrystallisable residue in the mother-liquors yielded 0·4 g. more of crystalline *product*, $[\alpha]_D^{16°}$ +13·9° ($l = 2$, $c = 3$ in methyl alcohol) (Found: C, 29·7; H, 4·1; N, 9·8; OMe, 10·8. $C_7H_{12}O_{10}N_2$ requires C, 29·55; H, 4·2; N, 9·5; OMe, 10·9%).

2 : 6-*Dimethyl* β-*Methylglucoside* 3 : 4-*Dinitrate* (VII).—0·25 G. of (VI) was methylated three times with Purdie's reagents; 0·28 g. of crystals were obtained from methyl alcohol, m. p. 74—76°, $[\alpha]_D^{20°}$ −13·7° ($l = 2$, $c = 7·5$ in chloroform) (Found: C, 34·7; H, 5·4; N, 8·9; OMe, 29·1. $C_9H_{16}O_{10}N_2$ requires C, 34·6; H, 5·1; N, 9·0; OMe, 29·8%).

2 : 6-*Dimethyl* β-*Methylglucoside* (VIII).—2·4 G. of (VII) in 24 ml. of alcohol were heated at 100° for 30 mins. with 24 ml. of 30% sodium hydroxide solution which had been saturated with hydrogen sulphide. After the alcohol had been distilled, much potassium carbonate was added and the solution was extracted nine times with chloroform. The chloroform extracts were dried (sodium sulphate) and evaporated, and the residual syrup was distilled at 150°/0·05 mm. The residue was negligible, and the distillate crystallised on trituration with ether. Recrystallisation from ether–hexane in the cold gave 1·3 g. of fine needles (slightly hygroscopic), m. p. 50—52°, $[\alpha]_D^{20°}$ −43·5° ($l = 2$, $c = 10·8$ in chloroform) (Found: C, 47·6; H, 8·2; OMe, 41·3. $C_9H_{18}O_6$ requires C, 48·6; H, 8·1; OMe, 41·8%).

p-*Toluenesulphonylation of* (VIII).—0·20 G. was treated in the usual way, and on being worked up, the crude product crystallised; recrystallisation from alcohol gave needles, m. p. 156—158° alone or mixed with authentic 3 : 4-di-*p*-toluenesulphonyl 2 : 6-dimethyl β-methylglucoside, m. p. 156—158° (Oldham and Rutherford, *loc. cit.*). These authors and Bell (J., 1936, 186) record $[\alpha]_D$ in chloroform −8·8° and −8·9° respectively. Our specimen had $[\alpha]_D^{18°}$

$-8{\cdot}2°$ ($l = 2$, $c = 8$ in chloroform) (Found: C, 52·3; H, 6·0; S, 11·3; OMe, 18·6. Calc. for $C_{23}H_{30}O_{10}S_2$: C, 52·1; H, 5·7; S, 12·1; OMe, 17·55%).

2 : 6-*Dimethyl Glucose* (IX).—1·20 G. of (VIII) were heated at 100° with 20 ml. of 0·6N-hydrochloric acid until a constant polarimetric reading was obtained (7 hrs.). After neutralisation by lead carbonate the product was worked up as in the preparation of 4 : 6-dimethyl glucose (Bell and Synge, 1937, *loc. cit.*), 1·0 g. of a colourless glass being obtained. This could not be crystallised. $[\alpha]_D^{17°}$ $+58{\cdot}3°$ (constant for 12 hrs.) ($l = 2$, $c = 2{\cdot}7$ in water) (Found: OMe, 29·8. $C_8H_{16}O_6$ requires OMe, 29·8%).

2 : 6-*Dimethyl Gluconophenylhydrazide*.—Oxidation of (IX) to the corresponding dimethyl gluconolactone was carried out by the method of Hudson and Isbell (*J. Amer. Chem. Soc.*, 1929, **51**, 2225), the manner of working up being slightly modified. To 0·88 g. of (IX), dissolved in 38 ml. of water, were added 3·3 g. of barium benzoate and 0·3 ml. of bromine. The mixture was shaken well, and kept in the dark until all reducing power (Fehling's solution) had disappeared (24 hrs.). After removal of all bromine by aëration, an exact equivalent of sulphuric acid was added to precipitate the barium, and the mixture was heated at 100° for ½ hr. When cool, the mixture was centrifuged, and the centrifugate was extracted three times with benzene to remove benzoic acid. (Owing to the breaking of a tube on the centrifuge, a loss of about 25% occurred at this stage.) Bromide was then eliminated by treatment with silver oxide, and silver was removed from the resulting filtrate by treatment with hydrogen sulphide. Evaporation of the clear filtrate from the silver sulphide yielded an almost colourless, non-reducing syrup, which was freed from traces of inorganic material by solution in chloroform, followed by filtration. This filtrate was evaporated, and the residue heated for 5 hrs. at 100°/0·01 mm. Yield, 0·46 g. of a syrup which did not crystallise, but displayed the expected solubilities of a dimethyl hexonolactone.

To a solution of this in dry ether was added 0·3 g. of freshly distilled phenylhydrazine. Almost immediately an oil separated. As this did not crystallise overnight, the mixture was boiled under reflux for 2 hrs.; crystallisation then commenced. Recrystallised from alcohol–ether–light petroleum, fine needles were obtained (0·2 g.), m. p. 127—129°, $[\alpha]_D^{17°}$ $+48{\cdot}6°$ ($l = 2$, $c = 3$ in ethyl alcohol) (Found: C, 53·4; H, 7·0; N, 10·0; OMe, 20·4. $C_{14}H_{22}O_6N_2$ requires C, 53·5; H, 7·0; N, 8·9; OMe, 19·7%).

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