CCI.—*The Constitution of the Disaccharides. Part XIII. The γ-Fructose Residue in Sucrose.*

By WALTER NORMAN HAWORTH, EDMUND LANGLEY HIRST, and VINCENT STANLEY NICHOLSON.

THE γ-fructose residue in sucrose was isolated by one of us in the form of tetramethyl γ-fructose (Haworth, J., 1915, **107**, 12; 1920, **117**, 199). This unstable sugar was characterised by its dextrorotation and by the ease with which it decolorised aqueous permanganate, but further study has revealed a remarkable and unexpected behaviour. In contact with dilute hydrochloric acid at 80°, or on digestion with acetic anhydride in presence of sodium acetate, this methylated ketose undergoes changes involving loss of three of its methoxyl groups as methyl alcohol. This circumstance explains many of the discordant results quoted in the literature of this sugar, and serves also to emphasise the danger attaching to the acceptance of preconceived ideas of the properties of methylated sugars.

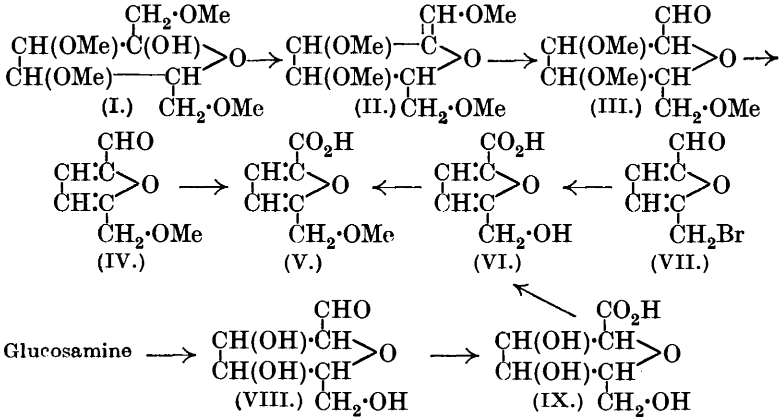
When 8% hydrochloric acid was used, more than a third of the product was collected as a typical aldehyde, having an odour like that of benzaldehyde and distilling at about 54°/0·07 mm. It was optically inactive, restored the colour to Schiff's reagent, reduced Fehling's solution, and decolorised permanganate instantly. The aldehyde was characterised by its giving crystalline derivatives; an *oxime*, m. p. 103—104°, and a *semicarbazone*, m. p. 166—167°. Its molecular composition, $C_7H_8O_3$, was recognised by this means, and its general properties suggested its relationship to furan.

The action of hot mineral acid on free sugars containing exposed hydroxyl groups, *e.g.* the pentoses, was already recognised as involving condensation with elimination of water, leading to the formation of furfural or similar products; but in the special case now under review, the hydroxyl positions in fructose are methylated, leaving only the reducing group exposed.

In a previous paper (Haworth and Hirst, J., 1926, 1858), reference was made to the tendency of tetramethyl γ-fructose to pass into furan derivatives during oxidative degradation, and it was there suggested that many of the anomalies attending the constitutional study of this sugar might be attributed to this behaviour. The present results extend and confirm this observation. It was also indicated that an explanation of this behaviour was to regard tetramethyl γ-fructose as a substituted hydrofuran (I), and this provisional formula is strongly supported by the series of transformations which are now recorded.

It is necessary to proceed with caution in the structural interpretation of these observations, and we have relied essentially on the isolation of crystalline products which in the last resort have been compared with substances of known constitution described in the literature. Evidence of the identity of the final products obtained by the conversion of tetramethyl γ-fructose into furan derivatives by contact with hydrochloric acid is now furnished.

The aldehyde, originating as already described, was identified as *ω-methoxy-5-methylfurfural* (IV), since it gave on oxidation with permanganate (compare Frankland and Aston, J., 1901, **79**, 515) *ω-methoxy-5-methylfuran-2-carboxylic acid* (V), m. p. 72—73°, the constitution of which was confirmed by comparison with the crystalline acid isolated from two known sources: ω-bromo-5-methylfurfural (VII) (Fenton and Gostling, J., 1899, **75**, 429) gave on hydrolysis and oxidation *ω-hydroxy-5-methylfuran-2-carboxylic acid* (VI), m. p. 165—167°, the constitution of which had been previously determined by conversion of the crystalline bromide into furan-2 : 5-dicarboxylic acid (dehydromucic acid), identical with that obtained from mucic acid (Hill and Jennings, *Amer. Chem. J.*, 1893, **15**, 159; Hill and Sawyer, *ibid.*, 1898, **20**, 169). When the ω-hydroxy-5-methylfuran-2-carboxylic acid (VI) isolated by these methods was methylated with methyl iodide and silver oxide, we obtained an ester which on hydrolysis gave the crystalline ω-methoxy-5-methylfuran-2-carboxylic acid (V), m. p. 72—73°, identical with that which we had isolated as a transformation product of tetramethyl γ-fructose.



