CCCXXVI.—*The Structure of the Normal and γ-Forms of Tetramethyl Glucose. Oxidation of Tetramethyl δ- and γ-Gluconolactones.*

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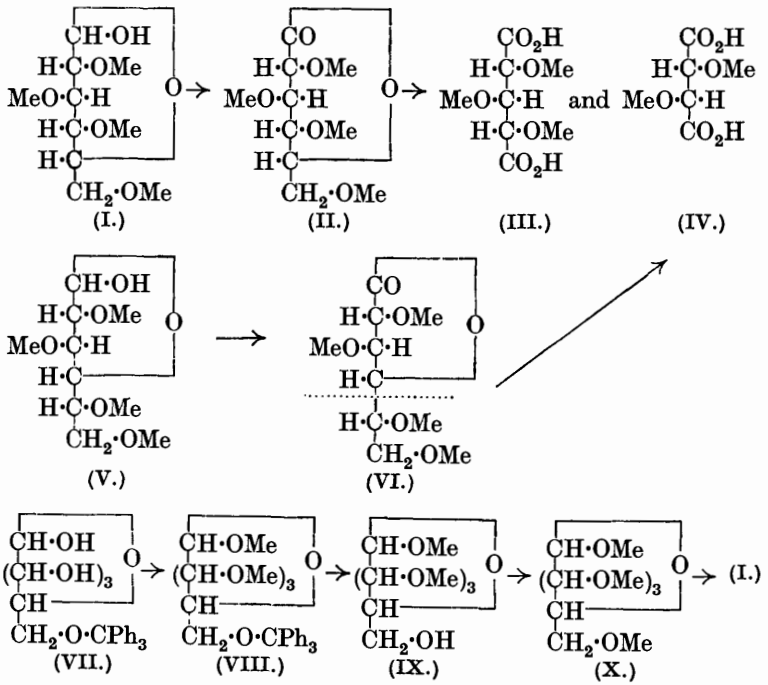
IN a paper on the revision of the structural formula of glucose (Charlton, Haworth, and Peat, J., 1926, 89), the constitution assigned to the usual form of tetramethyl glucose represented this sugar as an amylene oxide, whilst the butylene-oxide formula was assigned to its labile or γ-form. The experimental basis for these conclusions was the recognition that the lactones derived from these two sugars were, respectively, δ- and γ-lactones. These conclusions have been tested in the course of subsequent work (Drew, Goodyear, and Haworth, this vol., p. 1237), and further experimental data are now furnished which confirm the recognition of the two forms of the methylated sugar as 2 : 3 : 4 : 6-tetramethyl glucose (*i.e.*, the normal crystalline variety) and 2 : 3 : 5 : 6-tetramethyl glucose (the labile or γ-variety, which is a liquid). This inference with respect to the normal form of the sugar was supported by the direct oxidation of the normal crystalline sugar with nitric acid (Hirst, J., 1926, 350).

Tetramethyl δ-gluconolactone has been prepared in a condition of greater purity by preliminary conversion into the crystalline phenylhydrazide (m. p. 115°; $[\alpha]_D$ + 42·1° in ethyl alcohol) of the corresponding acid, followed by regeneration of the lactone from this derivative. The physical constants of the regenerated lactone differ but slightly from those already recorded, and the substance is still recognised as a liquid. On the other hand, the lactone derived

by oxidation of the liquid tetramethyl γ-glucose is crystalline, and the physical constants are also on record (Drew, Goodyear, and Haworth, *loc. cit.*).

The study of these two lactones has now been continued by the application of the method of direct oxidation with nitric acid. Tetramethyl δ-gluconolactone, when treated with this reagent, gave a mixture of methoxyglutaric and methoxysuccinic acids, which were separated and identified through their crystalline amides and methylamides. Whilst the comparison of the amides with authentic specimens could be made with a considerable measure of certainty, yet, for reasons already explained (Haworth and Jones, this vol., p. 2349), it appeared to be advantageous to strengthen the validity of such comparisons by the adoption of the methylamides as reference compounds; but it should be added that the preparation of the amides enables a more satisfactory estimate to be made of the yields of the products of oxidation. The experiments have shown that the δ-lactone is



