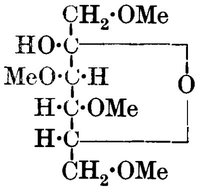
CCXLVI.—*The Structure of Fructose, γ-Fructose, and Sucrose.*

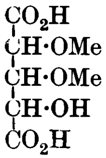
By WALTER NORMAN HAWORTH and EDMUND LANGLEY HIRST.

THE normal crystalline tetramethyl fructose, first isolated by Purdie and Paul (J., 1907, **91**, 289) and afterwards examined in greater detail by Steele (J., 1918, **113**, 257) and on two occasions by Irvine and Patterson, is a standard reference substance occupying in the stable series of fructose derivatives much the same position as crystalline tetramethyl glucose in the corresponding glucose series. The determination of its structure is therefore of signal importance, more especially as the solution of this problem has an important bearing on the constitutions of sucrose and inulin and directly concerns the constitution of the acetone derivatives of the sugars. It was shown by Irvine and Patterson (J., 1922, **121**, 2146) that the mono- and di-acetone derivatives of fructose are convertible into the crystalline lævorotatory tetramethyl fructose, to which, as the result of their experiments, they assigned the butylene-oxide formula (I), and in consequence they applied this formula also to the related acetone compounds. Investigations since conducted by other workers have adduced evidence in favour of an amylene-oxide structure for diacetone fructose, and necessarily also for normal tetramethyl fructose (compare Freudenberg and Doser, *Ber.*, 1923, **56**, 1245; Allpress, this vol., p. 1720). In view of this conflicting evidence, it seemed desirable to investigate the problem afresh.

It is necessary to discuss briefly the earlier evidence for the allocation of a butylene oxide structure to normal tetramethyl fructose. Irvine and Patterson (J., 1922, **121**, 2696) oxidised the sugar both with alkaline potassium permanganate and with nitric acid (*d* 1·2), isolating in the former case a dimethoxyhydroxybutyric acid; in the latter case they claim to have obtained dimethoxyhydroxyglutaric acid (II), recognised as the diethyl ester (III), for which, however, they recorded no titration figures, relying solely on the C and H values for their proof.

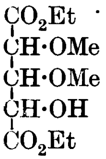
(I.)





$$\begin{array}{l} CO_2H \\ CH{\cdot}OMe \\ CH{\cdot}OMe \\ CH{\cdot}OH \\ CO_2H \end{array}$$

(II.)



$$\begin{array}{l} CO_2Et \\ CH{\cdot}OMe \\ CH{\cdot}OMe \\ CH{\cdot}OH \\ CO_2Et \end{array}$$

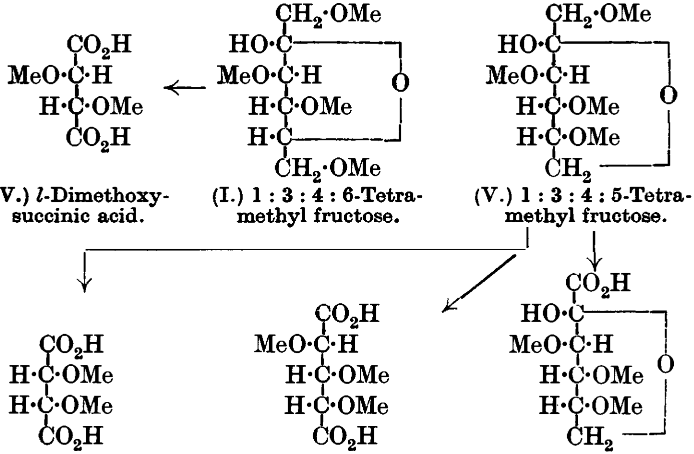
(III.)

