

XLV — *The Structure of the Normal Monosaccharides.*
Part IV. Glucose.

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IN Part I (Hirst and Purves, J., 1923, **123**, 1352) the reasons which had led to the general adoption of a butylene oxide formula for normal aldose derivatives were reviewed, the need of more definite chemical evidence was pointed out, and a method for studying the problem was outlined which has since furnished strong evidence that normal derivatives of xylose (*loc. cit.*), arabinose (Hirst and Robertson, J., 1925, **127**, 358), and rhamnose (Hirst and Macbeth, this vol., p. 22) are, in fact, amyleno-oxidic and not butylene-oxidic, as had hitherto been supposed. In the experiments now to be

described, the method has been extended to the hexose series. The oxidation of tetramethyl glucose, whose structural relationship to the normal methylglucosides and to glucose has been the subject of much investigation, has been studied and as a result it appears that the amylenoxide formula should be ascribed also to normal derivatives of glucose. This is in exact agreement with evidence as to the structure of glucose recently obtained by Charlton, Haworth, and Peat (this vol., p. 89), whose experiments were based on considerations of an entirely different nature. If this structure for glucose be accepted, changes in the nomenclature of certain derivatives will obviously be necessary analogous to the renaming of normal tetramethyl glucose as the 2 : 3 : 4 : 6- instead of the 2 : 3 : 5 : 6-derivative of glucose.

The principal method adopted in the present investigation was to oxidise tetramethyl glucose with nitric acid. The reaction between a normal trimethyl pentose (I) and nitric acid is simple in nature, involving only the oxidation to carboxyl of the reducing and the potential primary alcoholic groups situated respectively at the two ends of the pentose carbon chain. Trimethyl rhamnose (II) also reacted simply, the terminal group $\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$, produced by the action of the oxidising agent in forming trimethyl rhamnonic acid, giving quantitatively carboxyl and carbon dioxide. A methylated hexose, however, whether a 1 : 4- or a 1 : 5-oxide, presents a very different type of structure and it was to be expected that the course of oxidation would be more complicated. If the amylenoxide structure of tetramethyl glucose (III) be assumed, the first stage in the reaction would be the production of tetramethyl gluconic acid (IV), and its subsequent course would be determined by the action of nitric acid on the group $\cdot\text{CH}(\text{OMe})\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{OMe}$, with the ketone $\cdot\text{CH}(\text{OMe})\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OMe}$ as a probable intermediate product. It is well known that ketones of the type $\text{R}\cdot\text{CO}\cdot\text{R}'$ may be oxidised in different ways according to the experimental conditions. The main product from 2 : 3 : 4 : 6-tetramethyl glucose might therefore be either *d*-dimethoxysuccinic acid (V) or inactive xylotrimethoxyglutaric acid (VI), according as the break occurred between the 4th and 5th or between the 5th and 6th carbon atoms. It is evident that by a similar series of steps, shown in the accompanying scheme, butylene-oxidic tetramethyl glucose (VII) might also give dimethoxysuccinic acid, and it follows that the isolation of this acid alone would not enable precise conclusions to be drawn concerning the structure of tetramethyl glucose. The detection of xylotrimethoxyglutaric acid, on the other hand, would definitely indicate the presence of an amylenoxide linking. It was therefore necessary to establish experimental conditions such that the nature of the

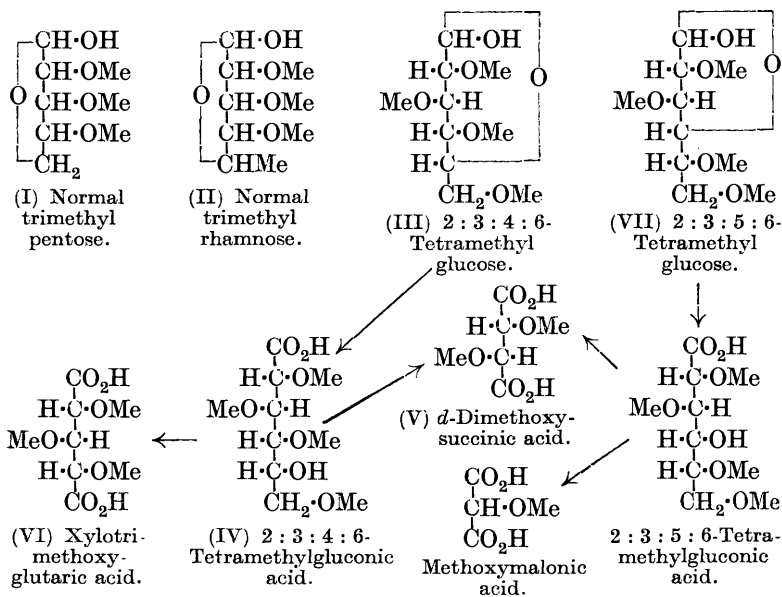
various oxidation products would lead definitely to the allocation of a structural formula.

