599. *Deoxy-sugars. Part VIII. The Constitution of αβ-Methyl-2-deoxy-D-glucofuranoside.*

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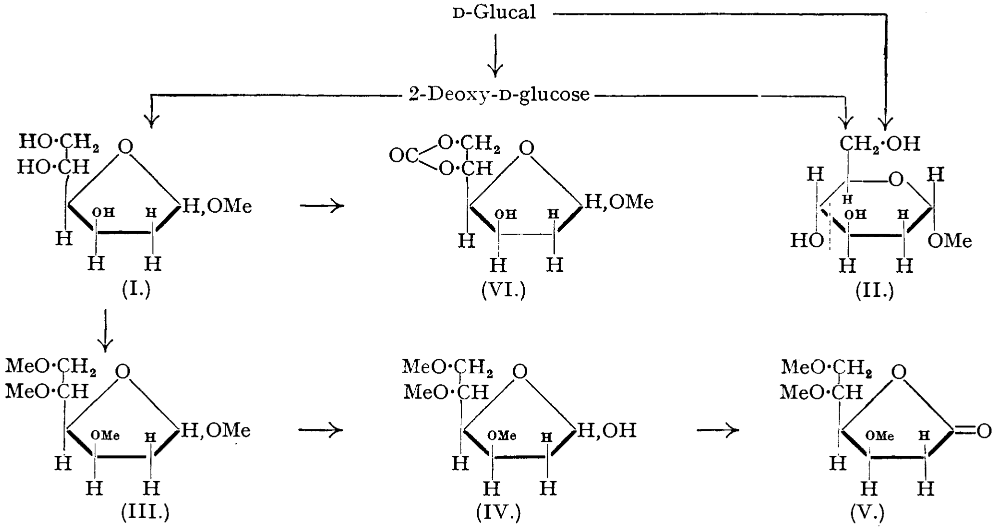
The synthesis of αβ-methyl-2-deoxy-D-glucofuranoside is described and its constitution established by oxidation with lead tetra-acetate, methylation, and formation of the characteristic furano-lactone.

The reactions of 2-deoxy-D-glucopyranose have been fairly extensively investigated. Thus Bergmann *et al.* (Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 545; Bergmann, *Annalen*, 1925, **443**, 223; Bergmann, Schotte, and Lechinsky, *Ber.*, 1922, **55**, 158) described the preparation of α- and β-methyl-2-deoxy-D-glucopyranosides and their methylated derivatives. The corresponding methylated lactone was later prepared by the usual methods (Hirst and Woolvin, *J.*, 1931, 1131; Levene and Mikeska, *J. Biol. Chem.*, 1930, **88**, 791). The reactions of 2-deoxy-D-glucofuranose and its derivatives have however received but scant attention. Since we have been interested in the reactions of 2-deoxy-pentoses and -hexoses, particularly in their furanose forms, we have compared the properties of the relatively accessible 2-deoxy-D-glucofuranose with those of other furanose derivatives of 2-deoxy-pentoses and -hexoses, and in particular with those of αβ-methyl-2-deoxy-D- and -L-ribofuranoside (this vol., p. 2836).

2-Deoxy-D-glucose was prepared by the improved method from glucal (this vol., pp. 1879 and 2841) and was converted by ethanethiol and concentrated hydrochloric acid into crystalline 2-*deoxy*-D-*glucose diethyl mercaptal*, acetylation of which with acetic anhydride in pyridine afforded the crystalline 3 : 4 : 5 : 6-*tetra-acetate*.

Prolonged treatment of 2-deoxy-D-glucose with 0·1% methanolic hydrogen chloride led to αβ-methyl-2-deoxy-D-glucopyranoside. Polarimetric investigation of the reaction on two samples showed that another reaction was taking place during the initial stages: after an initial change, which was probably mutarotation, the value of [α] fell to a minimum after about 9 minutes (Fig. 1; curve II). Isolation of the product at this stage yielded a liquid product which, as outlined below, was identified as αβ-*methyl*-2-*deoxy*-D-*glucofuranoside* (I).

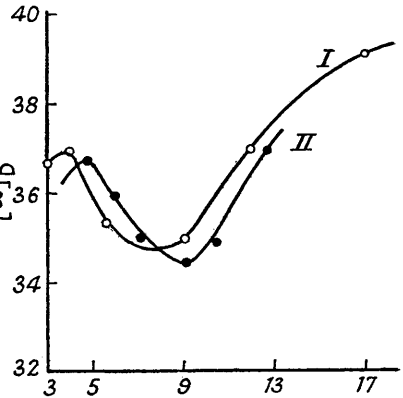


Hydrolysis of the glycoside with 0·005N-hydrochloric acid regenerated 2-deoxy-D-glucose. α-Methyl-2-deoxy-D-glucopyranoside (II) was prepared either from 2-deoxy-D-glucose by treatment with 2% methanolic hydrogen chloride at 40° for 50 minutes or from D-glucal by treatment with 2·5% methanolic hydrogen chloride at 60° for 1 hour.