With regard to the dimethoxyhydroxybutyric acid, it may be noted that the isolation of this compound, without definite proof being given of the position of the hydroxy-group in the molecule, does not suffice in itself to distinguish between a butylene- and an amylene-oxide structure. The oxidation with nitric acid raises a more serious problem, since the production of a dimethoxyhydroxyglutaric acid would appear at first sight to rule out an amylene oxide formula and, furthermore, is difficult to reconcile with the isolation during the present work of inactive dimethoxysuccinic acid and of trimethoxyglutaric acid.

When an oxidation was carried out, however, under the exact conditions recorded by Irvine and Patterson, it failed to give any dimethoxyhydroxyglutaric acid. An acid giving a well-defined methyl ester, $C_{10}H_{18}O_7$ (m. p. 119—120°), was obtained corresponding to the ethyl ester $C_{11}H_{20}O_7$ found by Irvine and

Patterson. On further examination, the methyl ester was shown to be a derivative of an acid, $C_8H_{15}O_5{\cdot}CO_2H$, which has a carboxyl content less than half that required by a dimethoxyhydroxyglutaric acid. It was a substance which could be made to undergo further reaction with nitric acid and occurred in continuously diminishing quantities as the conditions of oxidation were made more effective. A study of its properties endows this compound with special interest in connexion with other problems, some of which are discussed in this paper, and its examination is being continued.

The present paper deals with the application to normal tetramethyl fructose of the oxidation methods recently employed by one of us in the case of normal tetramethyl glucose (this vol., p. 350). Reference to the annexed butylene- and amylene-oxide formulæ for tetramethyl fructose will serve to show that the presence of the ketonic group in the molecule renders it probable that in both cases a variety of oxidation products will be the result of intensive oxidation. Considering the various ways in which the compound R·CO·R′ may be degraded by oxidation, and remembering that previous work has shown that the trimethoxyglutaric acids and the dimethoxysuccinic acids undergo no racemisation or inactivation under the experimental conditions adopted, it follows that 1 : 3 : 4 : 6-tetramethyl fructose could give rise to a number of compounds amongst which one might reasonably expect to find *l*-dimethoxysuccinic acid (IV), but not the inactive acid. A substance possessing the amylene oxide formula (V) would, on the other hand, be likely to yield inactive dimethoxysuccinic acid (VI) along with *d*-arabotrimethoxyglutaric acid (VII) as shown in the following scheme.



(IV.) *l*-Dimethoxysuccinic acid.

(I.) 1 : 3 : 4 : 6-Tetramethyl fructose.

(V.) 1 : 3 : 4 : 5-Tetramethyl fructose.

(VI.) *i*-Dimethoxysuccinic acid.

(VII) *d*-Arabotrimethoxyglutaric acid.

(VIII.)

In the same circumstances, neither an ethylene-oxide nor a propylene-oxide tetramethyl fructose could give rise to both inactive dimethoxysuccinic acid and *d*-arabotrimethoxyglutaric acid, and the production of these two acids by the oxidation of tetramethyl fructose would be decisively in favour of an amylene-oxide structure, the validity of the argument being again dependent on the absence of wandering of methyl groups during the oxidation process (compare this vol., p. 23).

The experimental details now recorded furnish evidence that both these acids (VI and VII) are in fact produced when normal crystalline tetramethyl fructose is oxidised with nitric acid, the sugar yielding, in favourable circumstances, nearly half its weight of the mixed acids, but no trace of *l*-dimethoxysuccinic acid (IV) was found. In identifying these substances reliance has been placed only on well-defined crystalline derivatives (the acid amides) which have been obtained in a pure condition. In order to impart even greater certainty to these results, inactive dimethoxysuccinamide was specially prepared from *meso*tartaric acid for purposes of comparison, whilst in the case of *d*-arabotrimethoxyglutaramide direct comparison was possible with the corresponding *l*-arabotrimethoxyglutaramide, which one of us had previously prepared on several occasions.