No simple explanation suffices to interpret the transformation of tetramethyl γ-fructose to this furan derivative. On the hypothesis that this sugar contains already a substituted hydrofuran ring (I), a reasonable explanation of the series of conversions is given in the formulæ above. On this interpretation, the first stage of the transformation from tetramethyl γ-fructose (I) to ω-methoxymethylfurfural (IV) is the elimination of water by removal of the reducing hydroxyl group along with hydrogen of the methylated primary alcohol residue in the first terminal position. This would give the compound (II), containing a methoxymethylene residue which, hydrolysing with ease to the hydroxymethylene group, thereafter functions as an acidic residue, the compound now being an enolic form of the aldehyde (III), and there can be little doubt that the introduction of an aldehyde group follows a course similar to that which is here represented. It may be that the compound (III) is readily formed from tetramethyl γ-fructose and may frequently be present in this sugar as an impurity. It is indeed a variety of trimethyl chitose, and the realisation of this has led us to investigate the transformation of glucosamine into chitose by the methods described by Fischer. This further extension of our work has readily afforded us an alternative means of identifying our products (IV) and (V).

Thus, it has already been shown by Fischer that glucosamine is converted by nitrous acid into chitose (VIII), and that the latter on oxidation with bromine passes into chitonic acid (IX). During acetylation in the presence of acetic anhydride and sodium acetate, chitonic acid lost two molecules of water and passed into ω-acetoxy-5-methylfuran-2-carboxylic acid, which on hydrolysis gave ω-hydroxy-5-methylfuran-2-carboxylic acid (VI). We have confirmed this series of transformations leading from glucosamine, and the final product (VI) was identical with the compound we had obtained as described above by interconversion from (VII). Finally, the specimen of hydroxymethylfurancarboxylic acid obtained from glucosamine gave on methylation ω-methoxy-5-methylfuran-2-carboxylic acid (V) identical with that obtained from tetramethyl γ-fructose.

Thus a cycle of inter-relationships has been established between γ-fructose derivatives on the one hand and glucosamine, chitose, and chitonic acid on the other. The allocation of the butylene oxide formula (I) to tetramethyl γ-fructose, representing this sugar as a substituted hydrofuran, therefore receives the same experimental sanction as the formulæ ascribed by Fischer (Fischer and Tiemann, *Ber.*, 1894, **27**, 138; Fischer and Andreae, *Ber.*, 1903, **36**, 2587) to chitose and to chitonic and chitaric acids. The results now indicated afford definite proof of the presence in tetramethyl γ-fructose of two terminal methoxy-groups, $-CH_2{\cdot}OMe$. These serve to distinguish the structural representation of this sugar from the amylene oxide type which is normal crystalline tetramethyl fructose (Haworth and Hirst, *loc. cit.*).

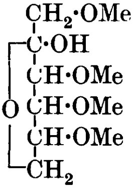
There now remains to be considered the evidence arising from the oxidation of tetramethyl γ-fructose (*a*) with nitric acid and (*b*) with permanganate. The latter degradation will be dealt with in a later paper, but we have again investigated the nitric acid method of oxidation employed by Haworth and Linnell (J., 1923, **123**, 294), and have conducted this work alongside a similar investigation on the normal crystalline tetramethyl fructose.

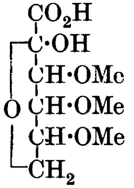
Previous knowledge of the behaviour of nitric acid towards aldoses had established a predilection in favour of the view that the reducing group of sugars was the first to suffer attack in the presence of such an oxidising medium. That such is not the case, however, with ketoses has been made abundantly clear by Haworth, Hirst, and Learner (this vol., p. 1040). It was, for example, shown that the first product of oxidation of normal crystalline tetramethyl fructose (X) was a trimethoxy-lactol acid (XI), giving a crystalline ethyl ester (XII) and a crystalline methyl ester; and the latter gives a higher methylated homologue (crystalline), which is converted into a crystalline amide by the agency of ammonia.

