CXLVII.—*The Structure of Glucal.*

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THE triacetyl derivative (II) of the unsaturated substance glucal (III) is formed when acetobromoglucopyranose (I) is reduced by zinc dust and acetic acid. The double bond in glucal is situated between the first and the second carbon atom (Fischer, *Ber.*, 1914, **47**, 196; Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509) and since three hydroxyl groups are present in the molecule a structural formula could be allocated if the position of the oxide ring were known. In view of the ease with which acyl groups can migrate the ring structure of glucal cannot be deduced with certainty from the fact that triacetyl glucal is obtained by the transformation of a glucopyranose derivative. It has been shown, however, that the analogous substances cellobial and gentiobial, each of which contains a glucal residue (Fischer and Fodor, *Ber.*, 1914, **47**, 2057; Bergmann and Freudenberg, *Ber.*, 1929, **62**, 2783), are obtainable from 4-glucosido-

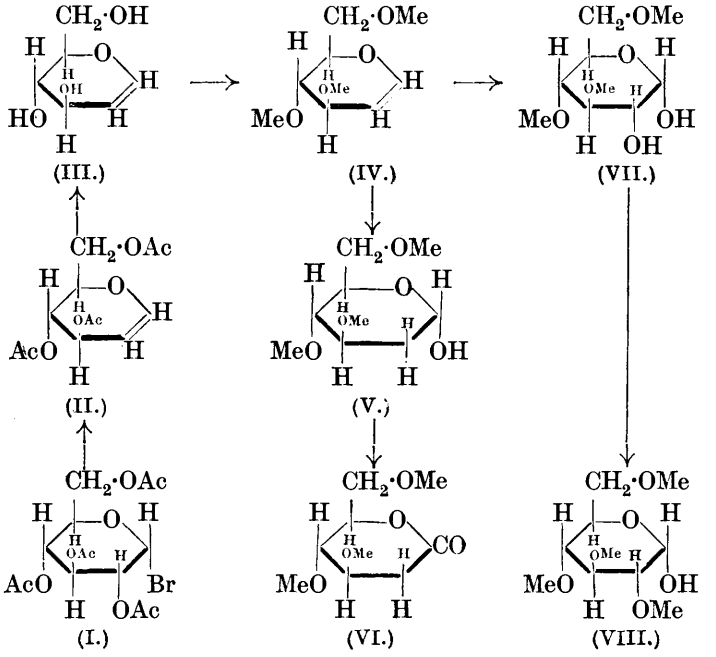
glucose and 6-glucosidoglucose respectively, and that the properties of 3-methyl glucal resemble those of the unsubstituted substance (Levene and Raymond, *J. Biol. Chem.*, 1930, **88**, 513). These observations provide evidence against the presence of a 1 : 4-, 1 : 6-, or 1 : 3-oxide ring in glucal and lead by inference to the view that no change of ring structure takes place during the formation of triacetyl glucal from acetobromoglucopyranose.

It seemed desirable, however, to determine by a simple and direct method the nature of the oxide ring in glucal. This has been achieved by studying the properties of the *trimethyl* derivative of glucal (IV), which was prepared by the simultaneous deacetylation and methylation of triacetyl glucal under the mildest possible experimental conditions in order to avoid as far as possible the formation of derivatives of ψ-glucal. That the trimethyl glucal now described retained the double bond between the first and the second carbon atom was proved by its transformation in the presence of dilute sulphuric acid into the same trimethyl 2-deoxyglucose (V) as was obtained by Levene and Mikeska (*J. Biol. Chem.*, 1930, **88**, 791) by the methylation of 2-deoxyglucose. The action of perbenzoic acid on trimethyl glucal in the presence of water gave rise to a syrup having the composition of trimethyl glucose (VII), and this after methylation and hydrolysis yielded crystalline 2 : 3 : 4 : 6-tetramethyl glucopyranose (VIII). Tetramethyl mannopyranose, the formation of which along with the glucose derivative was to be expected on stereochemical grounds, was present, if at all, in an amount too small for identification.

Since the double bond in trimethyl glucal involves positions 1 and 2, the methyl groups must occupy positions 3 : 4 : 5, 4 : 5 : 6, 3 : 5 : 6, or 3 : 4 : 6 according as the oxide ring is 1 : 6, 1 : 3, 1 : 4, or 1 : 5 respectively. No ring change can occur during the treatment of trimethyl glucal with perbenzoic acid or during the subsequent methylation and hydrolysis. The methyl groups in tetramethyl glucopyranose are at positions 2 : 3 : 4 and 6, from which it follows immediately that the three methyl groups in trimethyl glucal are at positions 3 : 4 and 6 and that trimethyl glucal and glucal possess the pyranose structure.