A structural formula for the monobasic acid $C_9H_{16}O_7$, isolated in the form of the methyl ester (m. p. 119—120°) during the present work and as the ethyl ester (m. p. 86—87°) by Irvine and Patterson, who applied to it the formula (III), may now be advanced. The methyl ester reduces Fehling's solution strongly, is affected by hot alkali, and undergoes complete methylation on the introduction of one methyl group, the resulting compound then becoming stable. The suggested formula (VIII) is based on these properties and on the fact that both dimethoxysuccinic acid and trimethoxyglutaric acid accompany this product as cleavage fragments of oxidation. It would thus appear that the first stage of the oxidation is the conversion of a $\cdot CH_2\cdot OMe$ group into $\cdot CO_2H$, a mechanism which is of considerable interest.

If the evidence now advanced be accepted, an amylene-oxide formula (V) is indicated for normal tetramethyl fructose and presumably also for those stable fructose derivatives which are directly convertible into this sugar. Various implications at once suggest themselves. To mention one or two only, the present work gives support to Freudenberg's formula for fructose diacetone as against that of Irvine and Patterson. Incidentally, in view of the close relationship (they give identical osazones) between the monomethyl fructose and the monomethyl glucose obtainable respectively from the fructose and glucose diacetones, our results support the claim of Levene and Meyer (*J. Biol. Chem.*, 1924, **60**, 173, etc.) that this monomethyl glucose is 3-methyl glucose and is not the 6-methyl derivative, which was the formula deduced by Irvine and Hogg (J., 1914, **105**, 1386) on the basis of their oxidation results. Furthermore, the corresponding monomethyl fructose cannot be the 6-methyl fructose, despite the supposed isolation of γ-methoxydihydroxybutyric acid by Irvine and Hynd (J., 1909, **95**, 1226) as a product of degradation. Both these oxidation products of the monomethyl sugars were evidently non-homogeneous and gave fortuitous and misleading analytical data pointing to the formulæ allocated by Irvine and his collaborators.

The disproof of Irvine's formula for normal fructose and its derivatives enables us to extend the generalisation of Charlton, Haworth, and Peat (this vol., p. 89; compare Hirst, *loc. cit.*), which allocated the amylene oxide structure to all normal aldoses. In this earlier paper, fructose could not be brought within the purview of this rule and this anomaly was discussed. The present work supports the view that ketoses are to be included in the generalisation that all sugars tend to exist normally as amylene oxide forms.

During their work on the isolation of the crystalline, lævorotatory tetramethyl fructose Purdie and Paul (*loc. cit.*) obtained evidence of the existence of a dextrorotatory isomeride. The latter was first isolated from methylated sucrose (Haworth, J., 1920, **117**, 207), and several attempts have been made to determine the constitution of this dextrorotatory tetramethyl γ-fructose. The position of this problem is now reviewed in the light of the new formula for normal fructose. It may be said at once that the determination of the structure of γ-fructose derivatives is probably the most difficult of all those encountered in the study of the simple hexoses. Various formulæ have already been applied to tetramethyl γ-fructose by workers other than ourselves (Irvine and Patterson, J., 1922, **121**, 2696; Bergmann, *ibid.*, 1923, **123**, 1277); and it is not surprising if oxidations conducted on this substance under apparently identical conditions lead, in the hands of different experimenters, to diverse results, since slight variations in method produce changes in the amount and composition of the products collected by subsequent distillation.

During the past year we have repeated the earlier work on the oxidation of this compound with nitric acid, and our complete results will shortly be published. Meanwhile it may be reported that among the products which are most constantly obtained by following the method of Haworth and Linnell (J., 1923, **123**, 294) is the crystalline substance, m. p. 83°, softening at 79°, which these authors stated they had isolated in an amount too small for recrystallisation or for complete analysis. We have examined this substance in greater detail and find that it is a furan derivative, m. p. 89°, mixed with another crystalline substance having a similar melting point, 89—90°, and affecting the analytical data of the former. The latter substance has a special interest and will be discussed in a later communication. It differs from the furan derivative in being stable to permanganate, optically active, and slightly affected by Fehling's solution, and by having a similar carbon content but higher percentages of hydrogen and methoxyl. The furan derivative distils readily, and contaminates what would appear to be homogeneous distillation products, from which it gradually separates on long standing. It is an acid, $C_8H_{10}O_5$, and its formation under almost all conditions when the oxidation is conducted with nitric acid suggests the facility with which methylated γ-fructose assumes the furan structure. It thus recalls the behaviour of glucosamine, which is converted, on treatment with nitrous and nitric acid, into substituted hydrofurans, and finally, by the action of dehydrating agents, into furancarboxylic acids.