With the insight and experience gained by investigation of this simpler example of the oxidation of a fructose derivative, we have now applied similar methods to the examination of the initial oxidation product of tetramethyl γ-fructose obtained by Haworth and Linnell by the use of dilute nitric acid. These authors recorded the isolation of an oxidation product giving the analysis: C, 50·5; H, 7·3; OR (calc. as OMe), 47·3%. This product was considered to be, on the basis of its analytical data and its general behaviour, a trimethoxy-δ-valerolactone, $C_8H_{14}O_5$ (Calc.: C, 50·5; H, 7·4; OMe, 48·9%). We have since isolated this product many times and in yields representing more than 70% of the tetramethyl γ-fructose employed and have confirmed these analytical figures repeatedly.

In view, however, of the exceptional behaviour of tetramethyl γ-fructose towards dilute mineral acids, it seemed to us reasonable to suspect that, although the same oxidation product appeared to be constantly formed, the analytical data might be influenced by the presence of traces of the transformation product (III), (IV), or (V), arising in the way we have demonstrated in the earlier part of this paper. If so, it appeared to us that Haworth and Linnell's oxidation product might be analogous in composition and structure to the initial product of oxidation of normal tetramethyl fructose, that is, that the supposed lactone $C_8H_{14}O_5$ might be the ethyl ester of a trimethoxy-lactol acid, $C_{11}H_{20}O_7$ (XVII), isomeric with (XII), for which the calculated figures are: C, 50·0; H, 7·6; OR (as OMe), 47·0%. This has indeed proved to be the case. The product, resembling a lactone in many of its properties, is unstable to alkali through retaining the free reducing group of the original sugar, and the titration data are for this reason slightly higher than those required for the lactol ester $C_{11}H_{20}O_7$, and may readily be interpreted to satisfy the lactone formula $C_8H_{14}O_5$. We have isolated the corresponding methyl ester (XV) in yields of 75%, but in this case also the carbon value is slightly high owing to the presence of furan derivatives or their intermediate compounds as impurity. That this substance is not a lactone is, however, shown by its conversion into the higher homologue (XVI) of the lactol methyl ester by further methylation. This product no longer reduced Fehling's solution, was comparatively stable towards alkali, and gave a titration value approximating closely to that required by this constitution. Treatment of this methylated product with methyl-alcoholic ammonia gave a crystalline amide (XVIII), m. p. 100—101°, the complete analysis of which established the molecular weight of the original ester, identifying it as being structurally analogous to the product of oxidation obtained under similar conditions from normal crystalline tetramethyl fructose.

(X.)





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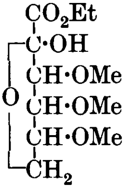
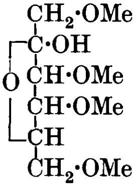
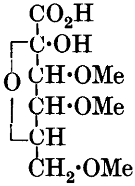


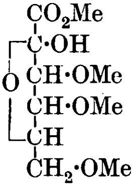
(XII.)

(XIII.)





(XIV.)



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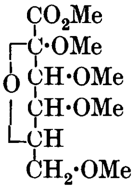
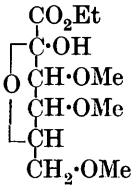
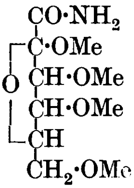


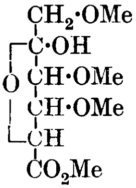
(XVI.)



(XVII.)



(XVIII.)



(XIX.)

The possibility has not escaped us that the methyl ester, $C_{10}H_{18}O_7$, might also be formulated as in (XIX), representing the carboxyl group in position 6 instead of in position 1 as given in formula (XV), but there are many indications which favour the latter structure. In the first place, the oxidations of both the normal and the γ-form of tetramethyl fructose proceeded on exactly parallel lines and led to analogous products. The oxidation of the normal sugar is definitely shown not to affect position 6 (Haworth, Hirst, and Learner, *loc. cit.*). Again, the action of hydrochloric acid on tetramethyl γ-fructose has in the present paper been shown to lead readily to an attack on the $-CH_2{\cdot}OMe$ group in position 1. In both cases the vulnerable position towards the action of nitric acid may be expected to be that of the group in position 1. The further oxidation of these products will form the subject of a future communication.

It seems probable that oxidation products similar to the above lactol esters have also been isolated by other workers in the course of investigations on derivatives of γ-fructose, *e.g.*, in the oxidation of tetramethyl γ-fructose with nitric acid as conducted by McOwan (J., 1926, 1737). This author allocated formulæ based on the analytical data given by liquid specimens which were probably not homogeneous. Doubtless the compound represented by (XV) was also obtained by the above author, who assigned to it the formula of a keto-ester containing a four-carbon chain, one of the alternatives suggested being that of a substituted acetoacetic ester.

