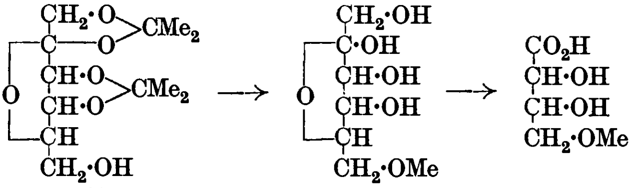
CLXXVI.—*The Constitution of α- and β-Fructose-diacetones. The Alleged Oxidative Degradation of the Derived Monomethyl and Tetramethyl Fructose.*

By Cameron Gordon Anderson, William Charlton, Walter Norman Haworth, and Vincent Stanley Nicholson.

Irvine and Hynd (J., 1909, **95**, 1220) in their investigations on the structure of α-fructose-diacetone (Fischer, *Ber.*, 1895, **28**, 1164) prepared a monomethyl derivative of the compound, and by elimination of the two acetone residues isolated a crystalline monomethyl fructose, m. p. 122—123°, $[\alpha]_D^{20^\circ}$ $-70{\cdot}5^\circ \longrightarrow -53{\cdot}1^\circ$. In repeating this preparation, we have isolated a sugar having the same constants, but after several recrystallisations the monomethyl fructose gave the following data: m. p. 128—130°, $[\alpha]_D^{20^\circ}$ in water $-84{\cdot}1^\circ \longrightarrow -53{\cdot}5^\circ$. The phenylosazone had m. p. 177—179° (Irvine and Hynd, *loc. cit.*, give m. p. 142—144°; and Irvine and Scott, J., 1913, **103**, 573, m. p. 164—165°). Irvine and Hynd recorded that, when oxidised with bromine water, monomethyl fructose gave as the principal product an acid recognised as αβ-dihydroxy-γ-methoxybutyric acid (III). This was fully analysed, titrated, and examined also as the barium salt. From these data they concluded that the constitution (II) should be assigned to monomethyl fructose, and therefore that the formula (I) should be allocated to α-fructose-diacetone.



(I.) (II.) (III.)

This work has been supplemented by further experiments (Irvine and Patterson, J., 1922, **121**, 2146) which go to show that both α-fructose-diacetone and the monomethyl fructose derived from it are derivatives of normal or ordinary fructose.

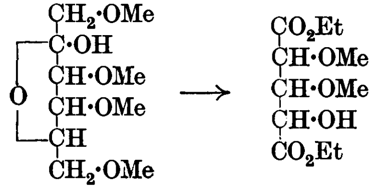
It is evident that if these experimental data could be substantiated, and if the formula (II) assigned to the monomethyl fructose were to hold, this would preclude the formulation of this normal fructose derivative as a 2 : 6-oxide or pyranose form, inasmuch as position 6 is occupied by a methyl group and therefore is not available for the attachment of the oxide ring. This problem has assumed importance in view of the determination of the ring structure of normal fructose by Haworth and Hirst (J., 1926, 1858) and by Haworth, Hirst, and Learner (J., 1927, 1040), who have demonstrated that normal fructose derivatives can only be formulated as a pyranose or 2 : 6-ring structure.

We have therefore deemed it advisable to repeat the work of Irvine and Hynd and, observing their conditions, we attempted to oxidise monomethyl fructose by agitating a solution of the sugar in the cold with bromine water, but we were surprised to find that the monomethyl fructose was recovered unchanged. Proceeding on the assumption that a more prolonged contact with the reagent was necessary to imitate the result described by Irvine and Hynd, we again repeated the experiment, at a higher temperature, keeping the monomethyl fructose in contact with bromine water with frequent agitation during 12 days. At the end of this period a negligible amount of an acid product was formed, and the monomethyl fructose was recovered unchanged in almost quantitative yield.