That Haworth and Linnell's liquid product, described as trimethoxy-δ-valerolactone, $C_8H_{14}O_5$, cannot have the constitution assigned to it has appeared to us extremely probable for some time, since subsequent experiments by one of us have demonstrated that this compound should be the optical isomeride of the dextrorotatory *l*-trimethyl-δ-arabonolactone produced by oxidation of normal *l*-trimethyl arabinose (Hirst and Robertson, J., 1925, **127**, 258) and therefore should be lævorotatory and have $[\alpha]_D$ $-145° \longrightarrow -22{\cdot}4°$; whereas it showed initially a low dextrorotation. Also the further oxidation product described as dimethyl *d*-trimethoxyglutarate should be lævorotatory if it has the constitution assigned to it, whereas it was actually dextrorotatory.

We have now no doubt that the inferences drawn by Haworth and Mitchell (J., 1923, **123**, 301) and by Haworth and Linnell (*loc. cit.*) from their experiments are invalid, and that the products described in the latter paper as liquid distillates were non-homogeneous, and the analyses, although many times repeated on different specimens, were in fortuitous agreement with calculated structural formulæ. Their conclusions are therefore held over for revision. This experience, along with that of Irvine and Hynd, Irvine and Patterson, and Irvine and Hogg (*loc. cit.*) commented on in this paper, renders it necessary to recognise that *structural formulæ cannot with any certainty be applied to liquid or crystalline degradation products in the sugar group unless these products can be compared with, or be further degraded to give, known crystalline reference deriv-*

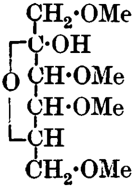
atives of definitely verified structures. This condition is fully satisfied in the present work on the constitution of normal fructose.

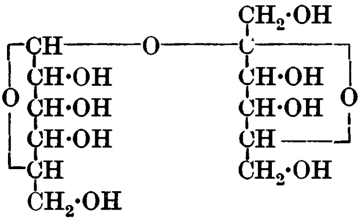
The second part of the generalisation given by Charlton, Haworth, and Peat (*loc. cit.*) was that the unstable or γ-variety of the aldoses conforms to the butylene-oxide type. Since normal fructose is in agreement with the generalisation as applied to normal aldoses, it is probable that the analogy of γ-fructose to the γ-aldoses also applies, and that tetramethyl γ-fructose is a butylene-oxide sugar. A further analogy is suggested by a comparison of the equilibrium values of the specific rotations of the two methylated arabinoses and the two fructoses, which contain similarly disposed but oppositely directed asymmetric groups :

(Amylene oxides.)	(γ-Sugars.)
Normal *l*-trimethyl arabinose, +127°.	*l*-Trimethyl γ-arabinose, −39° (butylene oxide).
Normal *d*-tetramethyl fructose, −123°.	*d*-Tetramethyl γ-fructose, +32°.

Of the several available formulæ for tetramethyl γ-fructose, (IX) seems to be the most probable, and the most satisfactory formula for sucrose on this basis is (X).