degraded to give a considerable yield (47%) of *i*-xylotrimethoxyglutaric acid (III) and a smaller yield (20%) of *d*-dimethoxysuccinic acid (IV), since the methylamides of these products were shown to be identical with authentic specimens prepared from other

sources. The isolation of the xylotrimethoxyglutaric acid affords definite proof that the oxygen of the oxide ring cannot be attached to carbon atom 2, 3, or 4, since the stereochemical arrangement of the groups associated with these carbon atoms is preserved in the *i*-xylotrimethoxyglutaric acid. On the other hand, the possibility of the attachment of the oxygen of the ring to carbon atom 6 in normal glucose derivatives is excluded by a large number of observations, amongst which may be mentioned (1) the oxidation of methylglucoside to the methylglucoside of glycuronic acid (Smolenski, *Rocz. Chem.*, 1923, **3**, 153); (2) the preparation herein described of 2 : 3 : 4-trimethyl β-methylglucoside (IX) [which is readily converted into normal tetramethyl methylglucoside (X)] from 6-triphenylmethyl glucose (VII), the constitution of which has been proved by Helferich, Klein, and Schäfer (*Annalen*, 1926, **447**, 19). The only remaining point for the attachment of the oxygen of the ring is the 5-position. The conclusion is therefore drawn that the structural formula (II) represents the constitution of tetramethyl δ-gluconolactone, and thus the formula (I), which represents crystalline tetramethyl glucose as an amylene oxide, is confirmed.

Similar experiments were conducted on the degradative oxidation of tetramethyl γ-gluconolactone, and these revealed the greater stability of this lactone towards nitric acid as compared with the δ-lactone. A further distinction is that a portion of the lactone appeared to undergo very profound degradation during the oxidation, a circumstance which has a definite bearing on the constitution of the substance. The only dibasic acids definitely recognised in the products from this treatment were oxalic acid and *d*-dimethoxysuccinic acid (IV), which was isolated as the amide and methylamide, both of which are crystalline, the latter compound being compared with an authentic specimen of the methylamide obtained ultimately from *d*-tartaric acid (compare Haworth and Jones, *loc. cit.*). An exhaustive but unsuccessful search was made for the presence of a glutaric acid derivative, the experimental conditions being such that the presence of a derivative of this acid could easily have been detected had it been formed. The isolation of *d*-dimethoxysuccinic acid from tetramethyl γ-gluconolactone proves definitely that the oxygen of the oxide ring cannot be attached to carbon atom 2 or 3, and thus the propylene-oxide formula for γ-glucose derivatives, advocated by Irvine and Patterson (J., 1922, **121**, 2152), is definitely disproved. Again, the oxygen of the ring cannot be attached at position 6, since tetramethyl γ-gluconolactone is derivable (in two stages) from 2 : 3 : 6-trimethyl glucose (Charlton, Haworth, and Peat, *loc. cit.*) but not from the 2 : 3 : 4-isomeride. The failure to isolate trimethoxyglutaric acid, when considered in relation to the

fact that the amylene-oxide structure has already been assigned to the δ-lactone, suffices to exclude the possibility of attachment of the oxide ring at carbon atom 5, and it follows, therefore, that the oxygen of the ring must be linked to carbon atom 4. Tetramethyl γ-glucose and its related lactone are thus seen to have a butylene- or γ-oxide structure (V and VI).

In the above reaction, scission of the lactone had occurred at the point indicated by the dotted line drawn between the fourth carbon atom, which is attached to one junction of the oxide ring, and the fifth carbon atom of the chain. Consideration of alternative methods by which a compound of formula (VI) could undergo scission appears to supply a reason for the failure to obtain *d*-dimethoxysuccinic acid in a yield greater than 20%. A comparison with the course which the oxidation of the δ-lactone takes, giving both a glutaric and a succinic acid derivative, suggests that if an analogous breakdown of the γ-lactone occurred, this might lead to the formation, not only of *d*-dimethoxysuccinic acid, but also of methoxymalonic acid. The isolation of the latter, which we failed to recognise, would be rendered difficult by reason of its instability. Indications were given of the presence of a dimethyl saccharolactone, which had presumably been formed by the oxidation of the terminal $-CH_2OMe$ group at position 6 to a carboxyl group. A similar oxidation of this terminal group is recorded in the case of 2 : 3 : 6-trimethyl glucose (Irvine and Hirst, J., 1922, **121**, 1213) and also with 2 : 3 : 5-trimethyl arabinose (Baker and Haworth, J., 1925, **127**, 365).