Endeavouring to explain the account given by Irvine and Hynd of the properties of their acid product, we subjected the regenerated monomethyl fructose to the same analytical tests as did the earlier authors. It is known that fructose reacts with bases to give complex substances, and we observed similarly that monomethyl fructose combined with barium hydroxide, and this explains the observation of Irvine and Hynd, who considered they had prepared a barium salt of their supposed degradation product. They appear to have been misled in supposing that the sugar underwent any appreciable degradative oxidation by the agency of cooled bromine water. The " principal product " recovered from the contact with bromine must have consisted almost entirely of unchanged monomethyl fructose. The stability of the monomethyl fructose is indeed only to be expected in view of the fact, which has long been known, that fructose itself exhibits a remarkable stability in contact with bromine water under the conditions described by Irvine and Hynd (Kiliani, *Annalen*, 1880, **205**, 145, 180; Bertrand, *Compt. rend.*, 1909, **149**, 225). Similarly the normal tetramethyl fructose and even its labile or γ-form are almost inert towards this reagent under these conditions.

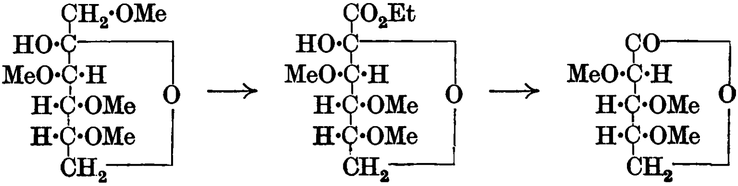
In support of their view that α-fructose-diacetone should be represented by the structural formula (I) Irvine and Patterson (*loc. cit.*) described the transformation of this substance into the monoacetone and, by methylation of the latter, into trimethyl fructose-monoacetone. The removal of the remaining acetone residue, followed by further methylation and hydrolysis, led to the isolation of the crystalline normal tetramethyl fructose, identical with that which had previously been isolated by the methylation of methylfructoside by Purdie and Paul (J., 1907, **91**, 289). In a subsequent paper Irvine and Patterson (J., 1922, **121**, 2696) submitted this crystalline tetramethyl fructose to oxidation with nitric acid and isolated a compound, m. p. 86—87°, which they designated diethyl dimethoxyhydroxyglutarate (V). On the basis of this work they ascribed to the methylated sugar the constitution represented by 1 : 3 : 4 : 6-tetramethyl fructose (IV).

(IV.)



(V.)

On repeating this work Haworth, Hirst, and Learner (J., 1927, 1040) isolated the same crystalline derivative having m. p. 87—88° and adduced evidence that this was not the diethyl ester of the substituted glutaric acid (V) but the monoethyl ester of a lactol acid formulated as the trimethyl fructuronic acid (VII). A confirmation of this view is now communicated in that it is shown that the crystalline oxidation product (VII) can be degraded by contact with acid permanganate to the crystalline d-2 : 3 : 4-*trimethyl* δ-*arabonolactone* (VIII).



(VI.) (VII.) (VIII.)

The identification of this product (VIII) was assisted by the circumstance that we had already obtained the corresponding *l*-enantiomorph (Drew, Goodyear, and Haworth, J., 1927, 1244), and the properties of these two substances are compared below :

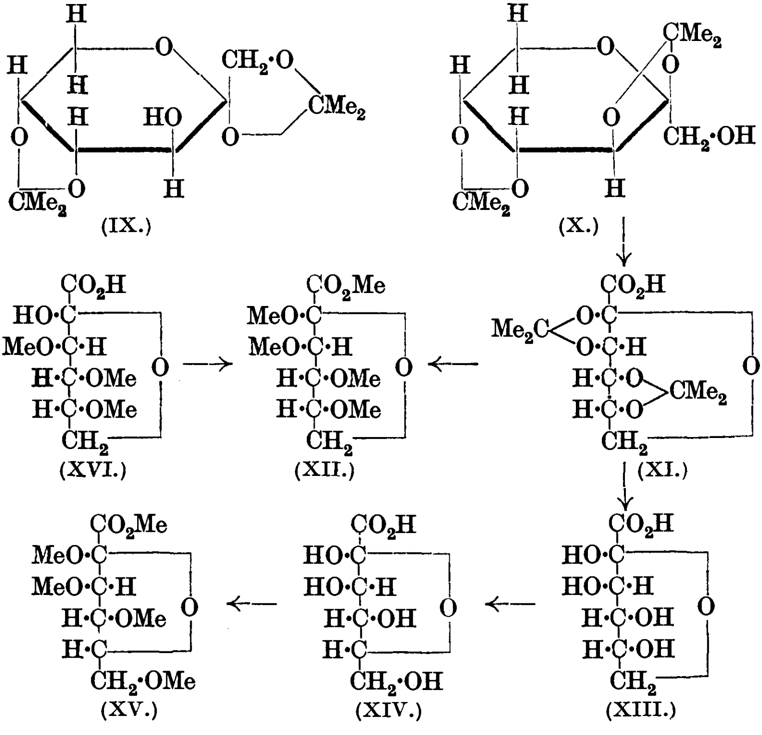
	d-2 : 3 : 4-Trimethyl δ-arabonolactone (from crystalline 1 : 3 : 4 : 5-tetramethyl fructose).	*l*-2 : 3 : 4-Trimethyl δ-arabonolactone (from *l*-arabinose).
Crystalline form	Long, colourless needles	Long, colourless needles
M. p.	44°	45°
$n_D^{18^\circ}$ (superfused)	1·4626	$n_D^{15\cdot5^\circ}$ 1·4630
$[\alpha]_D^{18^\circ}$ (initial)	−177·3°	$[\alpha]_D^{21^\circ}$ +179·5°