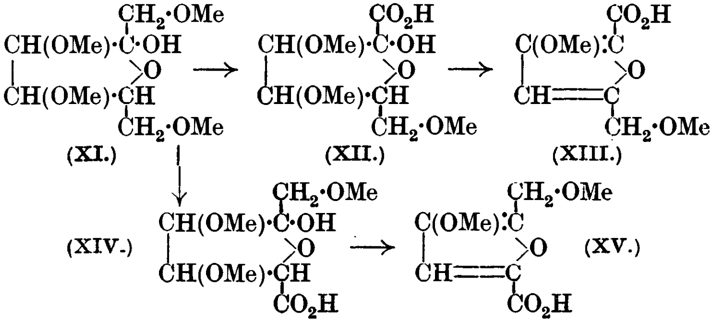
(IX.)





(X.)

Formula (IX) represents tetramethyl γ-fructose as being already a substituted hydrofuran, and its transformation to a furan complex may be explicable on the lines of the following scheme, the compound (XII) being analogous to that obtained (VIII) in the first stages of the oxidation of the normal sugar :



The composition and properties of the furancarboxylic acid which we have isolated by distillation of the products of the action of nitric acid correspond to the formula (XIII) or (XV), but for the present this formula is only tentatively given (Found: C, 51·4; H, 5·3; OMe, 33·1; *M*, by titration, calculated for a monobasic acid, 189. $C_8H_{10}O_5$ requires C, 51·6; H, 5·4; OMe, 33·3%; *M*, 186).

EXPERIMENTAL.

Methyl i-*Dimethoxysuccinate and* i-*Dimethoxysuccinamide.*—The crystalline ester obtained by boiling 5 g. of *meso*tartaric acid for 6 hours with 50 c.c. of methyl alcohol containing 2 g. of hydrogen chloride was isolated in the usual manner and dissolved in methyl iodide (20 c.c.) diluted with methyl alcohol (10 c.c.). Silver oxide (30 g.) was then added in small portions with shaking and efficient cooling, the reaction being very vigorous and tending to give rise to oxidation as well as methylation unless controlled. The silver residues were extracted with ether and on removal of the solvent methyl *i*-dimethoxysuccinate separated in flat plates. After recrystallisation from ether–light petroleum, the pure ester showed m.p. 67—68° (Found: C, 46·5; H, 7·0; OMe, 58·3. Calc. for $C_8H_{14}O_6$: C, 46·6; H, 6·8; OMe, 60·2%). A methyl-alcoholic solution of this ester saturated with ammonia deposited the diamide after a few hours in rectangular prisms, slightly soluble in water and methyl alcohol (much more so than *d*-dimethoxysuccinamide), which can be recrystallised from the latter solvent. When heated, the substance darkens slightly at 220° and melts at 245—246° (decomp.) (Found: OMe, 33·9. Calc. for $C_6H_{12}O_4N_2$: OMe, 35·2%).

Oxidation of Normal Crystalline Tetramethyl Fructose.—(a) *With nitric acid* (*d* 1·2). 5·5 G. of tetramethyl fructose (m. p. 95—97°, $[\alpha]_D$ $-121°$ in water for $c = 1·04$; OMe, 51%) were treated with 75 c.c. of nitric acid (*d* 1·2) under the conditions given by Irvine and Patterson (*loc. cit.*), and the product was isolated as the methyl ester in the standard way (compare Hirst, *loc. cit.*, etc.). A portion of the product crystallised, and this was separated from the liquid portion before distillation, adhering syrup being washed away with a mixture of ether and petroleum, in which the crystals were insoluble (yield of solid, 2·2 g.). The liquid portion together with the washings was then distilled, giving 1·75 g., b. p. about 150—160°/10 mm., n_D 1·4490. A small amount of crystalline material separated from the distillate on standing. The distillate was strongly lævorotatory, acid to litmus, contained reducing material, and was obviously a complex mixture. The crystalline material was very soluble in methyl alcohol and water, less soluble in ether, and only very slightly soluble in light petroleum. Recrystallisation from the last solvent gave rectangular plates, m. p. 119—120°, b. p. about 160°/12 mm., $[\alpha]_D$ $-107°$ in water ($c = 0·844$), $[\alpha]_D$ $-94°$ in methyl alcohol ($c = 1·342$). The substance was affected by hot alkali, giving a brown colour to the solution. It was strongly reducing (60 mg. gave 71 mg. Cu_2O on 10 minutes' boiling with excess of Fehling's solution). Analysis showed it to be the methyl ester, $C_{10}H_{18}O_7$, of a monobasic acid, $C_9H_{16}O_7$ (Found : C, 47·7 ; H, 7·2 ; OMe, 48·5. $C_{10}H_{18}O_7$ requires C, 48·0 ; H, 7·2 ; OMe, 49·6%). 0·1115 G. required 5·5 c.c. of *N*/10-alkali for hydrolysis (calc., 4·5 c.c.). The same quantity of methyl dimethoxyhydroxyglutarate requires 9·4 c.c. After the hydrolysis, which was carried out at 95°, the solution was coloured, and this instability in the presence of alkali indicates that the titration figure quoted above (typical of several concordant values) gives too high a value for the percentage of $\cdot CO_2Me$ present, the discrepancy of 1 c.c. between the found and the calculated value being thus explicable.

