CCCCXII.—*The Oxide-ring Structure of Normal and γ-Derivatives of Mannose. Preparation and Oxidation of Derivatives of γ-Mannonolactone and δ-Mannonolactone, with an Addendum on the Formulation of Normal and γ-Sugars as Derivatives of Pyran and Furan and the Suggestion of a New Nomenclature.*

By Edward Hague Goodyear and Walter Norman Haworth.

In continuing the study of lactones derived from sugars we have prepared several new derivatives in the mannose series. The ordinary γ-mannonolactone (III) was first prepared from mannonic acid by Fischer and Hirschberger (*Ber.*, 1889, **22**, 3218) and was obtained in purer condition by Nef (*Annalen*, 1914, **403**, 306) and by Hedenburg (*J. Amer. Chem. Soc.*, 1915, **37**, 345). The latter two authors also isolated an isomeric lactone, described originally as the "β" lactone, which is also obtainable from mannonic acid by adopting a different procedure for the anhydridation. We recommend that this "β" lactone should now be regarded as the δ-mannonolactone (VI) in view of the results obtained in a comparative study of lactones (compare Haworth and Nicholson, J., 1926, 1899). In the case of the parallel example from gluconic acid, the supposed "β" gluconolactone also should be described as δ-gluconolactone.

By solution of γ-mannonolactone in dry acetone containing 0·1% of hydrogen chloride, we have prepared the crystalline *γ-mannonolactone-monoacetone*, and under slightly different conditions the crystalline γ-mannonolactone-diacetone (II) has also been obtained. The latter is identical with the substance originally prepared by

Ohle and Berend (*Ber.*, 1925, **58**, 2590) from mannose-diacetone (I) by oxidation to the diacetone of mannonic acid, which, by loss of water, passes into the corresponding lactone. Specimens have been prepared by each of these methods and their identity established. The constitution (I) assigned to mannose-diacetone therefore receives confirmation.

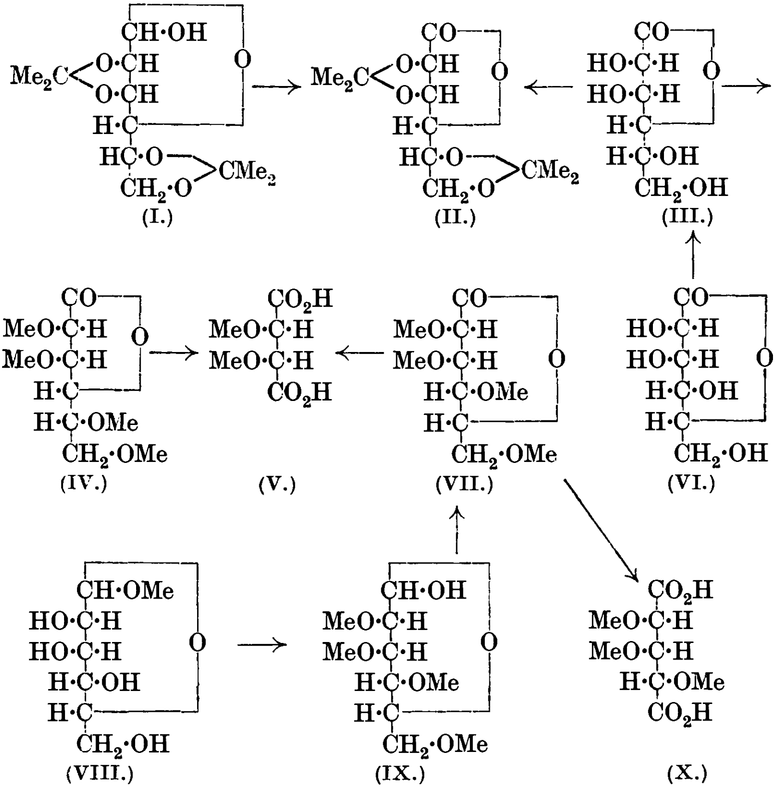
By methylation of γ-mannonolactone-monoacetone the crystalline *dimethyl γ-mannonolactone-monoacetone* was isolated, and on hydrolysis with dilute mineral acid this gave *dimethyl mannonolactone*. Acetylation of γ-mannonolactone gave rise to the *tetra-acetyl* derivative.

