198. *Crystalline 6-Methyl Glucose. A New Synthesis.*

By D. J. Bell.

6-Methyl glucose was first prepared in an amorphous state by Helferich and Becker (*Annalen*, 1924, **440**, 1) and was later obtained crystalline by Ohle and von Vargha (*Ber.*, 1929, **62**, 2435), who considered it to be the 5-derivative until Levene and Raymond (*J. Biol. Chem.*, 1932, **97**, 751) showed that the methyl group occupied position 6. Helferich and Becker's product has never been crystallised and the initial material (6-*p*-toluenesulphonyl monoacetoneglucose) used in Ohle and von Vargha's procedure is troublesome to prepare.

3 : 5-Benzylidene monoacetone glucose (Brigl and Grüner, *Ber.*, 1932, **65**, 1428; Zervas and Sessler, *Ber.*, 1933, **66**, 1326) ought to yield 6-methylglucose on direct methylation; unfortunately its preparation is relatively wasteful. 6-Acetyl monoacetoneglucose, however, is readily obtainable in one series of operations by acetylation of the crude product of the condensation of acetone and boric acid with glucose, described by von Vargha (*Ber.*, 1933, **66**, 704), no intermediate isolation being necessary. The acetyl compound, shaken with benzaldehyde and phosphoric oxide, gives an 80% yield of the 3 : 5-benzylidene derivative; simultaneous deacetylation and methylation with methyl sulphate and caustic soda then yields crystalline 3 : 5-*benzylidene* 6-*methyl monoacetoneglucose*. Simultaneous hydrolysis of the benzylidene and *iso*propylidene residues forms crystalline 6-methyl glucose, whose constants compare well with those recorded by the above authors.

Experimental.

6-*Acetyl Monoacetoneglucose*.—Various modifications of the following typical experiment were made without improving the yield. Glucose (75 g.) was treated with acetone, boric acid, and sulphuric acid exactly as described by von Vargha (*loc. cit.*). To the crude product, isolated by removal of the unchanged acetone by distillation, subsequent to neutralisation, 105 g. of acetic anhydride and 75 g. of fused sodium acetate were added and the whole was heated on the water-bath until a brown colour developed (15 mins.). Water (600 ml.) was then added to give a homogeneous solution; after 1 hour this was extracted five times with 100 ml. lots of benzene. The aqueous layer was then extracted ten times with 50 ml. lots of chloroform, the chloroform freed from acetic acid by shaking with saturated potassium bicarbonate solution, dried over sodium sulphate, and evaporated to dryness in a vacuum, leaving the product as an almost colourless syrup which immediately crystallised on cooling. Recrystallisation from ethyl alcohol gave 27 g. of needles, m. p. 145·5° (corr.), $[\alpha]_{D}^{16^\circ}$ − 6·7 (in chloroform; 1 = 4, c = 1·1). Fischer and Noth (*Ber.*, 1918, **51**, 321) reported m. p. 146° and $[\alpha]_D$ − 6·3° (their compound being then considered to be the 3-isomeride).

6-*Acetyl* 3 : 5-*Benzylidene Monoacetoneglucose.*—22 G. of 6-acetyl monoacetoneglucose, 88 ml. of freshly distilled benzaldehyde, and 22 g. of phosphoric oxide were shaken together for 4 hours, 200 ml. of benzene added, and the resulting solution filtered through charcoal. Water (500 ml.) was added to the filtrate, and the whole distilled in a vacuum at 60° until no more benzaldehyde distilled over. The crystalline residue was dissolved in benzene, and the solution washed with water, dried over sodium sulphate, and evaporated to dryness in a vacuum. The residual syrup crystallised immediately and on recrystallisation from alcohol gave needles, m. p. 126—127°. Yield, 25 g. (84·7%). Brigl and Grüner (*loc. cit.*) report m. p. 126—127°.