Both αβ-methyl-2-deoxy-D-glucofuranoside (I) and α-methyl-2-deoxy-D-glucopyranoside (II) possess hydroxyl groups on adjacent carbon atoms and hence both should be oxidised by lead tetra-acetate, each consuming 1 mole of the oxidising agent. In the glycofuranoside (I), the hydroxyl groups are *cis*, whereas in α-methyl-2-deoxy-D-glucopyranoside they are *trans* to each other. The former substance (Hockett and McClenahan *J. Amer. Chem. Soc.*, 1939, **61**,

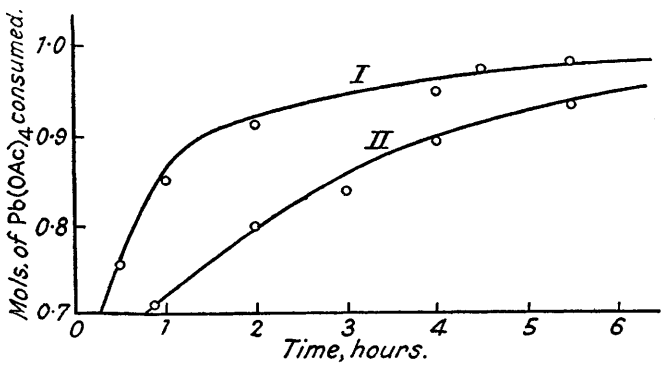
1667) should thus be oxidised by lead tetra-acetate at a faster rate than the latter. As expected, we found that (I) and (II) each consume 1 mole of oxidising agent, the rate of oxidation of (I) being much the faster (see Fig. 2). This indicated that (I) had been correctly designated as αβ-methyl-2-deoxy-D-glucofuranoside.

FIG. 1.



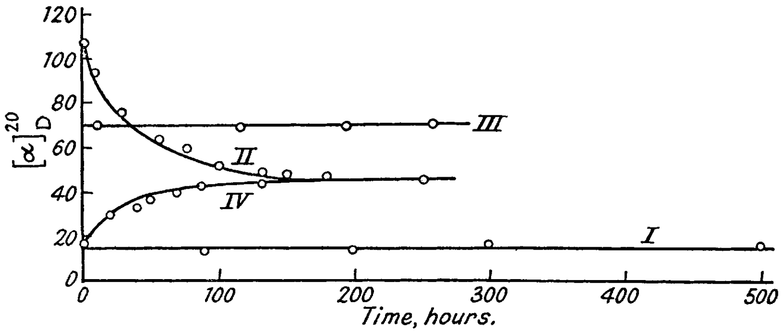
I. *Sample* I. II. *Sample* II.

FIG. 2.



I. *αβ-Methyl-2-deoxy-*D*-glucofuranoside.* II. *α-Methyl-2-deoxy-*D*-glucopyranoside.*

FIG. 3.



I. 3 : 5 : 6-*Trimethyl 2-deoxy-(γ)-gluconolactone.*
II. 3 : 4 : 6-*Trimethyl 2-deoxy-(δ)-gluconolactone.*
III. 2-*Deoxy-*D*-gluconolactone.*
IV. *Lactonisation of* 3 : 4 : 6-*trimethyl* D*-gluconic acid.*