The present constitutional position in regard to tetramethyl γ-fructose is that, as we have shown in the earlier part of this paper, this sugar cannot contain an amylene oxide ring, since there is present a $-CH_2{\cdot}OMe$ group in each of the terminal positions. The remaining possibilities are that the oxide ring is butylene-, propylene-, or ethylene-oxidic, but the 2 : 3-oxide ring is excluded inasmuch as 3-methyl fructose gives rise to a γ-methylfructoside (Allpress, J., 1926, 1720), and the 1 : 2-oxide is excluded by the above results. We definitely favour the allocation of a butylene oxide formula, since this affords the simplest explanation of the peculiar transformations which tetramethyl γ-fructose undergoes, leading with the greatest facility to furan compounds, and secondly, because in the series of aldoses the γ-sugars which have been studied are butylene oxidic.

EXPERIMENTAL.

For the sake of brevity, numerous preliminary experiments are given in condensed form as follows :

Purity of Tetramethyl γ-Fructose.—Tetramethyl γ-fructose is acted upon both by acids and by alkalis, and in order to obtain a pure specimen, prolonged contact of the sugar even with dilute acid, especially at high temperatures, must be avoided. If suitable precautions are not observed, the first distillation product may contain sufficient aldehydic material to give a pronounced colour to Schiff's reagent. Careful hydrolysis of heptamethyl sucrose (Haworth, J., 1915, **107**, 12; 1920, **117**, 199), the most convenient source, with 0·4% aqueous hydrochloric acid at 60° as originally recommended, followed by neutralisation of the acid with barium carbonate and extraction of the tetramethyl sugar with chloroform, yielded a product the physical constants of which were in agreement both with those previously recorded and with those of a specimen of tetramethyl γ-fructose which had been subjected to further rigorous purification. This was effected by means of bromine, which does not attack tetramethyl γ-fructose, but oxidises a methylated aldose (Haworth and Mitchell, *loc. cit.*). Tetramethyl γ-fructose in 20% aqueous solution was treated with half its weight of bromine for 16 hours at 35°. After removal of the bromine by aeration in the cold, the solution was neutralised with barium carbonate and the purified tetramethyl γ-fructose was extracted by chloroform and distilled. The final product was neutral to litmus, gave no colour with aniline acetate or Schiff's reagent, and had $[\alpha]_D^{16°} + 31·3°$ ($c = 2·015$) and $n_D^{13°}$ 1·4513.

With regard to the method of purification recommended by McOwan (*loc. cit.*), who employed alkaline hypoiodite, it was found that the action of very dilute alkali ($N/30$) on tetramethyl γ-fructose resulted in changes such that the solution very quickly contained material which gave a positive test with Schiff's reagent. Further details of these experiments will be communicated shortly, but in the meantime the results are sufficiently striking to warrant the opinion that the use of alkali at any stage of the purification of the sugar should be avoided. Even with neutral hypoiodite the purest samples of tetramethyl γ-fructose give a figure corresponding to a content of 2·8% of tetramethyl glucose. Incidentally, it was found to be undesirable to use octamethyl sucrose as a source of tetramethyl γ-fructose, inasmuch as a specimen, obtained in this way, which had not been subjected to the bromine treatment gave on oxidation with nitric acid small quantities of *d*-dimethoxysuccinic acid and *i*-xylotrimethoxyglutaric acid, both of which were recognised as their crystalline diamides (for method of isolation, see Hirst, J., 1926, 350).

Oxidation of Tetramethyl γ-Fructose with Nitric Acid.—A series of oxidations was carried out with both concentrated (*d* 1·42) and dilute (*d* 1·2) nitric acid under various conditions of temperature and times of oxidation, the products being isolated both as esters (methyl and ethyl) and also by simple distillation without the use of alcohol at any stage of the experiment. Details of the methods employed are given in earlier communications (Haworth and Hirst, *loc. cit.*) and it will be sufficient to give here a summary of the results.

I. *With nitric acid, d* 1·2. (Time, 20 hours at 60° or 9 hours at 90°.)

When the oxidation product was collected as an acid, *contact with alcohol being avoided*, distillation gave a strongly reducing syrup which was evidently a complex mixture of products. From this, crystals of the optically inactive acid $C_8H_{10}O_5$ (m. p. 88—89°; Haworth and Hirst, J., 1926, 1858) separated on standing. Fractionation of the remaining syrup failed to give any homogeneous material, and the colourless distillate, in addition to reducing Fehling's solution, was unstable when kept and became nearly black in the course of a few weeks.