This comparison leaves little doubt that our product was the stereoisomeride of the *l*-2 : 3 : 4-trimethyl δ-arabonolactone which had previously been prepared and we have also confirmed the identity of our *d*-2 : 3 : 4-trimethyl δ-arabonolactone by the preparation of it from *d*-arabinose (forthcoming paper by Haworth and Jones). Moreover the *d*-lactone has also been submitted to oxidation and has been shown to give rise to *d*-arabo-trimethoxyglutaric acid, characterised through its crystalline methylamide.

It is therefore clear that no conclusion can be reached other than that the tetramethyl fructose is to be represented as 1 : 3 : 4 : 5-tetramethyl fructopyranose (VI). This view is in agreement with the constitution (IX) now supported for α-fructose-diacetone.

The view that the monomethyl fructose derived from α-fructose-diacetone should be formulated as 3-methyl fructose and that in α-fructose-diacetone the substituted residues occupy the hydroxyl positions 1 : 2 and 4 : 5 (Freudenberg and Hixon, *Ber.*, 1923, **56**, 2119; Freudenberg and Doser, *ibid.*, p. 1243) is confirmed by these results (see preceding paper).

That the action of nitric acid on crystalline tetramethyl fructose (VI) should be principally to effect the oxidation of the $-CH_2{\cdot}OMe$ group in position 1 to carboxyl, was previously commented upon as a striking observation, especially so since the hydroxyl group in position 2, commonly designated the " reducing group " in fructose, evaded attack in this instance. It may be reflected, however, that the state of oxidation of the reducing group differs from that of an ordinary aldose sugar and may, indeed, in a sense be regarded as already completely oxidised in its condition as a potential keto-group. The tendency of fructose derivatives to undergo initial oxidation at the position 1 is also indicated in the series of experiments we have conducted on β-fructose-diacetone. The latter has been shown by Ohle (*Ber.*, 1925, **58**, 2577) to undergo oxidation with permanganate to the corresponding diacetone-fructuronic acid (XI), which on elimination of its acetone groups gave the unsubstituted fructuronic acid (XIII). We have examined the product (XI) and have shown that by simultaneous hydrolysis and methylation it gives rise to the crystalline methylated methyl ester (XII) which had previously been prepared by one of us from the lactol acid (XVI) (Haworth, Hirst, and Learner, *loc. cit.*). This experiment connects Ohle's results with our previous observations on the oxidation of crystalline tetramethyl fructose and



demonstrates that the oxidation of this sugar proceeds initially in the same way as the oxidation of β-fructose-diacetone. We regard the isolation by Ohle and his co-workers of the unsubstituted fructuronic acid (α-keto-gluconic acid) as being of special interest in this connexion, and the high lævorotation of this product seems to require that it should be represented preferably by the cyclic formula (XIII) rather than by the open-chain formula. There is, indeed, no doubt that on careful methylation it passes to the cyclic lactol ester (XII) which we have characterised through its identity with the crystalline substance obtained on esterifying and methylating the lactol acid (XVI).

Under other conditions, involving treatment of the fructuronic acid with mineral acid, followed by methylation, we isolated a liquid ester which seemed to be an isomeride and had a lower boiling point. This we have identified as the five-membered ring isomeride formulated as in (XV), which was previously obtained by one of us by the oxidation of tetramethyl γ-fructose. That this was so was demonstrated by conversion into its crystalline amide, m. p. 100—101°, which was shown to be identical with the crystalline amide isolated in the course of earlier work on the oxidation of tetramethyl γ-fructose (Haworth, Hirst, and Nicholson, J., 1927, 1513; compare also p. 2308).