When (I) was treated with carbonyl chloride in dry pyridine at −5°, it afforded a monocarbonate. Since carbonate residues are invariably attached to adjacent *cis*-hydroxyl groups (Haworth and Porter, *J.*, 1929, 2801; 1930, 151) [N.B. The hydroxyl group on $C_{(6)}$ of (I) can assume the *cis*-position relative to that on $C_{(5)}$], this compound is probably αβ-*methyl-2-deoxy-*D*-glucofuranoside* 5 : 6-*monocarbonate* (VI). Its formation supports the postulated five-membered ring structure of (I). Finally, conclusive proof of the structure was obtained by methylation and oxidation. When αβ-methyl-2-deoxy-D-glucofuranoside was methylated with methyl iodide and sodium in liquid ammonia (Muskat, *J. Amer. Chem. Soc.*, 1934, **56**, 693, 2449; Freudenberg and Boppel, *Ber.*, 1938, **71**, 2505), it afforded 3 : 5 : 6-*trimethyl* αβ-*methyl-2-deoxy-*D*-glucofuranoside* (III) as a colourless liquid. Hydrolysis of this with 0·005N-hydrochloric acid resulted in scission of the glycosidic grouping with formation of 3 : 5 : 6-*trimethyl 2-deoxy-*D*-glucofuranose* (IV) as a pale yellow liquid which with aniline in ethanol gave a crystalline *anilide*. Oxidation of 3 : 5 : 6-trimethyl 2-deoxy-D-glucose with bromine afforded 3 : 5 : 6-trimethyl 2-deoxy-D-gluconolactone (V), apparently identical with the lactone reported by Gakhokidze (*J. Gen. Chem. Russia*, 1946, **16**, 1907, 1914) who obtained it by an indirect method from 2-deoxycellobionic acid. The rate of hydrolysis of the methylated lactone (V) showed it to be, as designated above, a furano-lactone : hydrolysis was exceedingly slow in comparison with that of the corresponding pyrano-lactone, 3 : 4 : 6-trimethyl 2-deoxy-D-gluconolactone (Hirst and Woolvin, *J.*, 1931, 1131) (see Fig. 3). This completes the proof of structure of (I).

EXPERIMENTAL.

*2-Deoxy-*D*-glucose Diethyl Mercaptal.*—2-Deoxy-D-glucose (1·7 g.) was shaken with ethanethiol (1·4 g.) and concentrated hydrochloric acid (1·6 c.c.). The material soon solidified and more hydrochloric acid (1 c.c.) was added. On completion of the reaction, water (50 c.c.) was added and the separated solid washed on the filter with ether. Recrystallisation from methanol gave *2-deoxy-*D*-glucose diethyl mercaptal* (1·41 g.), m. p. 133·5°, $[\alpha]_D^{22}$ $-10°$ (*c*, 1·0 in methanol) (Found : C, 44·7; H, 8·2. $C_{10}H_{22}O_4S_2$ requires C, 44·4; H, 8·2%).

*2-Deoxy-*D*-glucose Diethyl Mercaptal* 3 : 4 : 5 : 6-*Tetra-acetate.*—2-Deoxy-D-glucose diethyl mercaptal (0·207 g.) was dissolved in pyridine (2 c.c.), and the solution cooled to 0°. Freshly distilled acetic anhydride (2 c.c.) was added during 15 minutes. The mixture was set aside at room temperature for 12 hours and was then poured into ice-water (70 c.c.). The separated oil rapidly crystallised and was well washed with water. On recrystallisation from mathanol it afforded *2-deoxy-*D*-glucose diethyl mercaptal* 3 : 4 : 5 : 6-*tetra-acetate* (0·208 g.), m. p. 75°, $[\alpha]_D^{18}$ $-27°$ (*c*, 1·34 in methanol) (Found : C, 49·6; H, 6·7. $C_{18}H_{30}O_8S_2$ requires C, 49·3; H, 6·9%).

*αβ-Methyl-2-deoxy-*D*-glucofuranoside* (I).—2-Deoxy-D-glucose (2·5 g.) was dissolved in 0·1% methanolic hydrogen chloride (50 c.c.), and the solution was shaken for 9 minutes and then neutralised with a large excess of silver carbonate. The decolorised, filtered solution was evaporated under diminished pressure at 40°, giving *αβ-methyl-2-deoxy-*D*-glucofuranoside* (with a trace of the pyranosides) as a colourless syrup, $n_D^{13\cdot5}$ 1·483, $[\alpha]_D^{20}$ $+43°$ (*c*, 1·04 in water), $+49°$ (*c*, 0·8 in ethanol) (Found : C, 47·1; H, 7·4; OMe, 18·0. $C_7H_{14}O_5$ requires C, 47·2; H, 7·8; OMe, 17·4%). When attempts were made to distil this compound [110—120° (bath temp.)/0·01 mm.], it apparently polymerised and the product is being further investigated.

*α-Methyl-2-deoxy-*D*-glucopyranoside* (II).—(*a*) 2-Deoxy-D-glucose (0·25 g.) in 2% methanolic hydrogen chloride (9 c.c.) was heated at 40° for 50 minutes. The solution was neutralised with silver carbonate, filtered before and after treatment with charcoal and then evaporated under diminished pressure at 40°, leaving a syrup which crystallised on trituration with ethyl acetate. Recrystallisation from ethyl alcohol gave α-methyl-2-deoxy-D-glucopyranoside (0·13 g.), m. p. 90—92°, $[\alpha]_D^{20}$ $+135°$ (*c*, 0·67 in water) [cf. Bergmann, Lechinsky, and Schotte (*Ber.*, 1922, **55**, 158; 1923, **56**, 1052) who give m. p. 91—92° and $[\alpha]_D^{23}$ $+137·9°$ in water].