This was ultimately accomplished by oxidising tetramethyl glucose for a short time with nitric acid of density 1.420. The reaction proceeded smoothly, was easy to control, and led to very little loss of material by side reactions. In this respect the reagent was much more satisfactory than the acid (*d* 1.2) which had previously been most frequently employed in the sugar group. With the latter, even at comparatively low temperatures, the more prolonged action necessary to effect the requisite oxidation invariably yielded considerable quantities of oxalic acid by a profound decomposition of the molecule. The product isolated in good yield was a mixture containing both *d*-dimethoxysuccinic acid and xylotrimethoxyglutaric acid, which were separated from each other by taking advantage of the different rates of formation of their very characteristic crystalline diamides. Dimethoxysuccinamide (Purdie and Irvine, J., 1901, **79**, 960) and xylotrimethoxyglutaramide (Hirst and Purves, *loc. cit.*) were thus obtained in a pure condition and their identity was placed beyond doubt by comparison with authentic specimens. It has already been indicated (Hirst and Macbeth, *loc. cit.*) that there appears to be no reason for suspecting any wandering of the methyl groups during oxidation, and it follows, therefore, from what has been said above, that normal tetramethyl glucose must be the 2 : 3 : 4 : 6-derivative possessing the amylenoxide formula (III), the possibility of a propylene or ethylene-oxide structure being entirely excluded by the nature of the products isolated.

The interest attached to this reaction and the desirability of accumulating as much evidence as possible concerning the oxidation of a fully methylated hexose led to a further study of the action of nitric acid and of alkaline potassium permanganate on tetramethyl glucose. The reaction appears to take an entirely different course from that of 2 : 3 : 6-trimethyl glucose when oxidised under precisely similar conditions (Irvine and Hirst, J., 1922, **124**, 1222). The latter gave with nitric acid (*d* 1.2) at 60° a dibasic acid (dimethylsaccharic acid), whereas tetramethyl glucose gives mainly tetramethylgluconic acid with a small quantity of dimethoxysuccinic acid, apparently without going through the intermediate stage of trimethylsaccharic acid. This difference is interesting, especially as butylene-oxidic trimethyl arabinose with a terminal group similar to that present in tetramethyl glucose can be oxidised to dimethoxyglutaric acid (Baker and Haworth, J., 1925, **127**, 365). A sufficient number of examples has not, however, been examined to justify any views as to whether this behaviour is the exception or the rule. Prolonged treatment of tetramethyl glucose with nitric acid (*d* 1.2)

at higher temperatures produces a complex mixture containing much oxalic acid and little or no trimethoxyglutaric acid, the chief constituent being dimethoxysuccinic acid. Oxidation with alkaline potassium permanganate gave oxalic acid and dimethoxysuccinic acid.

Summarising the evidence obtained from these experiments, it appears that the oxidation of amyleno-oxidic tetramethyl glucose with nitric acid leads first to 2 : 3 : 4 : 6-tetramethylgluconic acid. Further oxidation splits the carbon chain either between the 4th and 5th or between the 5th and 6th carbon atoms to give dimethoxysuccinic acid or xylotrimethoxyglutaric acid, and the relative proportions in which the two changes take place vary with the experimental conditions, the latter change being favoured by oxidation with stronger acid for a shorter time.



EXPERIMENTAL.

Stability of Dimethoxysuccinic Acid in Presence of Nitric Acid.—Dimethoxysuccinic acid was heated in nitric acid (*d* 1.42) for several hours at 100°. No oxidation and no change in the initial specific rotation, $[\alpha]_D + 69.5^\circ$ ($c = 1.375$), were observed. Previous experiments have demonstrated the stability of trimethoxyglutaric acid.