It is further demonstrated that Ohle's fructuronic acid can be represented by the six-membered ring formula (XIII), and that this in contact with dilute sulphuric acid can modify its ring structure to give a five-membered ring acid (XIV). This displacement of the original ring structure corresponds exactly to the change which accompanies the formation of γ-methylfructoside from ordinary fructose.

EXPERIMENTAL.

α-Fructose-diacetone and the Derived Monomethyl Fructose.—α-Fructose-diacetone, prepared by Fischer's method (*loc. cit.*), was methylated with methyl iodide and silver oxide, giving monomethyl α-fructose-diacetone having the constants given by Irvine and Hynd (*loc. cit.*), and the removal of the acetone residues was effected as described by these authors. The product was a crystalline monomethyl fructose, m. p. 122—123°, but after several recrystallisations the m. p. was raised to 128—130°, with slight sintering at 122°. $[\alpha]_D^{20°}$ in water ($c = 0{\cdot}92$) $-84{\cdot}1°$ (after 15 mins.) $\longrightarrow -53{\cdot}5°$ (Found: C, 43·2; H, 7·3; OMe, 16·0. Calc.: C, 43·25; H, 7·2; OMe, 16·0%). This sugar gave a phenylosazone, m. p. 165—169° before purification; but when it was recrystallised from aqueous ethyl alcohol its m. p. was raised to 177—179° (Irvine and Hynd give m. p. 142—144°, and Irvine and Scott, J., 1913, **103**, 573, give m. p. 164—165°. Compare also the preceding paper by Anderson, Charlton, and Haworth) (Found: C, 61·3; H, 6·7; OMe, 8·3; N, 15·1. Calc.: C, 61·3; H, 6·45; OMe, 8·3; N, 15·05%).

1 G. of the crystalline monomethyl fructose was dissolved in a little water and the solution was cooled and stirred during the addition of 2 g. of bromine dissolved in 60 c.c. of water. The operation occupied 8 hours. The solution having been kept exposed to the atmosphere over-night, loss of bromine was made good by the addition of a further quantity, and the solution was again shaken for 24 hours. The solution, still strongly reducing, was then evaporated at 40—50° under diminished pressure to half bulk, diluted, and again reduced to half bulk, this procedure being

repeated four times. Thereafter the solution was neutralised with silver carbonate, filtered, treated twice with hydrogen sulphide and then with charcoal, and filtered. The colourless neutral solution was evaporated under diminished pressure to a thick syrup, which reduced Fehling's solution strongly. On keeping, this syrup crystallised, and recrystallisation of the crude material from ethyl acetate gave monomethyl fructose (yield, 85%), m. p. 126—128° both alone and when mixed with the original material.

Since the conditions of the experiment had not been effective in promoting oxidation, they were modified in order to give prolonged contact with bromine water at an elevated temperature. Accordingly, the operation was repeated, 4 g. of monomethyl fructose being dissolved in water and 9·5 g. of bromine in water added with stirring during 1 hour. The solution was shaken during 24 hours without cooling, and was then kept for 40 hours at 18—20°. A test sample having shown that the product still reduced Fehling's solution strongly, the solution was kept at 25—30° for 1 day. More bromine water was added, but after 12 days, during which the reagents had been in contact, the reducing property had not disappeared. The hydrogen bromide was removed by means of litharge and the solution was filtered, shaken with silver oxide, again filtered, and treated with charcoal. The filtrate was now treated with hydrogen sulphide. A negligible quantity of silver sulphide was precipitated, indicating that very little organic acid was present as silver salt and that oxidation of the sugar had not taken place to an appreciable extent. The colourless solution was evaporated at 50°, and the residual syrup dissolved in water and digested at 70° with precipitated calcium carbonate, which neutralised the very faint acidity. The filtrate was evaporated to 5 c.c. and diluted with 100 c.c. of alcohol, which precipitated a slight film of a calcium salt (less than 0·1 g.). No calcium salt remained in the filtrate, and the latter was evaporated and yielded a syrup which became crystalline. Recrystallisation from ethyl acetate gave unchanged monomethyl fructose, m. p. 126—128°, identical with the original material and almost undiminished in quantity.