This result has an added significance at the present time in view of the easy transformation of glucal into α-methylmannoside (Bergmann and Schotte, *Ber.*, 1921, **54**, 1564). It has been shown recently (Haworth and Hirst, J., 1930, 2615) that, contrary to the views of Hudson (*J. Amer. Chem. Soc.*, 1930, **52**, 1680), the form of α-methylmannoside obtainable from glucal has the pyranose structure and it now appears that the reaction between perbenzoic acid and glucal in the presence of methyl alcohol proceeds normally and without

change of ring structure. In addition it follows that no migration of acetyl groups occurs during the reduction of acetobromoglucose and since acetobromomannose likewise gives rise on reduction to triacetyl glucal (Levene and Tipson, *J. Biol. Chem.*, 1931, **90**, 89) there is strong presumptive evidence that acetobromomannose is likewise pyranose in structure (contrast Hudson, *loc. cit.*).



When 3 : 4 : 6-trimethyl 2-deoxyglucose, obtained by the action of aqueous mineral acid on 3 : 4 : 6-trimethyl glucal, was oxidised by bromine it gave 3 : 4 : 6-trimethyl 2-deoxygluconic acid (Levene and Mikeska, *loc. cit.*), which was characterised as its crystalline *phenylhydrazide*. The lactone (VI) of the acid was prepared, and its identity with that described by Levene and Mikeska established by a measurement of its rotation in chloroform solution. The rotation in water was observed and a study was made of the rate of hydrolysis of the lactone in aqueous solution. At 19° the time required for the development of 25% of acid was identical with that observed with tetramethyl δ-mannonolactone. 3 : 4 : 6-Trimethyl 2-deoxygluconolactone is hydrolysed more slowly than 2 : 3 : 4 : 6-tetramethyl gluconolactone and it is noteworthy that the presence of the deoxy-group in position 2 not only retards the rate of hydrolysis of the lactone but also enhances to a remarkable degree the rate of

hydrolysis of the corresponding methylglycoside (compare Bergmann, Schotte, and Lechinsky, *Ber.*, 1922, **55**, 158). 3 : 4 : 6-Trimethyl 2-deoxyglucopyranose possesses in consequence some of the properties characteristic of furanose derivatives of the ordinary sugars. The evidence now submitted establishes, however, a direct structural relationship between this trimethyl 2-deoxyglucose, the corresponding lactone, and Bergmann's labile 2-deoxymethylglucoside on the one hand and tetramethyl glucopyranose on the other, and provides confirmation of the ring structures assigned by Levene and Mikeska (*loc. cit.*).

Another point which has emerged during the present work is concerned with the stereochemistry of the reaction between derivatives of glucal and perbenzoic acid. Glucal gives no detectable proportion of glucose derivatives when allowed to react with perbenzoic acid in the presence of water or methyl alcohol. On the other hand, trimethyl glucal gave under similar conditions an excess of trimethyl glucose (see above), 3-methyl glucal gave 3-methyl glucose (Levene and Raymond, *loc. cit.*), and triacetyl glucal yielded as the only recognised product a derivative of glucose (Tanaka, *Bull. Chem. Soc., Japan*, 1930, **5**, 214; Levene and Raymond, *loc. cit.*). We have now found on further examination that triacetyl glucal behaves normally when treated with perbenzoic acid and water, giving both glucose and mannose derivatives. The mannose was isolated in the form of its characteristic crystalline phenylhydrazone and under suitable conditions the yield of mannose was as high as 20% of the theoretical.

EXPERIMENTAL.

The Action of Perbenzoic Acid on Triacetyl Glucal.—Perbenzoic acid was prepared in excellent yield from benzoyl peroxide by Lévy and Lagrave's method (*Bull. Soc. chim.*, 1925, **37**, 1597).* Triacetyl glucal (2 g.) (Fischer, *loc. cit.*) was dissolved in ethyl acetate (10 c.c.) containing perbenzoic acid (1·3 g.). After the addition of water (2 c.c.) the mixture was shaken at room temperature for 4 hours and kept over-night. The emulsion was shaken with water, the aqueous layer removed, and the extraction with water repeated three times. The combined aqueous extracts were shaken twice with a little ether to remove benzoic acid and evaporated at 45°/12 mm. to a colourless glass (1·4 g.), which had $[\alpha]_D^{18°}$ + 90° (initial value

