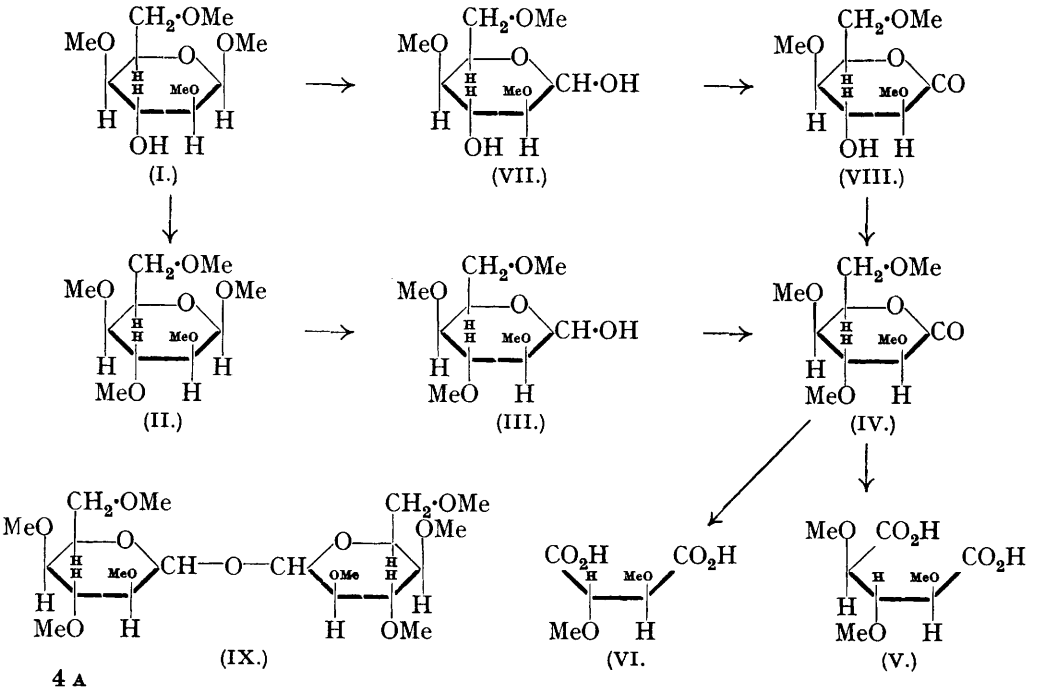
229. *The Conversion of* d-*Glucose into* d-*Idose.*

By W. H. G. Lake and S. Peat.

The alkaline hydrolysis of 2-*p*-toluenesulphonyl β-methylglucoside leads to the formation of at least two anhydromethylhexosides, namely, 2 : 3-anhydro-β-methylmannoside and 3 : 4-anhydro-β-methylaltroside. These products are isolated as the dimethyl derivatives. Treatment of *dimethyl* 3 : 4-*anhydro*-β-*methylaltroside* with sodium methoxide gives 2 : 4 : 6-*trimethyl* β-*methyl* d-*idopyranoside*, the constitution of which is established by oxidative methods. Crystalline *tetramethyl* d-*idono*-δ-*lactone* and *octamethyl di*-d-*idopyranose* are described together with a number of syrupy derivatives of idose. Comment is made upon certain unusual properties shown by these derivatives.

The alkaline hydrolysis of 2-*p*-toluenesulphonyl β-methylglucoside gives 2 : 3-anhydro-β-methylmannoside (Lake and Peat, J., 1938, 1417), which is isolated as crystalline dimethyl 2 : 3-anhydro-β-methylmannoside (Haworth, Hirst, and Panizzon, J., 1934, 154). This substance is always accompanied by a non-crystalline isomer, the constitution of which is the subject of the present communication.

Hydrolysis of the syrupy dimethyl anhydromethylhexoside with sodium methoxide led to the isolation in 65% yield of a crystalline trimethyl methylhexoside which was shown by the following reactions to be 2 : 4 : 6-*trimethyl* β-*methyl*-d-*idopyranoside* (I). Methylation of (I) gave a syrupy tetramethyl methylhexoside (II); this was rapidly hydrolysed by aqueous acid and yielded a tetramethyl hexose (III), which also was non-crystalline. By the oxidation of (III) with bromine water, a crystalline tetramethyl hexonolactone (IV) was obtained. The tetramethyl hexose and the lactone derived from it both showed unusual properties which are discussed below. When the crystalline lactone was oxidised with nitric acid, there was obtained i-*xylotrimethoxyglutaric acid* (V) and, in addition, a little l-*dimethoxysuccinic acid* (VI). These acids were separated and characterised as the methylamides. The formation of the trimethoxyglutaric acid (V) proves that the lactone (IV) belongs to the δ-series and that therefore (III) is pyranose in structure and (II) and (I) are methylpyranosides.