Incidentally, it may be remarked that the butylene-oxide ring structure of the γ-glucose residue in glucose-diacetone receives confirmation. Support is thus given to the inferences drawn by Karrer and Hurwitz (*Helv. Chim. Acta*, 1921, **4**, 728), although their conclusions and experimental methods were severely attacked by Irvine and Patterson (J., 1922, **121**, 2155), whose criticisms are seen to have been based on a misapprehension as to the structure of the monomethyl derivative of glucose-diacetone.

EXPERIMENTAL.

Preparation of Tetramethyl δ-Gluconolactone (II).—Specially purified tetramethyl glucose (I) (m. p. 86°) was converted into tetramethyl gluconic acid by digestion with bromine water at 60° until the solution no longer gave a positive Fehling's test. The lactone was then isolated by the usual method as a colourless liquid, b. p. 106—107°/0·04 mm.; $n_D^{14°}$ 1·4566; $[\alpha]_D^{22°}$ + 99° in water ($c = 2·27$; initial value), decreasing rapidly to the constant value $[\alpha]_D^{22°}$ + 30·8° after 8 hours. Attempts to induce the lactone to crystallise were unsuccessful, and further purification was effected

by regenerating the compound from the crystalline phenylhydrazide of the corresponding tetramethyl gluconic acid. The phenylhydrazide was prepared by the method described by Charlton, Haworth, and Peat (*loc. cit.*); recrystallised from benzene, it had m. p. 115°, $[\alpha]_D$ + 42·1° in ethyl alcohol (c = 1·0). Treatment with 5% aqueous hydrochloric acid for 3 hours on the water-bath served to regenerate the acid, and the lactone was isolated by evaporating the solution to dryness under diminished pressure and extracting the residue with dry chloroform admixed with a little ether. The phenylhydrazine hydrochloride was filtered off, the solvent evaporated under diminished pressure, and the residual syrup purified by repeated distillation in a high vacuum. The final distillate had b. p. 101°/0·06 mm.; $n_D^{14°}$ 1·4565; $[\alpha]_D^{18°}$ + 101° in water (c = 2·06; initial value), decreasing in the course of 8 hours to a constant value $[\alpha]_D^{18°}$ 29·6°. The regenerated lactone was therefore almost identical in physical properties with the original specimen, and further repeated attempts to induce crystallisation were unsuccessful.

Oxidation of Tetramethyl δ-Gluconolactone.—A specimen of the lactone (4·0 g.), which had been purified as above, was dissolved in nitric acid (32 c.c.; d 1·42). A vigorous reaction took place at 70°. This was moderated by cooling the reaction vessel, and after 1 hour the temperature was raised to 90° and the reaction allowed to proceed to completion (6 hours). The solution was diluted with water and the reaction product isolated as the methyl ester as described below for the tetramethyl γ-gluconolactone. The esterified product was distilled, giving a colourless liquid (A) (yield, 2·7 g.), b. p. 98—100°/0·05 mm.; $n_D^{15°}$ 1·4400; $[\alpha]_D^{16°}$ + 21·7° in water (c = 2·2). This material appeared to be a mixture containing approximately 30% of methyl *d*-dimethoxysuccinate and 70% of methyl *i*-xylotrimethoxyglutarate (Found: C, 46·8; H, 7·2; OMe, 61·3. Calc.: C, 47·6; H, 7·1; OMe, 61·5%). The presence of both these substances was proved by the isolation of the corresponding crystalline amides and methylamides.

Amides.—The distillate (A) (1·0 g.) was dissolved in 6 c.c. of methyl alcohol saturated with ammonia and kept for 70 hours, during which 0·19 g. of *d*-dimethoxysuccinamide separated as clusters of long needles. These darkened when heated above 200°, melted at 270° to a dark liquid, and decomposed rapidly at 283°; $[\alpha]_D$ + 94° in water (c = 0·51). Direct comparison with an authentic specimen established the identity of this material. The disturbance of the solution consequent upon the removal of the dimethoxysuccinamide induced rapid crystallisation of a second substance of markedly different habit and appearance; this was filtered off after 4 days, and washed with methyl alcohol and ether; yield, 0·25 g.;

m. p. 197°. It was optically inactive. Comparison with an authentic specimen prepared from xylose proved its identity with *i*-xylotrimethoxyglutaramide.