When γ-mannonolactone was methylated with methyl iodide and silver oxide in the presence of acetone, that is, under the conditions described by Levene and Simms (*J. Biol. Chem.*, 1925, **65**, 46), a mixture of crystalline products was obtained, from which were isolated (*a*) tetramethyl γ-mannonolactone (IV), which gave a crystalline *phenylhydrazide*, and (*b*) dimethyl γ-mannonolactone-monoacetone, identical with the specimen above-mentioned. When, however, acetone was avoided as a solvent during the methylation of γ-mannonolactone, only tetramethyl γ-mannonolactone was obtained. This showed $[\alpha]_D^{18°}$ + 65·2° falling to 61·2° in 9 days (compare Drew, Goodyear, and Haworth, this vol., pp. 1242—3).

In an attempt to prepare the tetramethyl derivative from δ-mannonolactone by direct methylation, we were only able to recognise in the products the tetramethyl γ-mannonolactone, and it seems clear that the 1 : 5 ring in the unsubstituted δ-lactone undergoes conversion into a 1 : 4 ring under the conditions employed. During the process of methylation, water is formed; this appears to open the lactone ring, which again closes to give the stable γ-lactone. The tetramethyl δ-mannonolactone was prepared, however, from α-methylmannoside (VIII) by the indirect method, namely, methylation followed by hydrolysis to normal tetramethyl mannose (IX) and oxidation of this sugar by means of bromine water. The tetramethyl δ-mannonolactone (VII) is isolated by conversion first into the crystalline phenylhydrazide, and after regeneration from this derivative is recognisable as a crystalline product, m. p. 23—25°, having $[\alpha]_D^{18°}$ + 150° (initial).

The constitution of each of these tetramethyl derivatives was determined by direct oxidation with nitric acid. Tetramethyl γ-mannonolactone (IV) gave on oxidation *i*-dimethoxysuccinic acid (V), which was identified as the crystalline methyl ester and as the crystalline *methylamide*, the latter being compared with a specimen prepared from *meso*tartaric acid by Haworth and Jones (this vol.,

p. 2352). This lactone should therefore be indexed as 2 : 3 : 5 : 6-tetramethyl mannonolactone (IV). The corresponding δ-lactone (VII) gave on oxidation a small yield of *i*-dimethoxysuccinic acid (V) and also, in a larger yield, *d*-arabo-trimethoxyglutaric acid (X), which was identified as the crystalline methylamide (m. p. 209)°. This was enantiomorphous with a specimen of the methylamide of the *l*-variety of the acid obtained by Haworth and Jones (*loc. cit.*), with which it was compared. This δ-lactone should therefore be indexed as 2 : 3 : 4 : 6-tetramethyl mannonolactone (VII).



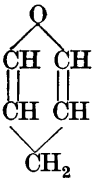
The bearing of these results on the structure of the constituent sugars is evident. Since a lactone of formula (VII) is derived from tetramethyl mannose (IX), which in turn has been prepared from α-methylmannoside, it follows that the latter has a 1 : 5 or amylene oxide ring structure (VIII). Similarly it has been shown that mannose-diacetone is a derivative of γ-mannose (I) (Irvine and Skinner, J., 1926, 1089; compare Ohle and Berend, *loc. cit.*). This gives rise on oxidation to the same γ-mannonolactone-diacetone (II) as we have obtained direct from γ-mannonolactone (III), and since the latter gives on methylation a tetramethyl γ-mannonolactone of constitution (IV), it is demonstrated that the γ-mannose derivative has a constitution containing a butylene or 1 : 4 oxide ring. This conclusion is, however, dependent upon there having been no displacement of the ring during methylation of the γ-lactone, and this is unlikely to have occurred; and secondly upon there having been no such displacement during the introduction of acetone residues into the γ-mannonolactone. The latter contingency also is on the whole unlikely, because the γ-lactone contains two pairs of hydroxyl groups which are already favourably situated for *cis*-condensation with acetone residues and are also attached to contiguous carbon atoms. Moreover the γ-lactone is the stabilised form into which the δ-lactone is convertible.