To confirm its identity, the regenerated sugar was converted into the diacetone compound by treatment with acetone containing 0·4% of hydrogen chloride. The product was isolated in the usual way and yielded crystals, m. p. 114—115°, $[\alpha]_{\mathrm{D}}^{\gamma^{\circ}}$ — 134·5° (Found : C, 57·1 ; H, 8·1 ; OMe, 11·7. Calc. : C, 56·9 ; H, 8·0 ; OMe, 11·3%).

Irvine and Hynd assumed the presence of about 6% of tartaric anhydride in their oxidation product, which assumption enabled them to bring their analytical figures into closer agreement with the theoretical figures.

A solution containing monomethyl fructose (0·2485 g.) and 20 c.c. of 0·42*N*-barium hydroxide was heated on a water-bath for 5 minutes; it was then cooled and, although dark in colour, was neutralised with *N*-hydrochloric acid by titration in presence of phenolphthalein. This showed that 0·104 g. of barium had been retained by the sugar.

Again, monomethyl fructose (0·4798 g.), dissolved in water, was heated during 5 minutes at 100° in the presence of 15 c.c. of 0·42*N*-barium hydroxide. The solution was cooled, carbon dioxide admitted to remove excess of barium hydroxide, and the solution filtered. Titration of this solution indicated the presence of 0·266 g. Ba. It would thus appear that the monomethyl fructose had combined with barium hydroxide, and Irvine and Hynd's titration results and barium estimations are explicable without the need of assuming that any oxidation with bromine to an organic acid had taken place.

Oxidation of Tetramethyl Fructopyranose.—Crystalline tetramethyl fructose, m. p. 98—99°, $[\alpha]_D$ − 124° (in water), was oxidised with nitric acid (*d* 1·2) at 90° under the conditions described by Haworth, Hirst, and Learner (*loc. cit.*), and the lactol acid, $C_9H_{16}O_7$ (XVI), was converted into the crystalline ethyl ester, $C_{11}H_{20}O_7$, m. p. 87—88°, $[\alpha]_D$ − 98° in water. This product was identical with that described by Irvine and Patterson (*loc. cit.*) as the ethyl ester of a dibasic acid, but which has since been shown to be the ethyl ester of the monobasic acid above mentioned (Haworth and Hirst, J., 1926, 1858). The crystalline ester (1·6 g.) was hydrolysed by heating with 2/3*N*-sulphuric acid (12 c.c.) at 85° for 2½ hours. A further quantity of 12 c.c. of 2/3*N*-sulphuric acid was then added along with 11·2 c.c. of a solution of barium permanganate (900 c.c. of solution were equivalent to 8 g. of oxygen), which was slowly admitted from a burette, and the solution was constantly shaken. This quantity of permanganate was calculated to provide one atomic proportion of oxygen for the oxidation of the liberated organic acid. The solution was then made alkaline with baryta and kept for some hours, and the excess of baryta was removed by admitting carbon dioxide. The precipitated barium salts were collected and washed, and the filtrate and washings were concentrated under diminished pressure. The concentrated solution, containing the barium salt of an organic acid, was treated with sufficient dilute sulphuric acid to precipitate the whole of the barium as sulphate. The filtrate was evaporated under diminished pressure, and the organic residue was dissolved in warm dry ether. This solution was filtered, the ether evaporated, and the viscid residue distilled under 0·05 mm. The colourless distillate solidified on keeping, and after draining on porous tile in a cool dry atmosphere, the product was obtained as long needles, m. p. 44°. It showed $[\alpha]_D^{18°}$ − 177·3°, diminishing to − 111·4° (after 1 hour), − 83° (2 hours), − 10·2° (2 days). The general appearance, crystalline form, and melting point were identical with those displayed by the enantiomorphous *l*-2 : 3 : 4-trimethyl δ-arabonolactone, and the latter also showed $[\alpha]_D^{21°}$ 179·5° in water ($c = 1{\cdot}41$). The rate of hydration or mutarotation also corresponded with the recognition of this substance as d-2 : 3 : 4-*trimethyl δ-arabonolactone* (Found : C, 50·25; H, 7·5; OMe, 46·9. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 48·9%).