Methylamides.—The distillate (A) (1·4 g.) was dissolved in methyl alcohol (8 c.c.) saturated with methylamine; after 3 days, the solvent and the excess of methylamine were removed by evaporation in a vacuum desiccator. The residual solid mass was dissolved in 30 c.c. of boiling ethyl acetate, the solution cooled, and the resulting crystals were washed with a little ethyl acetate and then with ether; m. p. 158—163° (yield, 0·34 g.). Recrystallisation from ethyl acetate now gave the methylamide of *i*-xylotrimethoxyglutaric acid in long needles which, alone or when mixed with an authentic specimen prepared from xylose, melted at 165—167°. The substance was optically inactive (Found: C, 48·3; H, 8·3; N, 11·5; OMe, 34·3. Calc. for $C_{10}H_{20}O_5N_2$: C, 48·4; H, 8·1; N, 11·3; OMe, 37·5%). The mother-liquor from the first crop of crystals, on evaporation to dryness under diminished pressure, gave a residue which was recrystallised three times from ether–ethyl acetate (equal vols.); yield, 0·05 g.; long needles, m. p. 206°, alone or when mixed with a specimen of the methylamide of *d*-dimethoxysuccinic acid prepared from *d*-tartaric acid.

Oxidation of Tetramethyl γ-Gluconolactone (VI).—The lactone used was a crystalline specimen, m. p. 26—27°, conforming exactly with the polarimetric standards for the material prepared by Drew, Goodyear, and Haworth from tetramethyl γ-glucose (this vol., p. 1242). This lactone (3·4 g.) was dissolved in nitric acid (26 c.c.; *d* 1·42) and heated on the water-bath at 80° for ½ hour, but showed no appreciable change; the temperature was accordingly raised to 90°, but the reaction was sluggish and had not reached completion after 5 hours at this temperature; nevertheless it was decided to examine the products at this stage. The solution was diluted with water and the nitric acid removed by distillation under diminished pressure with frequent additions of water. The residue was esterified with methyl alcohol (50 c.c.) containing hydrogen chloride (2·4 g.), the mineral acid neutralised with silver carbonate, and the filtered solution evaporated to a syrup which contained a small quantity of mineral matter. The latter was removed by dissolving the syrup in benzene, and the subsequent evaporation of the solvent served to remove all traces of water. Distillation of the esterified product was difficult owing to the presence in small amount of a substance which underwent transformation when heated at 120° in a vacuum. This gave a minute quantity of a volatile liquid, probably methyl alcohol, of which the sudden evolution in the form of vapour caused violent bumping. The reaction product was there-

fore heated at 135—140°/11 mm. until this transformation was complete. Distillation now proceeded smoothly and gave (*a*) 0·3 g. of a colourless liquid which solidified in the receiver and was mainly methyl oxalate—some of this material had been collected during the preliminary heating; (*b*) 0·7 g., b. p. 135—140°/12 mm., $n_D^{15°}$ 1·4365; (*c*) 0·85 g., b. p. 140—160°/12 mm., $n_D^{15°}$ 1·4442, $[\alpha]_D$ + 57° in water (c = 1·1; initial value), decreasing to + 50° after several days; (*d*) residue, 0·2 g. Fractions (*b*) and (*c*) were colourless liquids which developed an acid reaction in aqueous solution; neutralisation of these solutions indicated the presence of a lactone. This observation, together with previous experience gained in distilling the esters of γ-hydroxy-acids, suggested that the transformations which preceded distillation were due to the elimination of methyl alcohol from the ester of a γ-hydroxy-acid, with the formation of a lactone. The presence of a lactone was further demonstrated by the change in rotation of the aqueous solution when kept for several days.