The results now communicated assign to the mannose derivatives of the normal and the γ-series the same structural relationships as those of the normal and the γ-derivatives of glucose, of fructose, of arabinose, and of xylose, all of which have been shown by direct oxidation methods applied to their related lactones to be amylene oxides in their normal forms and butylene oxides in their labile or γ-forms (Avery, Haworth, and Hirst, this vol., p. 2308; Haworth, Hirst, and Learner, *ibid.*, p. 2432; Haworth, Hirst, and Miller, *ibid.*, p. 2436; Haworth and Jones, *loc. cit.*). In a later paper it will be shown that these same structural relationships have been fully proved also for galactose in its normal and γ-forms. So far, therefore, as it is possible to generalise from these direct oxidation results it is seen that the conclusions reached confirm entirely the structural formulæ which were adduced from a study of the comparative rates of hydrolysis of the two series of lactones in aqueous solution, as determined (*a*) by the polarimetric method (Drew, Goodyear, and Haworth, *loc. cit.*) and (*b*) by the conductivity method. The generalisation advanced by Charlton, Haworth, and Peat (J., 1926, 89), which stated that the normal sugars tend to exist in amylene oxide forms and the labile or γ-sugars in butylene oxide forms, is again supported by the collateral data obtained from the oxidation of the methylated lactones.

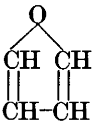
Addendum.

The normal sugars are thus seen to be representatives of the parent form indicated by pyran, and the labile or γ-sugars have as their parent substance furan. The two types of normal and labile sugars might well be described as the pyran- and furan-types. Thus, arabinose in its normal form is tetrahydroxytetrahydropyran

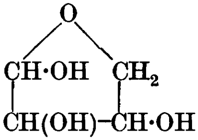
(A), whilst in its labile or γ-form it is tetrahydroxymethyltetrahydrofuran (B).



Pyran.

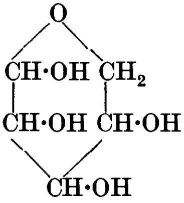


Furan.

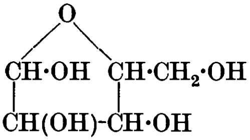


Furanose (a tetrose)
(Trihydroxytetrahydrofuran).

(A)



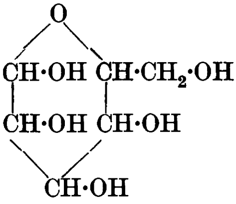
A Normal Pentose.
[Pyranose (Arabo-, etc.)].



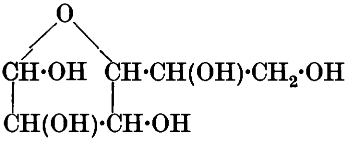
(B)

A γ-Pentose.
[Xylo-furanose (and also Arabo-, ribo-, lyxo-furanose)].

(C)

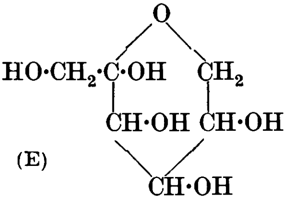


A Normal Aldo-hexose
[Gluco (etc.) -pyranose].



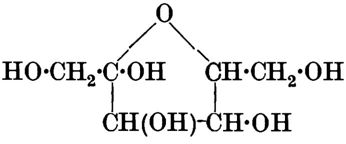
(D)

A γ-Aldo-hexose.
[Gluco (etc.) -furanose].



(E)

A Normal Keto-hexose.
[Fructo-pyranose].



(F)

A γ-Keto-hexose.
[Fructo-furanose].

There is urgent need for the adoption of a simplified, concise, standard nomenclature in the sugar group which will define the essential structural differences between a normal sugar form and a labile or so-called γ-sugar form. Such a revised nomenclature should be capable of expressing also the stereochemical relationships of the various pentoses, hexoses, etc., which may occur in either structural form.

On the basis of the conclusions now reached, the formula (A) must be accepted as a general representation of a normal sugar, which might be described as a pyranose. The normal sugars arabinose, xylose, etc., may then be described as arabo-*pyran*ose, xylo-*pyran*ose, and both the structure and the configuration would be at once intelligible from this nomenclature. The corresponding labile or γ-isomerides may be described as arabo-*furan*ose, xylo-*furan*ose, etc. (B). Proceeding in a similar manner to the representation of a hexose, it is only necessary to modify the formula (A) by the introduction of a primary alcohol group as a side chain, in order to indicate (as a hexa-pyranose) the structural relationships of the normal hexoses, and this modification, having regard to both the structural and the stereochemical arrangement involved, would be recognisable under the name of gluco-*pyran*ose (C), manno-*pyran*ose, galacto-*pyran*ose, etc., whilst the labile or γ-sugars would similarly be described as gluco-*furan*ose, manno-*furan*ose, etc. (D).

Similarly in the cases of normal and γ-fructoses, which have been shown by one of us to have the constitutional formulæ (E) and (F), the corresponding nomenclature would apply : fructo-*pyran*ose for the normal sugar, and fructo-*furan*ose for the labile form (Haworth and Hirst, J., 1926, 1858; Haworth, Hirst, and Learner, this vol., p. 1040; Haworth, Hirst, and Nicholson, *ibid.*, p. 1513; Avery, Haworth, and Hirst, *loc. cit.*; Haworth, Hirst, and Learner, this vol., p. 2432).