Experiments with β-Fructose-diacetone.

(A) *Combined Hydrolysis and Methylation of Potassium Fructuronate-diacetone. Isolation of Methyl Tetramethyl Fructuronate* (XII) *and the Crystalline Amide.*—The above potassium salt was prepared from 10 g. of β-fructose-diacetone (m. p. 97°. Found : C, 55·4; H, 8·1%) by oxidation with alkaline permanganate (yield, 8 g.) (Ohle, *loc. cit.*).

The potassium salt (6 g.), dissolved in 20 c.c. of water, was heated at 40° during stirring in presence of 5 c.c. of methyl sulphate. After 15 minutes, 10 c.c. of 30% sodium hydroxide solution were added and the temperature was raised to 60°. Methylation was then continued in the usual way at 70°, 25 c.c. of methyl sulphate and 50 c.c. of 30% sodium hydroxide solution being used. The solution was finally heated at 100° for ½ hour, cooled, and acidified with dilute sulphuric acid until it gave a faintly acid test with Congo-red. An equal volume of ethyl alcohol (rectified spirit) was added and the sodium sulphate was thus precipitated. The filtrate was concentrated to 20 c.c. and the methylation process repeated in the above manner, but without the preliminary heating in presence of methyl sulphate.

The product was thereafter extracted in the usual way and submitted to further treatment with Purdie's reagents. The resulting liquid substance was collected and distilled (b. p. 100—103°/0·05 mm., $n_D^{20°}$ 1·4532); it then crystallised on nucleation with a specimen of methyl tetramethyl fructuronate (XII) (Haworth and Hirst, J., 1926, 1858). Recrystallisation of this specimen from ether gave colourless hexagonal plates, $[\alpha]_D^{22°}$ − 130° (in water); m. p. 102—103° either alone or in admixture with a specimen obtained by oxidation methods from normal tetramethyl fructose by Haworth and Hirst (Found : C, 50·3; H, 7·7; OMe, 55·7. Calc. : C, 50·0; H, 7·6; OMe, 58·7%).

Formation of Tetramethyl Fructuronamide.—A methyl-alcoholic solution of the above methyl ester was saturated with dry ammonia at 0° and kept for 5 days. Evaporation of the solvent yielded the crystalline amide, m. p. 118—119°, which has already been described by Haworth, Hirst, and Learner (*loc. cit.*) and formulated as a six-atom ring form obtainable from tetramethyl fructopyranose.

(B) *Methylation of Fructuronic Acid.*—The potassium salt (8 g.) already mentioned above was dissolved in 120 c.c. of *N*-sulphuric acid and heated at 45° for 24 hours. The two acetone residues were thus eliminated from the liberated fructuronic acid-diacetone, the hydrolysis being followed by means of polarimetric observations. The cooled solution was neutralised, and submitted to methylation with methyl sulphate and alkali, and finally with methyl iodide and silver oxide. The extracted syrupy product gave the following fractions on distillation under 0·17—0·13 mm. : (1) 1·2 g., b. p. 87°, $n_D^{14^\circ}$ 1·4490; (2) 2·7 g., b. p. 96—98°, $n_D^{14^\circ}$ 1·4550; (3) 0·45 g., b. p. 100°, $n_D^{14^\circ}$ 1·4617. The fractions (2) and (3) crystallised spontaneously and after draining on porous tile and purification from ether gave colourless plates, m. p. 101—102°, identical with the methyl tetramethyl fructuronate (XII), m. p. 102—103°, described above under (A). Fraction (1) was dissolved in dry methyl alcohol and saturated at 0° with ammonia. After the solution had been kept for 3 days, the solvent was evaporated; the residual syrup, on extraction with light petroleum, yielded the highly characteristic, long needles of the amide, having m. p. 100—101° alone or when mixed with the specimen prepared by Haworth, Hirst, and Nicholson (*loc. cit.*) from tetramethyl γ-fructose. More of this amide was prepared from the material absorbed by porous tile from the crystallised fractions (2) and (3). It was evident, therefore, that prolonged contact of the potassium salt with dilute sulphuric acid had led to displacement of the oxide-ring in a portion of the products, inasmuch as the amide, m. p. 100—101°, has been shown by Haworth, Hirst, and Nicholson to be a derivative of a five-atom ring form obtainable from tetramethyl fructofuranose.

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