(*b*) D-Glucal (1·13 g.) was dissolved in 2·5% methanolic hydrogen chloride (29 c.c.), and the solution heated at 60° for 1 hour. The neutralised solution (silver carbonate) was evaporated, leaving a crystalline product (0·81 g., m. p. 91—92°), identical with that above (Found : OMe, 17·3. Calc. for $C_7H_{14}O_5$: OMe, 17·4%).

4 : 6-*Benzylidene α-Methyl-2-deoxy-*D*-glucopyranoside.*—Dry α-methyl-2-deoxy-D-glucopyranoside (4 g.) and finely powdered anhydrous zinc chloride (3 g.) were shaken together vigorously with freshly distilled benzaldehyde (10 c.c.) for 60 hours. The resulting syrup was poured into a mixture of water and light petroleum (b. p. 60—80°). The residual syrup was triturated repeatedly with ethanol, whereupon 4 : 6-benzylidene α-methyl-2-deoxy-D-glucopyranoside was obtained in long colourless needles (3·2 g.), m. p. 137—139°, $[\alpha]_D^{19}$ $+77°$ (*c*, 0·7 in ethanol) (Found : C, 62·8; H, 6·2. Calc. for $C_{14}H_{18}O_5$: C, 63·1; H, 6·7%).

Lead Tetra-acetate Oxidations.—(*a*) αβ-Methyl-2-deoxy-D-glucofuranoside (0·0417 g.) was dissolved in dry ethanol (25 c.c.) and glacial acetic acid (20 c.c.). Lead tetra-acetate (50 c.c. of a 0·131N-solution in acetic acid) was added and the solution was made up to 100 c.c. with glacial acetic acid. The reaction was followed titrimetrically and was substantially complete in 3 hours (see Fig. 2), 1 mole of lead tetra-acetate being consumed.

(*b*) The same procedure was carried out using αβ-methyl-2-deoxy-D-glucopyranoside (0·0438 g.). The reaction was complete in 6 hours, 1 mole of lead tetra-acetate being consumed.

3 : 5 : 6-*Trimethyl αβ-Methyl-2-deoxy-*D*-glucofuranoside.*—Sodium (0·8 g.) was added slowly to liquid ammonia (80 c.c.), and the mixture stirred vigorously for 4½ hours. On completion of the addition, the stirring was continued for a further ½ hour, and then αβ-methyl-2-deoxy-D-glucofuranoside (1·0 g.) was added and the stirring continued. Methyl iodide (6 c.c.) was added at a rate of 2 c.c. per hour, and stirring was continued on completion of the addition for a further ½ hour. The ammonia was allowed to evaporate off and the residual solid was extracted with chloroform. The extract was dried ($MgSO_4$) and then evaporated under diminished pressure, to yield a brown syrup (*A*) (Found : OMe, 26·4%). The syrup (*A*) was re-methylated four times by the same procedure. After the third re-methylation it showed OMe, 46·8% and after the fourth re-methylation OMe, 54·6%.

The experiment was repeated on a larger scale, αβ-methyl-2-deoxy-D-glucofuranoside (3 g.) being methylated four times in liquid ammonia (100 c.c.) with sodium (0·75 g.) and methyl iodide (2·0 c.c.). A light-brown liquid (1·8 g.) was obtained which on distillation gave 3 : 5 : 6-*trimethyl αβ-methyl-2-deoxy-*D*-glucofuranoside* as a colourless mobile liquid (0·8 g.), b. p. 110—115° (bath temp.)/0·03 mm., n_D^{19} 1·4760, $[\alpha]_D^{21}$ $+56°$ (*c*, 1·2 in chloroform) (Found : C, 54·8; H, 9·0; OMe, 56·3. $C_{10}H_{20}O_5$ requires C, 54·6; H, 9·0; OMe, 56·3%).