The sugars higher in the series, such as the heptoses, occurring in either form would be definable as hepta-*pyran*oses or hepta-*furan*oses, the device which is already current being used for distinguishing between the configurations, namely, glucohepta-*pyran*ose, etc., instead of " glucoheptose (normal) of the amylene oxide form."

It is not without significance that the naturally occurring pigments such as the anthocyanins, occurring as glucosides, contain as an essential part of their structure a pyran residue, and that the anthoxanthins or hydroxyflavones contain the related pyrone group. It is conceivable that this residue is traceable to its origin as a normal sugar, suggesting that these colouring matters of plants are transformation products intimately related in their structure to the sugar group. The suggestion has already been made that phenols originate through an aldol type of condensation between the aldehyde group of an aldohexose of position (6) in the chain, giving a hexahydroxyhexahydrobenzene of the type of inositol, which then passes by elimination of water to the polyhydric phenols (Haworth, *J. Soc. Chem. Ind.*, 1927, **46**, 295). On the other hand, the frequent occurrence of furan residues in natural products suggests that these are similarly traceable to the pre-existing γ-sugar. We have already shown that tetramethyl γ-fructose passes with remarkable ease into a furan derivative (Haworth, Hirst, and Nicholson, this vol., p. 1513).

EXPERIMENTAL.

Methylation of γ-Mannonolactone.—Crystalline γ-mannonolactone, prepared by the methods described by Nef and by Hedenburg (*loc. cit.*), was methylated with methyl iodide and silver oxide in presence of methyl alcohol as solvent. The product was treated with the same reagents in the presence of acetone (Levene and Simms, *J. Biol. Chem.*, 1925, **65**, 46) and thereafter twice with the methylating agents without any extraneous solvent; it then became partly crystalline. This product was distilled under diminished pressure, subjected to two further methylations, and again distilled. The major portion (70% yield), b. p. 100—105°/0·06 mm., became partly crystalline and the crystals were collected on porous tile and recrystallised from light petroleum (voluminous needles, m. p. 109—110°). A second crop consisted of both needles and plates, m. p. 83°. Recrystallisation of the latter from boiling carbon tetrachloride gave prisms, m. p. 110°, showing no depression of melting point in admixture with the needles. This material gave OMe, 30·25%. It was clear that the compound crystallising in needles could also be obtained from carbon tetrachloride in the form of prisms. It showed $[\alpha]_D^{20^\circ}$ + 64·2° in water ($c = 1{\cdot}1$), changing to + 55·8° in 9 days (Found : C, 53·5; H, 7·3. $C_{11}H_{18}O_6$ requires C, 53·6; H, 7·3%). These analytical figures agree with those required for a *monoacetone* derivative of dimethyl γ-mannonolactone, and that this was actually the product obtained was shown by an alternative method of preparation which is described later.

In order to investigate the reason for the occurrence of this compound a further lot of γ-mannonolactone was methylated (*a*) in the presence of acetone, and a further quantity (*b*) in the absence of acetone, only methyl alcohol being used as the extraneous solvent. In the former case, the same mixture of products was isolated, the chief of these being the compound, m. p. 110°, but in the latter case (*b*) an apparently homogeneous product was obtained, m. p. 108°, from ligroin; $[\alpha]_D^{18^\circ}$ + 65·2° in water ($c = 1{\cdot}038$), falling to 61·2° after 9 days; $[\alpha]_{5461}^{18^\circ}$ + 77·0°, falling to 71·8° in 9 days (Found : C, 51·1; H, 7·6; OMe, 52·2. Calc. for $C_{10}H_{18}O_6$: C, 51·25; H, 7·7; OMe, 54·2%). This substance was obtained either as colourless plates or as long, transparent needles 1—2 cm. in length. Both forms had the same melting point.

When heated with phenylhydrazine, this product, which appeared to be the genuine tetramethyl γ-mannonolactone, gave a crystalline *phenylhydrazide*, m. p. 167° (from ether) (Found : C, 55·5; H, 7·6; OMe, 32·9; N, 8·4. $C_{16}H_{26}O_6$ requires C, 56·1; H, 7·6; OMe, 36·3; N, 8·2%). These analytical data suffice to show that the substance was the phenylhydrazide of a tetramethylmannonic acid.