Methylation (1 g. of the ester dissolved in 6 c.c. of methyl iodide and treated with 5 g. of silver oxide) revealed one free hydroxyl group, which methylates very readily. The product (which is formed quantitatively) is crystalline, easily soluble in methyl alcohol, slightly soluble in ether, and scarcely at all soluble in petroleum. Recrystallisation from ether–petroleum gave plates, m.p. 102—103°, $[\alpha]_D$ $-116°$ in methyl alcohol ($c = 0·700$), $[\alpha]_D$ $-129°$ in water ($c = 1·040$). The new substance gave no colour with hot alkali and did not reduce Fehling's solution even on continued boiling. The methyl group thus introduced is held firmly and is apparently not removed by boiling with 5% aqueous hydrochloric acid, as after this treatment the substance was still without reducing power (Found : C, 49·7 ; H, 7·6 ; OMe, 57·5 ; CO_2Me, 22·8. $C_{11}H_{20}O_7$ requires C, 50·0 ; H, 7·6 ; OMe, 58·7 ; CO_2Me, 22·4%).

(b) *With nitric acid* (*d* 1·42). A solution of 7·0 g. of tetramethyl fructose in 50 c.c. of nitric acid (*d* 1·42) was warmed gradually until oxidation commenced (about 70°), and the reaction was then controlled by warming and cooling in such a way that the evolution of oxides of nitrogen never became violent. Finally, the mixture was heated at 90° for 1 hour. The nitric acid was removed by distillation at 50°/10 mm. in the usual way, and the product esterified. A portion of the final product crystallised and was removed before distillation [compare section (*a*) above]. This experiment gave : (I) 0·9 g. of crystals, m. p. 119—120°, identical with the material previously described; (II) 2·8 g., b. p. 135—140°/10 mm., $n_D^{18°}$ 1·4370; (III) 1·35 g., b. p. 145—160°/10 mm., $n_D^{18°}$ 1·4488. This crystallised partly on standing, the supernatant liquor then showing $n_D^{18°}$ 1·4450. The crystals had m. p. 119°. The amount of oxalic acid produced was negligible. In other oxidations, it was found that longer treatment with nitric acid at 90° diminished the amount of the crystalline material obtainable, and *vice versa.* Thus, for example, 3·0 g. of tetramethyl fructose, after being heated for 8 hours at 90—95° with nitric acid, gave (I) 0·18 g. of crystals; (II) 1·2 g., b. p. 135—140°/10 mm., $n_D^{17^\circ}$ 1·4375; (III) 0·7 g., b. p. 145—170°/10 mm. Again the amount of oxalic acid was negligible.