3 : 5-*Benzylidene* 6-*Methyl Monoacetoneglucose.*—50 G. of the above compound, dissolved in 250 ml. of acetone, were methylated at 50° with 65 g. of methyl sulphate (4 mols.) and 160 ml. of 30% caustic soda solution. The reagents were added in 1/10-portions at 10 minute intervals. On evaporation of the acetone, a crystalline mixture of methylated and unmethylated deacetylated material separated. After two further treatments in acetone the product was dissolved in benzene and washed with water, and the solution dried over sodium sulphate and evaporated in a vacuum. The 40 g. of crystalline material obtained, on recrystallisation from 75% alcohol, left 5 g. of a crystalline residue of unknown composition undissolved. The purified *product* (28 g.) had m. p. 95—96° and $[\alpha]_{D}^{20^\circ}$ + 3·8° (in chloroform; 1 = 2, c = 7·0) (Found : OMe, 9·4. $C_{17}H_{22}O_6$ requires OMe, 9·6%).

6-*Methyl Glucose.*—26 G. of benzylidene methyl monoacetoneglucose were heated on the boiling water-bath with 134 ml. of N-sulphuric acid and 134 ml. of alcohol until a constant rotation was obtained :

Time (hrs.)	1	1·5	2	2·5	3
$[\alpha]_D$ (calcd. on free sugar)	+41·0°	49·0°	49·7°	53·5°	54·3° (const.)

The alcohol was distilled off, the acid neutralised by barium carbonate, and the filtered solution evaporated in a vacuum. The residual colourless syrup crystallised immediately; it was dissolved in alcohol and filtered through charcoal, an equal volume of benzene added, and the solution evaporated to half bulk. On cooling, large needles separated, m. p. 143—145° (heating at the ordinary rate). Ohle and von Vargha reported 143—144° as the m. p. of their supposed 5-methyl derivative, and Levene and Raymond 153—154° on rapid heating. Recrystallisation of our product and various rates of heating failed to raise the m. p. above 145° (Found : OMe, 16·0. Calc. for $C_7H_{14}O_6$: OMe, 15·99%).

Dissolved in water, the crystals showed downward mutarotation, the points when plotted graphically giving a perfectly smooth curve (c = 3, l = 2) :

Time (mins.)	0	5	10	30	60	120	20 (hrs.)
$[\alpha]_{D}^{16^\circ}$	+ 110° (by extrapolation)	102·5°	98·7°	89·9°	81·1°	73·7°	55·0° (const.)

Ohle and von Vargha reported, for supposedly 5-methyl glucose, $[\alpha]_D$ 101·2° (3 mins.), falling to 59·92°(const.) in 3 hours. Levene and Raymond, for two samples of 6-methyl glucose, reported 101·8° (1 min.), falling to 56·0° (const.; 5 hrs.), and 104·5°, falling to 58·5°.

6-*Methyl Glucosazone.*—In order to confirm the constitution of the sugar described above, the osazone was prepared and recrystallised from methyl alcohol until a constant sharp m. p. was obtained, 190° (corr.) (Found : OMe, 8·3. Calc. for $C_{19}H_{22}O_4N_4$: OMe, 8·3%). The product consisted of large, pale yellow needles, which, when dissolved in ethyl alcohol, showed mutarotation (l = 2, c = 0·47) :

Time (hrs.)	0	2	16	36	60 and 72
$[\alpha]_D$	−75°	−64·2°	−53·6°	−52·5°	−48°

The following constants are recorded for 6-methyl glucosazone in the literature :

Authors.	M. p.	$[\alpha]_D$ in alcohol. Initial.	Final.
Ohle and von Vargha (1)	178°	−69·6°	−46·4°
Helferich and Günther (2)	184—187 (corr.)	−69, no mutarotation	
Levene and Raymond (3)	183	−70·5	−44·0

(1) *Ber.*, 1929, **62**, 2425. (2) *Ber.*, 1931, **64**, 1276. (3) *J. Biol. Chem.*, 1932, **97**, 751.

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PHYSIOLOGICAL LABORATORY, ABERDEEN.

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