Amides and Methylamides.—Both fractions (*b*) and (*c*) yielded crystalline *d*-dimethoxysuccinamide when dissolved in methyl-alcoholic ammonia. In one experiment, 0·120 g. of (*b*) gave after 4 days 0·064 g. of long needles, which were filtered off and washed with methyl alcohol and ether; these darkened at 245°, began to melt with decomposition at 270°, and decomposed entirely at 283°. Control experiments made in the same apparatus and under identical conditions, in which specimens of the *d*-dimethoxysuccinamide prepared from *d*-tartaric acid were employed, gave identical results; $[\alpha]_D^{20°}$ + 95° (c = 1·1) (Found: C, 40·8; H, 7·1; N, 15·7; OMe, 34·7. Calc. for $C_6H_{12}O_4N_2$: C, 40·9; H, 6·8; N, 15·9; OMe, 35·2%). Further proof of identity was furnished by preparing the corresponding methylamide. From 0·15 g. of fraction (*b*) in 1·1 c.c. of methyl alcohol saturated with methylamine, a mixture of syrup and crystals was obtained by removal of the solvent under diminished pressure. The crude crystalline material weighed 0·06 g., and on recrystallisation from ethyl acetate gave needles which, alone or mixed with an authentic specimen of the methylamide of *d*-dimethoxysuccinic acid prepared from *d*-tartaric acid, melted at 204° (Found: C, 46·7; H, 7·9; N, 13·8. Calc. for $C_8H_{16}O_4N_2$: C, 47·05; H, 7·8; N, 13·7%).

Fraction (*c*) (0·500 g.) gave analytically pure *d*-dimethoxysuccinamide (0·068 g.), m. p. 270° (decomp. 282°) (Found: C, 40·9; H, 7·1; N, 15·5%). An exhaustive examination was made of the syrup remaining after evaporation of the mother-liquors from the amide formations. A further very minute quantity of *d*-dimethoxysuccinamide was obtained, but no other crystalline material. In particular, no trimethoxyglutaramide could be isolated. For this

examination the whole of the remaining portions of (*b*) and (*c*) were treated with methyl alcohol and ammonia. *Titration of fraction* (*c*): 0·1040 G. required 3·9 c.c. of *N*/10-sodium hydroxide for neutralisation of the lactone portion, and 8·3 c.c. (total) of *N*/10-sodium hydroxide for hydrolysis and neutralisation. These figures, in conjunction with the yield of crystalline amide (which gives an approximate estimate of the amount of dimethoxysuccinic ester present), indicated that the major portion of (*c*) consisted of a dibasic lactone-ester, possibly the methyl ester of dimethyl saccharolactone. The amount of unchanged tetramethyl γ-gluconolactone was apparently very small, and this was confirmed by the failure to isolate the characteristic and easily recognisable crystalline phenylhydrazide of the corresponding tetramethyl gluconic acid.

[With ABRAHAM LEARNER.]

Methylation of Triphenylmethyl Glucose (VII).—Crystalline triphenylmethyl glucose (3·0 g.) (as prepared by Helferich, Klein, and Schäfer, *loc. cit.*) was dissolved in methyl iodide and treated in the usual manner with silver oxide. The operation was repeated three times, and the crude product so obtained gave OMe, 21·7 (Calc. for $C_{29}H_{34}O_6$: OMe, 25·9%), the low value being attributable to the presence of a small quantity of triphenylcarbinol. The methylated product was hydrolysed by 100 c.c. of methyl alcohol containing 0·5% of hydrogen chloride. After being kept for 5 minutes at 65° and for 2½ hours at room temperature, the solution was neutralised with silver carbonate. The residual syrup obtained after evaporation of the solvent was extracted with warm water. The aqueous extract, evaporated at 50° under diminished pressure, yielded a syrup which crystallised partially when nucleated with a specimen of 2 : 3 : 4-trimethyl β-methylglucoside. Purification of this material by distillation from a bath at 135°/0·1 mm. yielded a colourless liquid which crystallised on cooling. The crystals were drained on porous earthenware, and recrystallised from light petroleum, giving matted needles; these, alone or when mixed with a specimen of 2 : 3 : 4-trimethyl β-methylglucoside (IX) prepared from gentiobiose, melted at 92—93° (Found: C, 50·7; H, 8·6. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5%).

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