When methyl alcohol was used for esterification, the distilled product invariably gave the strongly reducing methyl ester, $C_{10}H_{18}O_7$, of the acid the ethyl ester of which was obtained under different conditions of working by Haworth and Linnell (*loc. cit.*). The prolonged treatment with nitric acid required in this experiment led to the formation of a considerable quantity of oxalic acid.

II. *With nitric acid, d* 1·42. By the use of the stronger acid, the time required for the oxidation was curtailed, much of the decomposition caused by long contact with an acid medium thus being obviated. Isolation of the product as methyl ester now gave in larger yield (up to 75% of the weight of the sugar used) a methyl ester, the physical properties of which approximated to $n_D^{15°}$ 1·4500; $[\alpha]_D + 30°$ in water, and gave analytical figures in fairly close agreement with those required by a compound of formula $C_{10}H_{18}O_7$ (Found: C, 48·4; H, 7·6; OMe, 49·6. Calc.: C, 48·0; H, 7·2; OMe, 49·6%). Under similar conditions of oxidation but with the use of ethyl alcohol for esterification, equivalent yields of the substance described by Haworth and Linnell were obtained. The analytical figures formerly given were confirmed and found to correspond with those required by a substance of formula $C_{11}H_{20}O_7$.

The methyl ester was unstable to alkali and vigorously reduced Fehling's solution, accurate titration figures being therefore impossible to obtain. It was unstable even on being kept at the ordinary temperature in a desiccator, showed a progressive increase in the value of n_D amounting to + 0·004 approximately after 3 weeks, and became distinctly darker in colour.

Methylation of the Product $C_{10}H_{18}O_7$.—With the view of determining the nature of the reducing group present, the strongly reducing methyl ester $C_{10}H_{18}O_7$ was methylated with Purdie's reagents. The product on distillation gave a main fraction distilling at a bath temperature of 165°/16 mm.; $n_D^{20°}$ 1·4392; $[\alpha]_D + 9°$ in methyl alcohol (Found: C, 49·9; H, 7·8; OMe, 57·0; CO_2Me, 24·0. $C_{11}H_{20}O_7$ requires C, 50·0; H, 7·6; OMe, 58·7; CO_2Me, 22·4%). It was now non-reducing. Amide formation was effected by dissolving the ester in methyl alcohol saturated with ammonia. No deposition of crystals occurred until the solvent had been evaporated; the residual syrup then crystallised. The long needles so obtained were drained on porous earthenware and washed with ether and light petroleum; they then melted at 95—100°.

Preparation of the Amide $C_{10}H_{19}O_6N$, m. p. 100—101°.—The results described up to this point were regarded as merely preliminary in view of the uncertainty attaching to any interpretation based solely on the examination of liquid substances. It had become apparent during the course of the experiments that the action of acid on the strongly reducing oxidation products, unless carefully controlled, led to profound and complex changes even during the processes necessary for the isolation and characterisation of the substances in question. Accordingly, another series of experiments was carried out in which the contact with acid was reduced to the minimum and the sensitive reducing group was protected as soon as possible by methylation. In this way substantial yields of the above-mentioned crystalline amide (m. p. 95—100°) were obtained, amounting to 40% by weight of the tetramethyl γ-fructose used.

Ten g. of tetramethyl γ-fructose were treated with 70 c.c. of nitric acid (*d* 1·420). Vigorous oxidation began at 70°; the temperature was thereafter gradually raised in the course of an hour to 92° and maintained for 1¾ hours. The nitric acid was then removed in the usual way at 50°/15 mm., the distillation with repeated addition of water being carried on for 5 hours only. Methyl alcohol was added, and distilled off to remove water, and the residual syrup was boiled for 4 hours with 70 c.c. of methyl alcohol. Removal of the solvent yielded a syrup which still contained a little nitric acid but was soluble in methyl iodide. The solution in methyl iodide was neutralised with silver oxide (3 g.), and methylation with silver oxide (30 g.) then proceeded under the usual conditions, the reaction being sufficiently vigorous in the cold to cause the solvent to boil. The product was purified by distillation, giving (*a*) 1·2 g., mainly methyl oxalate and solvent; (*b*) 4·4 g., bath temp. 161°/16 mm., $n_D^{15°}$ 1·4422; (*c*) 3·0 g., bath temp. 166°/16 mm., $n_D^{15°}$ 1·4442; and (*d*) 1·1 g., bath temp. 180°/16 mm., $n_D^{15°}$ 1·4470. There was no sign of decomposition at any stage of the distillation. Fractions (*b*) and (*c*) appeared to be essentially the same product or mixture of products.