Oxidation of Tetramethyl Glucose with Nitric Acid (*d* 1.42).—When a solution of tetramethyl glucose (5 g. of carefully recrystallised

material conforming to the accepted standards) in nitric acid (40 c.c. ; d 1.42) was kept at room temperature, oxidation began after 5 minutes; thereafter the reaction was controlled by gradual heating in such a way that evolution of oxides of nitrogen never became rapid. After $\frac{1}{2}$ hour, the temperature was raised to 90° and kept at this point for 2 hours; the evolution of gas had then almost ceased. Water (2 vols.) was added, and the excess of nitric acid removed by careful distillation at $40^\circ/9$ mm., with the addition of water in the usual manner. The dry oxidation product was a glass soluble with difficulty in methyl alcohol. It contained no oxalic acid. After esterification by boiling with methyl alcohol (50 c.c.) containing 4% of hydrogen chloride, the product was distilled under diminished pressure (for details of the method used, see previous papers). The main fraction (2.65 g.) was a colourless oil, b. p. $135\text{--}140^\circ/10$ mm. (bath at $150\text{--}155^\circ$), n_D^{20} 1.4375. The first and last fractions (0.4 and 0.8 g., respectively) showed n_D^{20} 1.4345 and 1.4416.

Examination of the Oxidation Product.—The main fraction was soluble in water and all the usual organic solvents. $[\alpha]_D = +31.5^\circ$ in methyl alcohol ($c = 2.085$) and $+33^\circ$ in aqueous ethyl alcohol ($c = 0.8$), and the characteristic change in rotation shown by lactones was not observed. The absence of lactonic substances was further shown by the compound titrating as an ester. The physical and chemical properties agreed most closely with those required for a mixture of 60% of methyl *d*-dimethoxysuccinate and 40% of methyl xylotrimethoxyglutarate (Found : C, 47.0; H, 7.05; OMe, 58.9; 0.106 g. required 9.0 c.c. of *N*/10-alkali for hydrolysis. Calc. for the above mixture : C, 47.2; H, 7.0; OMe, 60.9%; 9.5 c.c. The b. p., rotation, and refractive index are also in accord with this view. [Methyl *d*-dimethoxysuccinate has b. p. $135^\circ/12$ mm., n_D^{20} 1.4340, $[\alpha]_D +81^\circ$ in methyl alcohol ($c = 6.26$) (compare Purdie and Barbour, J., 1901, **79**, 971), and methyl xylotrimethoxyglutarate has b. p. $132^\circ/12$ mm., n_D^{15} 1.4402, and is optically inactive.]

Complete confirmation of these views was obtained by the formation in good yield of crystalline dimethoxysuccinamide and xylotrimethoxyglutaramide by the action of ammonia on the mixed esters. A solution of 1.0 g. in 8 c.c. of methyl alcohol saturated with dry ammonia began, after a few hours, to deposit crystals in characteristic, opaque, white tufts. These were collected at the end of 3 days, and after being washed with alcohol and ether and dried at 105° were found to be pure dimethoxysuccinamide (yield 0.36 g.). The substance was insoluble in cold organic solvents, but slightly soluble in water, in which the value $[\alpha]_D +95^\circ$ ($c = 0.80$) was observed. It sublimed in long needles on being heated in a vacuum

(compare Purdie and Irvine, *loc. cit.*), showed no definite m. p., but when heated fairly quickly showed the following sequence of changes: darkened at about 245°, melted partly with decomposition at 269°, and was completely decomposed at 276° (Found: OMe, 34.3. Calc., OMe, 35.2%). Its properties were in exact agreement with those of an authentic specimen of the amide prepared from methyl *d*-dimethoxysuccinate.

The mother-liquor of the dimethoxysuccinamide was kept for a further 4 days. Colour changes took place similar to those observed during the formation of xylotrimethoxyglutaramide (*loc. cit.*), and 7 days from the beginning of the experiment another crop of crystals began to be deposited as flat, transparent prisms, resembling xylotrimethoxyglutaramide in crystalline form. After 12 days, 0.25 g. was collected. This material showed a moderate solubility in water and could be recrystallised from an alcohol-ether mixture. It was optically inactive (tested in 2% solution in water). It melted in air to give a dark blue liquid, m. p. 194—195°, and at 194—195° when mixed with an authentic specimen of the glutaramide prepared from xylose (Found: C, 43.5; H, 7.4; OMe, 41.1. Calc.: C, 43.6; H, 7.3; OMe, 42.3%).

Further quantities of dimethoxysuccinamide were obtained by treating with ammonia in methyl alcohol the first and the last fraction. No oxamide could be detected.