γ-Mannonolactone-monoacetone.—γ-Mannonolactone was shaken with dry acetone containing a trace of hydrogen chloride (about 0·1%). Complete solution occurred in 20 minutes, and then the mineral acid was neutralised with silver carbonate. After filtration and evaporation, colourless crystals, m. p. 132°, were collected and also a second crop, m. p. 117° (impure diacetone derivative). Recrystallisation of the former product from acetone and ligroin gave colourless needles (yield, 85%), m. p. 133°; $[\alpha]_D^{20°}$ + 55·4° in water ($c = 1·62$) (Found : C, 49·1; H, 6·6. $C_9H_{14}O_6$ requires C, 49·5; H, 6·4%).

γ-Mannonolactone-diacetone.—Finely divided γ-mannonolactone (6 g.) was shaken with 400 c.c. of dry acetone containing 0·2% of hydrogen chloride. After 3 hours, when most of the lactone had dissolved, the mineral acid was removed with silver carbonate and the acetone evaporated under diminished pressure. Extraction of the crystalline residue with large volumes of light petroleum yielded colourless crystals, m. p. 122—125°; after recrystallisation from ligroin, m. p. 126°. $[\alpha]_D^{20°}$ + 50·6° in chloroform ($c = 1$); + 73·65° in 50% alcohol, falling to 45·9° after 20 days (Found : C, 55·8; H, 7·15. Calc. for $C_{12}H_{18}O_6$: C, 55·8; H, 7·0%). The melting point and physical constants agreed with those of γ-mannonolactone-diacetone observed by Ohle and Berend (*Ber.*, 1925, **58**, 2590) and the substance was identical with a specimen prepared by their method.

Dimethyl γ-Mannonolactone-monoacetone.—The above specimen of γ-mannonolactone-monoacetone was methylated by means of silver oxide and methyl iodide. The product crystallised from ether in bulky needles, m. p. 110°, and this was found to be identical with the product obtained above during the methylation of γ-mannonolactone in the presence of acetone (Found : OMe, 25·5. Calc. : OMe, 25·3%).

Dimethyl γ-Mannonolactone.—Hydrolysis of the above product with 0·1% aqueous hydrochloric acid gave a crystalline substance which crystallised from ethyl acetate–light petroleum in white needles, m. p. 109—110°; $[\alpha]_D^{20°}$ + 61·1° in water ($c = 1·03$), falling to 60·5° in 19 days. Yield, 60%. This was *dimethyl γ-mannonolactone* (Found : C, 46·6; H, 7·1; OMe, 28·9. $C_6H_{14}O_6$ requires C, 46·6; H, 6·8; OMe, 30·1%).

Tetra-acetyl γ-Mannonolactone.—A mixture of γ-mannonolactone

(1 g.), acetic anhydride (5 g.), and dry pyridine (6·7 g.) was shaken for 45 minutes until a clear solution was obtained, and this was kept in a stoppered vessel in the ice-chest for 2 days. After dilution with 50 c.c. of cold chloroform the solution was poured on powdered ice. The chloroform extract of this product was washed with water and sodium carbonate solution, dried, and evaporated. This gave a syrup which crystallised from ether in needles, m. p. 115—117°; the yield was 0·5 g. Recrystallisation from dry ether raised the m. p. to 120°. $[\alpha]_D + 44{\cdot}9°$ in chloroform ($c = 1{\cdot}56$) (Found: C, 48·6; H, 5·3. $C_{14}H_{18}O_{10}$ requires C, 48·55; H, 5·2%). This appeared to be the tetra-acetyl derivative of γ-mannonolactone.

Attempted Preparation of Derivatives of δ-Mannonolactone.—This crystalline substance, first described by Nef (*loc. cit.*) as β-mannonolactone, was prepared by Nef's method as modified by Hedenburg (*loc. cit.*). M. p. 162° (after recrystallisation from boiling ethyl alcohol); $[\alpha]_D^{20°} + 114{\cdot}0°$ in water ($c = 1{\cdot}24$), falling to $+ 27{\cdot}5°$ after 21 hours. 20 G. of pure calcium mannonate gave 6·5 g. of this lactone.

This substance was treated with methyl iodide and silver oxide twice in the presence of methyl alcohol and once in the presence of acetone. The semi-crystalline product was drained on a tile and extracted with light petroleum, which removed a mobile liquid having $n_D^{18°}$ 1·4370. The crystals (m. p. 108°) showed no depression of m. p. in admixture with the specimen of tetramethyl γ-mannonolactone (Found: OMe, 52·2. Calc.: OMe, 54·2%). It thus appeared that the δ-lactone had been transformed into a γ-lactone during condensation with acetone which had been used as solvent in the methylation process.