Fraction (*b*) was a colourless, mobile syrup without action on Fehling's solution and was not decomposed to give coloured substances by hot alkali; $[\alpha]_D - 8°$ in methyl alcohol ($c = 2·452$) (Found: C, 49·0; H, 7·5; OMe, 57·0; CO_2Me, 32·0%). The analytical figures revealed that the distillate was not a single substance, but amide formation proved that it consisted very largely of the methyl ester (methylated), $C_{11}H_{20}O_7$. A solution of 1·3 g. in 10 c.c. of methyl alcohol saturated with ammonia deposited no crystalline material after being kept for a week. The clear solution was then allowed to evaporate, whereupon the resulting syrup crystallised. The crystals were extracted with boiling light petroleum (b. p. 60—80°) and could easily be recrystallised from this solvent. The yield of pure recrystallised material was 0·5 g. In all, from 6·3 g. of fractions (*b*) and (*c*), 3·0 g. of pure recrystallised *amide* were obtained. It crystallised from light petroleum in tufts of interlacing needles resembling cotton-wool in appearance. It was very soluble in methyl and ethyl alcohols and water, less soluble in acetone, and slightly soluble in ether. M. p. 100—101°; $[\alpha]_D -76°$ in water ($c = 1·099$) (Found: C, 48·0; H, 7·8; N, 5·4; N, by titration, 5·5; OMe, 47·7. $C_{10}H_{19}O_6N$ requires C, 48·2; H, 7·6; N, 5·6; OMe, 49·8%).

The residue, after extraction with light petroleum, contained some solid matter embedded in a stiff gum. The syrup was removed by extraction with benzene, and the powdery residue was recrystallised from alcohol containing light petroleum. M. p. 177—178°. This material was insoluble in the usual organic solvents except ethyl and methyl alcohols. It was readily soluble in water. Apparently it was not a pure substance, but the analytical figures indicated clearly that it represented the amide of that portion of the original oxidation product which was responsible for the low value of carbon and the high value of CO_2Me. Yield, 0·6 g. from 6 g. of ester (Found: C, 40·3; H, 6·2; N, 12·2; OMe, 39·1%).

The Action of Acetic Anhydride and Sodium Acetate on Tetramethyl γ-Fructose.—Tetramethyl γ-fructose (5 g.), anhydrous sodium acetate (5 g.), and acetic anhydride (50 g.) were heated together at 120° for 1½ hours and then at the boiling point of the mixture for another hour. The solution was then poured into water (4 vols.), and after a few hours the product was extracted with chloroform. Removal of the solvent left a syrup containing acetic acid, which was removed by keeping the mixture in a desiccator over potassium hydroxide. Distillation now gave a series of fractions with a wide range of boiling points and refractive indices, revealing the presence of a complex mixture of substances, the lowest-boiling fraction of which represented the most homogeneous portion. This (0·7 g.;

b. p. about 55°/0·01 mm.; $n_D^{13^\circ}$ 1·4985) was a colourless oil which darkened when kept and gave all the reactions of an unstable aldehyde. It had the odour of furfural, readily combined with phenylhydrazine to give a liquid phenylhydrazide, reduced Fehling's solution, gave Schiff's test for aldehydes, and produced an intense red colour with aniline acetate. It showed slight acidity towards litmus, but this was probably due to the presence of impurities. Analysis showed that the product was not a single substance (Found: C, 57·4; H, 6·6; OMe, 31·7%), but it was proved to be largely ω-methoxy-5-methylfurfural by the following series of reactions. Treated with semicarbazide hydrochloride and sodium acetate, a concentrated aqueous solution of the aldehyde immediately gave a precipitate of the crystalline semicarbazone, m. p. 166—167° after recrystallisation from alcohol. Similar treatment with hydroxylamine hydrochloride and sodium acetate gave the oxime as a mobile oil which readily crystallised. Recrystallised from light petroleum (b. p. 40—60°) containing a little ether, it was obtained in colourless, matted needles, m. p. 103—104°. Further details and analytical figures for these compounds are given in the following paragraph.

The Action of Hydrochloric Acid on Tetramethyl γ-Fructose. Preparation of ω-Methoxy-5-methylfurfural.—ω-Methoxymethylfurfural was more readily obtainable by the action of hydrochloric acid on tetramethyl γ-fructose. Tetramethyl γ-fructose was mixed with twice its weight of 8% hydrochloric acid and heated at 80°. The solution darkened and methyl alcohol distilled over, this being identified by the usual tests. After treatment in this way for 1½ hours, the solution was cooled and repeatedly extracted with chloroform. The extracts were neutralised with sodium carbonate, dried, and filtered. After removal of chloroform, a mobile syrup remained (70%), which was divided into two fractions by distillation: I, b. p. about 54°/0·07 mm., n_D 1·4908 (yield over 30%); II, b. p. up to 82°/0·04 mm., n_D 1·4597. Fraction I had a powerful aldehydic odour, restored the colour to Schiff's reagent, gave a red coloration with aniline acetate, and immediately decolorised neutral permanganate.