Oxidation with Nitric Acid (d 1.2) at 75°.—A solution of 5.5 g. of tetramethyl glucose in 85 c.c. of nitric acid (*d* 1.2) was heated at 75° for 12 hours until the reaction appeared to be complete. The oxidation products (isolated as before after esterification) were (a) methyl oxalate (1 g.), (b) a clear yellow syrup (3.5 g.), b. p. 138—149°/9 mm. (bath at 150—156°), n_D^{20} 1.4415, $[\alpha]_D + 54^\circ$ in alcohol ($c = 1.348$), $[\alpha]_D + 53^\circ$ in aqueous alcohol ($c = 0.50$), decreasing to $+ 43^\circ$. This material on treatment with ammonia in methyl alcohol gave a small quantity of oxamide and much *d*-dimethoxysuccinamide. No xylotrimethoxyglutaric acid could be detected. The oxidation products under these conditions form a complex mixture, but consist principally of oxalic acid and dimethoxysuccinic acid. The high refractive index, the drop in rotation shown by the solution in aqueous alcohol, and the titration figures are in agreement with the view that some tetramethylgluconolactone was present in the main fraction (Found: C, 46.5; H, 6.6; OMe, 54.7%; 0.178 g. required 14.2 c.c. of *N*/10-alkali for hydrolysis, partly as lactone, partly as ester). The analysis of the corresponding lead salt is in accord with these views (Found: Pb, 50.0; OMe, 18.6%).

Oxidation with Nitric Acid (d 1.2) at 60°.—A solution of 7 g. of tetramethyl glucose in 50 c.c. of nitric acid (*d* 1.2) was heated at

85° until oxidation commenced, the temperature being then lowered to 60° and the reaction allowed to continue for 4½ hours. The product was treated in the way already described and was finally distilled. After a first fraction of 0.85 g., the greater part (4.0 g.) of the material was collected at 142—143°/9 mm. It could not be separated into its components by fractional distillation. The distillate was a neutral, clear syrup which developed acidity in contact with water; n_D^{20} 1.4526, $[\alpha]_D + 108^\circ$ in benzene ($c = 1.176$). In water the initial value, $[\alpha]_D + 80^\circ$ ($c = 1.792$), dropped rapidly to 64° after 28 minutes, 54.5° after 83 minutes, 45° after 158 minutes, and 39° after 280 minutes; the final value was 35°. This behaviour is characteristic of δ -lactones. Titration with alkali showed that the substance was partly lactonic and partly esteric in character. 0.1502 G. required (a) 5.0 c.c. of *N*/10-alkali as lactone, (b) 3.0 c.c. of *N*/10-alkali as ester (Found: C, 50.1; H, 7.5; OMe, 53.5%). 0.8 G. dissolved in 6 c.c. of methyl alcohol saturated with ammonia gave crystals of dimethoxysuccinamide (0.05 g.) in a few hours. These observations proved that the methyl ester of trimethoxysaccharolactone, if present at all, must have been there in very minute quantity, and the material under examination appeared to consist of 80% of tetramethylgluconolactone and 20% of methyl dimethoxysuccinate. This mixture requires C, 50.3; H, 7.5; OMe, 54.5% and 0.150 g. would require (a) 5.1 c.c. of *N*/10-alkali as lactone, (b) 2.9 c.c. of *N*/10-alkali as ester, whilst the b. p. and the initial and final values of $[\alpha]_D$ are in agreement with those expected.

(For the properties of dimethoxysuccinic acid derivatives, see Purdie and Irvine, *loc. cit.*; for those of tetramethylgluconolactone, see Pryde, J., 1924, 125, 520; Charlton, Haworth, and Peat, *loc. cit.*)

Oxidation with Potassium Permanganate.—Tetramethyl glucose (5 g.) was dissolved in water (100 c.c.) rendered just alkaline with potassium hydroxide, and to the solution, heated at 75°, was added gradually potassium permanganate (25 g.) dissolved in hot water. The colour of the permanganate solution disappeared quickly at first, but very slowly towards the end. After filtering and passing carbon dioxide through the filtrate to remove free alkali, the solution was evaporated to small bulk at 50°/12 mm. The greater portion of the potassium was removed by means of perchloric acid and after elimination of the remaining water the product (partly free acid and partly potassium salt) was esterified with acid methyl alcohol. On isolating and distilling the ester, 0.6 g. was obtained as a first fraction. This was almost entirely methyl oxalate (the identity of which was confirmed by transforming it into oxamide). The main fraction

(2 g.) showed b. p. 130—135°/9 mm. (bath at 145°), n_D^{20} 1.4342, $[\alpha]_D + 43^\circ$ ($c = 1.68$) in methyl alcohol [Found: OMe, 55.5; CO₂Me (by titration), 64%]. When it was treated with ammonia in methyl alcohol, oxamide was first formed followed by much dimethoxysuccinamide (50% by weight of the ester used; properties as above). It was evident, therefore, that the products were essentially oxalic acid and dimethoxysuccinic acid, the amount of trimethoxyglutaric acid being negligible.

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