3 : 5 : 6-*Trimethyl 2-Deoxy-*D*-glucofuranose.*—A solution of 3 : 5 : 6-trimethyl αβ-methyl-2-deoxy-D-glucofuranoside (0·5 g.) in 0·005N-hydrochloric acid (30 c.c.) was heated for 2·5 hours at 60° ($[\alpha]_D^{19}$ $+52° \longrightarrow -19°$). The solution, neutralised with silver carbonate in the presence of charcoal, was

centrifuged and the liquid evaporated to a small volume. The residue was extracted with chloroform, and the extract washed successively with sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Evaporation of the solvent yielded a syrup which distilled as a very pale yellow liquid, giving 3 : 5 : 6-*trimethyl* 2-*deoxy*-D-*glucofuranose* (0·35 g.), b. p. 130° (bath temp.)/0·05 mm., n_D^{18} 1·4590, $[\alpha]_D^{18}$ +24° (*c*, 0·73 in chloroform) (Found : C, 51·9; H, 8·6; OMe, 44·3. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

The above product (0·1 g.) in dry ethanol (2 c.c.) was heated at 80—90° for 8 hours with freshly distilled aniline (2 c.c.) in dry benzene (1 c.c.). The water formed was removed by azeotropic distillation with the ethanol–benzene. The solution was concentrated under diminished pressure to a syrup, which crystallised on trituration with dry light petroleum (b. p. 40—60°) and was 3 : 5 : 6-*trimethyl* 2-*deoxy*-D-*glucofuranose anilide* (0·04 g.), m. p. 136—138°, $[\alpha]_D^{19}$ −19·2° (*c*, 0·9 in ethanol), $[\alpha]_D^{19}$ −52° (initial value) $\longrightarrow$ −47° (mutarotation still incomplete after 48 hours) (*c*, 0·8 in dry pyridine) (Found C, 63·8; H, 7·8. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·2%).

3 : 5 : 6-*Trimethyl* 2-*Deoxy*-D-*gluconolactone*.—3 : 5 : 6-Trimethyl 2-deoxy-D-glucofuranose (0·24 g.) was dissolved in water (4 c.c.) and oxidised with bromine (6 c.c.). The product, isolated in the usual way, was a syrup which was lactonised by being heated for 3 hours at 90°/0·05 mm. Distillation of the product gave syrupy 3 : 5 : 6-trimethyl 2-deoxy-D-gluconolactone (0·06 g.) which slowly crystallised and then had m. p. 96—97°, $[\alpha]_D^{23}$ +12° (*c*, 0·65 in water) unchanged after 200 hours (Found : OMe, 45·3. Calc. for $C_9H_{16}O_5$: OMe, 45·5%) (cf. Gakhokidze, *loc. cit.*, who records m. p. 98°).

*αβ-Methyl-2-deoxy-*D*-glucofuranoside* 5 : 6-*Monocarbonate*.—αβ-Methyl-2-deoxy-D-glucofuranoside (1·1 g.) was dissolved in dry pyridine (20 c.c.) at 0°, and the solution stirred vigorously. Carbonyl chloride was passed slowly through the solution for 1 hour, the temperature being kept at −5° in order to avoid formation of an amorphous mass. The reaction mixture was kept at room temperature for 0·5 hour and was then poured into ice-water (200 c.c.) with rapid stirring. The solution was immediately neutralised with an equivalent of barium carbonate and filtered. The filtrate was extracted several times with ethyl acetate, and the extract was washed with water. After being dried ($MgSO_4$) the solvent was distilled off, leaving a syrup which did not reduce Fehling's solution and gave a precipitate of barium carbonate on addition of a solution of barium hydroxide. The product was distilled and *αβ-methyl-2-deoxy-*D*-glucofuranoside* 5 : 6-*monocarbonate* (0·46 g.) was obtained as a colourless syrup, b. p. 100° (bath temp.)/0·05 mm., n_D^{20} 1·6500, $[\alpha]_D^{21}$ +59° (*c*, 0·82 in water) (Found : C, 46·8; H, 6·4; OMe, 15·3. $C_8H_{12}O_6$ requires C, 47·0; H, 5·9; OMe, 15·6%).

2-*Deoxy*-D-*gluconolactone*.—2-Deoxy-D-glucose (0·22 g.) was dissolved in water (6 c.c.) and oxidised with bromine (1·2 c.c.) at 40° and for 3 days, and the product isolated in the usual way, giving 2-deoxy-D-gluconic acid (0·14 g.), m. p. 142—144° (cf. Levene and Mikeska, *J. Biol. Chem.*, 1930, **88**, 791, who give m. p. 145°). When the acid was heated in a vacuum at 90—100° (bath temp.) for 2 hours it yielded 2-deoxy-D-gluconolactone (0·08 g.), having m. p. 94—96°, $[\alpha]_D^{19}$ +72° (*c*, 1·0 in water) (Found : C, 44·1; H, 6·0. Calc. for $C_6H_{10}O_5$: C, 44·4; H, 6·2%). Some properties of this lactone are shown in Fig. 3.

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