* This method is similar to that submitted by Tiffeneau ("Organic Syntheses," **8**, p. 30) with the exception that one-tenth the concentration (not amount) of sulphuric acid is employed. Both methods give perbenzoic acid in good yield and accordingly we withdraw the statement previously made (J., 1930, 2639). (E. L. H.)

in water; *c*, 0·5), + 82° (equilibrium value after 4 hours). This material (1·35 g.) was deacetylated by treatment with 6% aqueous sodium hydroxide (10 c.c.) at 18° for 15 minutes. The addition of phenylhydrazine (1·5 g.), dissolved in glacial acetic acid (3·5 c.c.), gave in a few minutes at room temperature a copious precipitate (0·33 g.) of mannosephenylhydrazone, m. p. 190°. When the separation of mannosephenylhydrazone had ceased, the clear solution was heated for 2 hours at 100° with an excess of phenylhydrazine. Glucosazone was obtained in good yield and was recognised by its characteristic appearance and the m. p. 206°.

Trimethyl Glucal.—Triacetyl glucal (10 g.), dissolved in acetone (100 c.c.), was subjected to simultaneous deacetylation and methylation at 47° by methyl sulphate (32 c.c.) and 30% aqueous sodium hydroxide (74 c.c.). After the addition of the reagents, which occupied 2 hours, the solution was heated for 1 hour at 50°. The acetone was then removed by distillation under diminished pressure and the product was extracted from the aqueous solution by chloroform. By distillation under diminished pressure the methylated glucal (4·3 g.), b. p. 65—75°/0·04 mm., $n^{20°}$ 1·4621, was separated from coloured impurities, the formation of which could not be avoided even by use of the mildest possible experimental conditions. Methylation was completed by one treatment with methyl iodide and silver oxide, giving a colourless mobile oil, b. p. 45°/0·03 mm., $n_D^{20°}$ 1·4558, $[\alpha]_D^{18°}$ + 19·6° in water (*c*, 1·1) (Found : C, 57·2; H, 8·7; OMe, 49·3. $C_9H_{16}O_4$ requires C, 57·4; H, 8·5; OMe, 49·5%). This material retained in full the unsaturated properties of glucal. It was unstable in hot alkaline solutions, giving dark-coloured decomposition products. In addition to normal trimethyl glucal some trimethyl ψ-glucal appeared to be present (see next paragraph).

Perbenzoic Acid and Trimethyl Glucal.—A solution of trimethyl glucal (7·4 g.) in water (50 c.c.) was shaken for 6½ hours at 18° with ether (55 c.c.) containing perbenzoic acid (7·4 g.). The reaction proceeded so vigorously that during the first 15 minutes cooling was necessary. The aqueous layer was separated, and the ethereal layer extracted several times with water. The united aqueous portions, after neutralisation with sodium bicarbonate, were concentrated under diminished pressure to a syrup, which was dissolved in ether to remove sodium benzoate. Removal of the ether left a pale yellow, viscid syrup (A) (5·9 g.) which could not be crystallised but had the composition of a trimethyl hexose (Found : OMe, 38·5. Calc. : OMe, 41·9%). $[\alpha]_D^{19°}$ + 64° (initial value in water; *c*, 0·9), + 58° (equilibrium value). In another experiment, when trimethyl glucal was shaken for 3 hours at 0° with perbenzoic acid in the presence of water, the resulting mixture of trimethyl hexoses had

$[\alpha]_D^{18°}$ + 75° in water (*c*, 1·0), + 70° (equilibrium value after 2 hours).

The syrup (A) was methylated twice by methyl iodide and silver oxide, giving quantitatively a product which had a low methoxyl content (OMe, 53%) and could not be methylated further. The deficiency in methoxyl appeared to be due to the presence of some derivative of ψ-glucal in the trimethyl glucal used. The impurity was removed in the form of decomposition products when the methylation was completed by methyl sulphate and alkali (yield, 60%). The fully methylated product (1·7 g.) was heated with 6% hydrochloric acid at 100° for 6 hours, the course of the hydrolysis being followed polarimetrically. During this period the rotation changed from $[\alpha]_D^{18°}$ − 7° to + 56°. After neutralisation with barium carbonate the aqueous solution was extracted 9 times with chloroform. Removal of the solvent left a pale yellow, viscid syrup (1·22 g.) which rapidly crystallised and on recrystallisation from light petroleum gave 2 : 3 : 4 : 6-tetramethyl glucopyranose as long needles, m. p. 84—85°, $[\alpha]_D^{20°}$ + 100° (initial value in water; *c*, 0·4), + 83° (equilibrium value). A mixed m. p. determination with an authentic specimen showed no depression. The petroleum mother-liquors gave on evaporation a pale straw-coloured syrup (0·4 g.), $[\alpha]_D^{18°}$ + 54° (equilibrium value in water; *c*, 1·0), which had the composition of a tetramethyl hexose (Found : OMe, 51·8%) and gave, when heated with alcoholic aniline, mainly tetramethyl glucopyranose anilide.