The *semicarbazone* was prepared and twice recrystallised from alcohol; it melted at 166—167° and was identical with that obtained by the action of acetic anhydride and sodium acetate on tetramethyl γ-fructose (Found: C, 48·7; H, 5·5; OMe, 15·4; N, 21·7. $C_8H_{11}O_3N_3$ requires C, 48·7; H, 5·6; OMe, 15·7; N, 21·3%). The *oxime* also was prepared; after recrystallisation from light petroleum and ether, it melted at 103—104° and was identical with that obtained and described in the previous section (Found:

C, 54·1; H, 5·9; N, 9·1; OMe, 18·8. $C_7H_9O_3N$ requires C, 54·2; H, 5·8; N, 9·05; OMe, 20·0%).

Fraction II contained some of the aldehyde already examined, and probably some unchanged tetramethyl γ-fructose and intermediate products.

In order to study the effect of more drastic treatment with mineral acid, the following experiment was carried out: The sugar (10 g.) was treated with concentrated hydrochloric acid (4 c.c.), the temperature being very gradually raised until at 80° a liquid began to distil. This was methyl alcohol. After remaining over-night at room temperature, the mixture was heated at 50°/0·1 mm. until the methyl alcohol and water had been removed, leaving a residue (6 g.). The bath temperature was then raised and, the first two drops being rejected, a fraction (4·4 g.) was obtained, b. p. 70—75°/0·4 mm., $n_D^{15^\circ}$ 1·5060. A small, dark residue remained.

Refractionation of 3 g. of the above material gave (1) 0·3 g., b. p. below 50°/0·05 mm., $n_D^{15^\circ}$ 1·5020; (2) 1·7 g., b. p. 53°/0·05 mm., $n_D^{15^\circ}$ 1·5105; (3) 0·9 g., b. p. above 55°/0·05 mm., $n_D^{15^\circ}$ 1·5078. The middle fraction was crude *ω-methoxy-5-methylfurfural* (Found: C, 58·3; H, 6·0; OMe, 24·1. $C_7H_8O_3$ requires C, 60·0; H, 5·7; OMe, 22·1%). The oxime (m. p. 103—104°) and the semicarbazone (m. p. 166—167°) were prepared by the methods given above and were identical with the corresponding derivatives of the aldehyde prepared by the action of acetic anhydride on tetramethyl γ-fructose. Mixed melting-point determinations of the corresponding oximes and semicarbazones gave no depression, the values being 103—104° and 166—167° respectively.

The analytical figures given by the aldehyde indicated that a small quantity of a more highly methylated substance was present, and attempts were made to obtain the pure aldehyde by regenerating it from the crystalline semicarbazone. Hydrolysis by dilute hydrochloric acid or by oxalic acid failed to give satisfactory results. The use of 18% hydrochloric acid appeared to liberate the aldehyde, but it changed at once to a dark, viscid mass which still retained the characteristic odour of the aldehyde.

Oxidation of ω-Methoxy-5-methylfurfural to give ω-Methoxy-5-methylfuran-2-carboxylic Acid.—The oxidation was carried out by Frankland and Aston's method (J., 1901, **79**, 515). Calcium hydroxide (1·5 g.) was made into a paste with water (5 c.c.), and the aldehyde (1 g.) was added; 13·6 c.c. of a solution of potassium permanganate containing 5·5 g. per 100 c.c. were then added, with constant stirring, during 30 minutes, the temperature being maintained throughout at 10° by addition of ice as required. The mixture was heated on the steam-bath and filtered hot, and the precipitated manganese oxides were repeatedly washed with hot water. The united filtrates were evaporated to dryness under diminished pressure, and the acidified residue extracted with dry ether. The extract yielded a dark syrup, which was dissolved in a little water and carefully neutralised with dilute sodium hydroxide solution. Evaporation under diminished pressure gave the sodium salt, which, after being freed from some syrupy material by washing with ether, was clean and hard. A solution of it in a very slight deficiency of dilute hydrochloric acid was evaporated to dryness under diminished pressure, and the free organic acid extracted by dry ether. Removal of the ether gave a mobile syrup which crystallised when stirred. The solid was drained on porous earthenware and the pure *ω-methoxy-5-methylfuran-2-carboxylic acid* was obtained by recrystallisation from light petroleum; it melted at 72—73° after slight softening at 69° and was optically inactive (Found: C, 54·0; H, 5·1; OMe, 18·9. $C_7H_8O_4$ requires C, 53·9; H, 5·1; OMe, 19·9%. 0·1996 G. required 12·7 c.c. of N/10-NaOH for neutralisation. Calc. for $C_7H_8O_4$, 12·8 c.c.).