Examination of the portion, b. p. 135—140°/10 *mm.* This was essentially a mixture of methyl *i*-dimethoxysuccinate and methyl *d*-arabotrimethoxyglutarate in approximately equal proportions. It showed $[\alpha]_D$ -26° in methyl alcohol ($c = 1{\cdot}142$) and -28° in water ($c = 1{\cdot}768$). Since methyl *l*-arabotrimethoxyglutarate gives $[\alpha]_D + 50^\circ$ in methyl alcohol, the above mixture should presumably give $[\alpha]_D$ -25° (Found : C, 47·0; H, 7·0; OMe, 58·5; CO_2Me, 50·0. Calc. for the above mixture : C, 47·3; H, 7·0; OMe, 61·1; CO_2Me, 52·2%). The presence of both these substances was shown by the isolation of their crystalline diamides. To effect this, the mixture of esters (1 g.) was dissolved in methyl alcohol (5 c.c.) saturated with ammonia, and the solution kept at room temperature. This experiment has been carried out on several occasions, and in the majority of these a first crop of practically pure *i*-dimethoxysuccinamide was filtered off after 24 hours, followed by a rapid crystallisation of a mixture of dimethoxysuccinamide and trimethoxyglutaramide. The trimethoxyglutaramide was isolated from this mixture by recrystallisation from methyl alcohol, care being taken not to dissolve the whole of the material in the hot methyl alcohol, the undissolved portion containing most of the dimethoxysuccinamide. On some occasions, however, both amides came down together and separation was then effected by taking advantage of the preferential solubility of the trimethoxyglutaramide in methyl alcohol. A careful search was made for *l*-dimethoxysuccinamide, but various control analyses, determinations of specific rotation, etc., carried out on samples of the mixed amides, the residues from recrystallisations, etc., failed to give the slightest indication of its presence. In every case, the figures obtained agreed with those required for a mixture in some proportion of *i*-dimethoxysuccinamide and *d*-arabotrimethoxyglutaramide. Every experiment made on the formation of amides from the liquid ester yielded a final deposit (after some 4 or 5 days) of almost pure trimethoxyglutaramide.

Fuller details of a typical experiment are given. 2 G. of the syrup, dissolved in 12 c.c. of methyl alcohol saturated with ammonia, deposited during 18 hours 0·25 g. of *i*-dimethoxysuccinamide in characteristic hard tufts or crusts. Washed with methyl alcohol and ether, this material showed m. p. 245° after darkening at 220°.

It was optically inactive. Mixed m. p. with an authentic specimen of *i*-dimethoxysuccinamide, 245° (Found : C, 40·9; H, 7·0; OMe, 34·0; N, 15·7. Calc. : C, 40·8; H, 6·8; OMe, 35·2; N, 15·9%). The mother-liquor now deposited fairly rapidly a second fraction of mixed amides as a fine white powder (0·52 g.), $[\alpha]_D$ −36° in water ($c = 0{\cdot}51$) (Found : OMe, 38·0%). By careful recrystallisation from methyl alcohol, 0·25 g. of trimethoxyglutaramide was obtained, m. p. 230—232°, $[\alpha]_D$ in water −49° ($c = 0{\cdot}95$). In the course of 12 days a final fraction (0·2 g.) separated, m. p. 226—230°, $[\alpha]_D$ in water −47·7° ($c = 0{\cdot}692$). The recrystallised material (short needles or prisms) showed m. p. 232—233°, $[\alpha]_D$ −49° in water ($c = 0{\cdot}879$). The corresponding figures for the arabotrimethoxyglutaramide derived from *l*-arabinose are, respectively, m. p. 233°, $[\alpha]$ + 50° in water (Found : C, 43·3; H, 7·1; N, 12·4; OMe, 40·2. $C_8H_{16}O_5N_2$ requires C, 43·6; H, 7·3; OMe, 42·2; N, 12·7%).

UNIVERSITY OF BIRMINGHAM, EDGBASTON.

UNIVERSITY OF DURHAM, ARMSTRONG COLLEGE,
NEWCASTLE-UPON-TYNE.

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