Oxidation of Tetramethyl γ-Mannonolactone.—This crystalline lactone (1·5 g.) was heated with 13 c.c. of nitric acid (*d* 1·42) at 100° for about 15 minutes in order to initiate the oxidation. The bath was maintained at 95—100° for a further 7 hours, and the solution was then cooled and diluted, and the nitric acid removed as completely as possible by distillation under diminished pressure, followed by repeated dilution and further distillation. The syrupy residue, which contained crystals, was esterified with 4% methyl-alcoholic hydrogen chloride, and the product (0·85 g.) distilled under 0·1 mm.: Fraction I, from bath at 110—115°; 0·25 g., which crystallised immediately. Fraction II, bath at 115—120°; 0·4 g., which crystallised on nucleation with methyl dimethoxysuccinate. Fraction III, bath at 120—140°; 0·1 g., which was partly crystalline.

Fractions I and II were identical, since each gave on recrystallisation from light petroleum a crystalline ester, m. p. 68°, which was identical with a specimen of methyl ester prepared from *meso*-tartaric acid, and this was confirmed by a mixed m. p. determination. The substance was therefore methyl *i*-dimethoxysuccinate (Found: C, 46·45; H, 9·6; OMe, 59·3. Calc.: C, 46·6; H, 9·6; OMe, 60·1%).

0·1 G. of this compound was converted into the methylamide by dissolving it in a saturated solution of methylamine in methyl alcohol. Crystals separated after 2 days, m. p. after recrystallisation 209°, giving no depression in admixture with *i*-dimethoxysuccinomethylamide prepared from *meso*tartaric acid by Haworth and Jones (*loc. cit.*) (Found: C, 47·1; H, 7·6; N, 13·1. Calc.: C, 47·1; H, 7·8; N, 13·7%).

Oxidation of Tetramethyl δ-Mannonolactone.—Crystalline 2 : 3 : 4 : 6-tetramethyl δ-mannonolactone (2·7 g.) prepared by the method described by Drew, Goodyear, and Haworth (this vol., p. 1243) was oxidised by digestion at 90° with 20 c.c. of nitric acid (*d* 1·42). The reaction proceeded smoothly, and after $4\frac{1}{4}$ hours the evolution of brown fumes had ceased and a colourless solution remained. After dilution the nitric acid was repeatedly evaporated at 40° in a vacuum with addition of water, and finally a syrup was obtained which was dissolved in 80 c.c. of methyl-alcoholic hydrogen chloride (3·5%) and digested at 70° for 6 hours. The cooled solution was neutralised with silver carbonate, and the ester obtained (2·3 g.) by the usual method of isolation. This distilled at 95—100°/0·07 mm. and showed $[\alpha]_D^{18^\circ} - 27{\cdot}3^\circ$ (in water, $c = 1{\cdot}21$). The ester gave on solution in methyl-alcoholic ammonia the crystalline amide, m. p. 255°. The ester was, however, identified by means of the following preparation of the crystalline methylamide.

The liquid ester (0·5 g.) was dissolved in methyl alcohol, and the solution was saturated with methylamine. Having been kept for 2 days, the solution was evaporated and gave a solid residue which was recrystallised from ethyl acetate. The first crop of crystals (0·14 g.) had m. p. 155—160° and obviously contained a slight impurity, which was removed on a further crystallisation from the same solvent. This gave a colourless, crystalline product (0·04 g.), m. p. 208—209°, identical with the specimen of *i*-dimethoxysuccinomethylamide prepared by Haworth and Jones from *meso*-tartaric acid. A second crop of crystals was obtained by concentrating all the mother-liquors; colourless needles (0·3 g.), m. p. 172°. This substance was recognised as *d*-arabo-trimethoxyglutaromethylamide, $[\alpha]_D^{18^\circ} - 59{\cdot}7^\circ$ in water ($c = 0{\cdot}94$), the enantiomorph of the *l*-variety described by Haworth and Jones (*loc. cit.*) as having m. p. 172°, $[\alpha]_D^{18^\circ} + 59{\cdot}9^\circ$ in water ($c = 1$) (Found: C, 48·3; H, 8·3; N, 11·0; OMe, 36·3. Calc.: C, 48·35; H, 8·1; N, 11·2; OMe, 37·5%).

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