Preparation of ω-Methoxy-5-methylfuran-2-carboxylic Acid from ω-Bromo-5-methylfurfural.—The ω-bromomethylfurfural was prepared by Fenton and Gostling's method (J., 1899, **75**, 429), the following modification giving an improved yield. Fructose (15 g.) was covered with dry chloroform (250 c.c.) saturated with hydrogen bromide. The mixture was heated at 60—65° for one hour and then kept at room temperature over-night. The product (4·9 g.), after recrystallisation from ether, had m. p. 60—61°. The pure crystalline ω-bromomethylfurfural (7 g.) was simultaneously hydrolysed and oxidised by means of silver oxide (60 g.) suspended in boiling water (Fenton and Gostling, *loc. cit.*). Isolation of the ω-hydroxymethylfurancarboxylic acid yielded a light brown, crystalline solid as crude product (5·6 g.), recrystallisation of which from ethyl acetate gave material having m. p. 159—161°; this m. p. was raised to 165·5—167° (turning brown at 158°) by two further crystallisations from alcohol–toluene. Fischer and Andreae give m. p. 165—167° (turning brown at 157°) (Found: C, 50·5; H, 4·3. Calc.: C, 50·7; H, 4·2%).

Methylation of ω-Hydroxy-5-methylfuran-2-carboxylic Acid.—The acid (1 g.) was heated at 45—50° with methyl iodide (20 g.) and silver oxide (10 g.), addition of methyl alcohol (4 c.c.) being necessary to effect solution of the acid. Isolation of the product was followed immediately by a second methylation under similar conditions, the addition of only 1 c.c. of methyl alcohol now being necessary. For the third methylation no methyl alcohol was required. The product, on distillation, gave *methyl ω-methoxy-*

5-methylfuran-2-carboxylate (0·8 g.) as a colourless liquid, b. p. about 61°/0·05 mm., $n_D^{12.5°}$ 1·4938 (Found: OMe, 35·3. $C_8H_{10}O_4$ requires OMe, 36·5%).

ω-Methoxy-5-methylfuran-2-carboxylic Acid.—The above ester (0·2 g.) was warmed on the water-bath for 2 hours with a 1% aqueous solution of sodium hydroxide (10 c.c.). Hydrochloric acid was then added until the solution was acid to Congo-paper, and the product was isolated by extraction with ether. Evaporation of the solvent gave a colourless syrup which immediately crystallised. Recrystallisation from light petroleum (b. p. 40—60°) gave pure ω-methoxymethylfurancarboxylic acid, which, alone or mixed with a specimen prepared from tetramethyl γ-fructose, melted at 72—74° after softening slightly at 69°.

Preparation of ω-Methoxy-5-methylfuran-2-carboxylic Acid from Glucosamine.—Glucosamine hydrochloride (10 g.) was treated with nitrous acid to give chitose, and the latter, without being isolated, was oxidised by bromine to chitonic acid. The calcium salt of this, after being recrystallised from water (yield, 3·3 g. Found: Ca, 9·35. Calc.: Ca, 9·3%), was converted (2·8 g.) into ω-acetoxymethylfurancarboxylic acid by the action of sodium acetate and acetic anhydride. The product (1·9 g.), recrystallised from ether, had m. p. 115—118° (Found: C, 52·0; H, 4·7. Calc. for $C_8H_8O_5$: C, 52·2; H, 4·4%).

The acetyl compound was hydrolysed by means of baryta, and the free acid obtained melted, alone or mixed with ω-hydroxymethylfurancarboxylic acid prepared from ω-bromomethylfurfural, at 165—167°, colouring slightly at about 156°. The hydroxy-acid (0·5 g.) was heated with methyl iodide (10 g.), silver oxide (5 g.), and methyl alcohol (2—3 c.c.) at 45—50°; the methyl ester thus obtained was hydrolysed by means of *N*/4-sodium hydroxide (30 c.c.) for 2 hours on the water-bath, and the solution of the sodium salt was acidified. The ω-methoxy-5-methylfuran-2-carboxylic acid, after recrystallisation from ether, melted at 72—73°, alone or mixed with the specimens prepared from tetramethyl γ-fructose and from ω-bromomethylfurfural.

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