3 : 4 : 6-*Trimethyl* 2-*Deoxyglucose from Trimethyl Glucal.*—A solution of trimethyl glucal (3·6 g.) in 2*N*-sulphuric acid (36 c.c.) was kept at room temperature until a test with bromine showed that no unsaturated material was present (7 days). After neutralisation with sodium bicarbonate the solution was extracted 9 times with chloroform. Removal of the solvent gave a pale yellow syrup (3·0 g.), which on distillation gave a colourless syrup (2·4 g.), b. p. 102—105°/0·01 mm., $n_D^{18°}$ 1·4622. The distillate crystallised spontaneously and after removal of adhering syrup by draining on porous earthenware, and recrystallisation from ether–light petroleum, gave 3 : 4 : 6-trimethyl 2-deoxyglucose as needles, m. p. 59—60°, $[\alpha]_D^{18°}$ + 61° (in water 5 mins. after dissolution; *c*, 1·1), + 35° (equilibrium value after 3 hrs.) in agreement with the constants recorded by Levene and Mikeska (*loc. cit.*) (Found : OMe, 45·2. Calc. for $C_9H_{18}O_5$: OMe, 45·1%).

3 : 4 : 6-*Trimethyl* 2-*Deoxygluconolactone.*—Trimethyl 2-deoxyglucose (1·5 g.), dissolved in water (15 c.c.), was oxidised by bromine (3·3 c.c.) at 35—40° for 67 hours until the reducing properties had disappeared. The excess of bromine was removed by aeration, the

hydrobromic acid was removed by silver carbonate, and the organic acid was liberated from its silver salt by titration with hydrochloric acid. The filtered aqueous solution was evaporated to a syrup (1·5 g.) under diminished pressure, and lactonisation was completed by heating for 1 hour at 100°/12 mm. On distillation, 3 : 4 : 6-trimethyl 2-deoxygluconolactone was obtained as a colourless oil (1 g.), b. p. about 120°/0·04 mm., $n_D^{17°}$ 1·4606. When heated on the water-bath for 90 minutes with phenylhydrazine (0·05 g.), the lactone (0·1 g.) gave the crystalline *phenylhydrazide* of 3 : 4 : 6-trimethyl 2-deoxygluconic acid, which, after recrystallisation from ethyl acetate, was obtained as colourless silky needles, m. p. 125° (Found : C, 57·9; H, 8·1; N, 9·3; OMe, 29·9. $C_{15}H_{24}O_5N_2$ requires C, 57·7; H, 7·7; N, 9·0; OMe, 29·8%).

The rotation of the lactone in chloroform ($[\alpha]_D^{20°}$ + 87°, *c* 0·7) was identical with that of the trimethyl 2-deoxygluconolactone prepared by Levene and Mikeska (*loc. cit.*). In water (*c*, 1·2) the rotation was $[\alpha]_D^{19°}$ + 106° (initial value); 94° (10 hrs.); 77° (30 hrs.); 65° (50 hrs.); 61° (70 hrs.); 55° (100 hrs.); 51° (130 hrs.); 50° (150 hrs.); 49° (180 hrs., constant equilibrium value). The rotation of the acid was determined by dissolving a weighed quantity of the lactone in an excess of *N*-sodium hydroxide. After 15 minutes the exact amount of *N*-sulphuric acid equivalent to the sodium hydroxide was added and the solution was made up to a known volume with water. The following observations were then made: $[\alpha]_D^{19°}$ + 24° (initial value; *c* 0·8, calc. as lactone); 32° (20 hrs.); 35° (40 hrs.); 38° (50 hrs.); 40° (68 hrs.); 43° (90 hrs.); 46° (140 hrs.); 47° (180 hrs.); 49° (240 hrs., constant equilibrium value). The rate of hydrolysis of the lactone in aqueous solution was identical with that of tetramethyl δ-mannonolactone, the time required for the development of 25% of acid from the lactone being in each case 17 hours. At equilibrium the percentage of lactone present was 30%.

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