It is seen that the acid (V) could be formed by the oxidation of a methylated sugar having the configuration of *d*-glucose, *l*-glucose, *d*-idose, or *l*-idose. Of these possibilities, *d*-glucose and *l*-glucose are excluded by a comparison of the properties of the tetramethyl sugar (III) and the tetramethyl lactone (IV) with the corresponding known derivatives of glucose.

It has been shown that the crystalline trimethyl methylhexoside (I) must have a pyranoside structure. Moreover, since (I) is formed from a derivative of methylglucopyranoside by a series of reactions in which no scission of the pyranoside ring is observed, it is legitimate to conclude that the β-methylhexopyranoside ring remains intact throughout and that no opportunity is afforded for a Walden inversion on C_5 to take place. Such an inversion is implied if (III) has the configuration of *l*-idose. It is clear, therefore, that the substance (I) is trimethyl methyl-*d*-idopyranoside and that the derivatives (II), (III), and (IV) retain the configuration of *d*-idose.

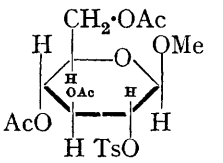
Trimethyl β-methyl-*d*-idopyranoside (I) was easily hydrolysed by aqueous acid to give *trimethyl* d-*idose* (VII) as a syrup. Oxidation of the latter substance with bromine water yielded a syrupy lactone (VIII). It was evident that this lactone belonged to the δ-series, for on methylation with methyl iodide and silver oxide it was transformed into the crystalline *tetramethyl* d-*idono*-δ-*lactone* (IV). Inasmuch as the sugar (VII) is oxidised to a δ-lactone (VIII) it is reasonable to conclude that in (VII) [and therefore in (I)] a methoxyl group is situated on C_4 and for that reason the formation of the more stable γ-lactone is not possible. When the lactone (VIII) was treated with liquid ammonia, a syrupy *amide* was obtained which gave a negative Weerman test for α-hydroxy-amides, an indication of the presence of a methoxyl group on C_2.

It is obvious that, if in the trimethyl idose (VII) methoxyl groups occupy positions 2 and 4, the third methoxyl group must be situated on either C_3 or C_6. No direct evidence is available to distinguish between these alternatives. Nevertheless, formulation of (VII) as the 2 : 3 : 4-trimethyl isomer would necessarily imply that, in the anhydromethylhexoside from which it is derived, the anhydro-ring involves C_6 and is situated, therefore, at positions 3 : 6, 2 : 6, or 4 : 6. The first possibility is excluded on the grounds that in all known 3 : 6-anhydro-sugars the anhydro-ring is stable to the action of sodium methoxide and the second and third types are regarded as highly improbable in this case not only for stereochemical reasons but also because it is difficult to envisage the production of a *d*-idose derivative from a *d*-glucose derivative through the intermediate formation of either of these anhydro-types. For these reasons the formulation of (VII) as 2 : 4 : 6-*trimethyl* d-*idopyranose* is adopted.

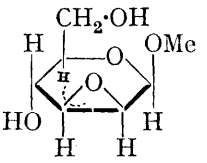
The conversion of *d*-glucose into *d*-idose requires that optical inversion should occur on C_2, C_3, and C_4. Such inversion would be the natural consequence of the intermediate formation and fission of two anhydro-ring compounds taking place in the following sequence. It is to be noted that the general principles already enunciated concerning the formation and fission of anhydro-ring systems are adhered to in this case. The first and chief product of the action of sodium methoxide on triacetyl 2-*p*-toluenesulphonyl β-methylglucopyranoside (X) is 2 : 3-anhydro-β-methylmannoside (XI). It is from this product that the crystalline dimethyl derivative described in the earlier paper is derived. It is now to be postulated that in the presence of the excess of sodium methoxide, fission of the newly formed anhydro-ring occurs at the point indicated by the dotted line in formula (XI) and that moreover Na^+ replaces the H^+ of the alcoholic hydroxyl groups. The hypothetical intermediate (XII) is thus formed. In the subsequent rearrangement the negatively charged oxygen on C_3 is involved in ring closure with the positively charged C_4 and concomitant inversion occurs on C_4 with the production of (XIII). When the alkali is neutralised (as it is in the process of isolation), (XIII) gives 3 : 4-anhydro-β-methyl-*d*-altropyranoside (XIV). The syrupy dimethyl anhydromethylhexoside which is the subject of this communication is thus 2 : 6-*dimethyl* 3 : 4-*anhydro*-β-*methyl*-d-*altropyranoside* (XV). When this substance is treated with sodium methoxide under the specified conditions, fission of the anhydro-ring occurs, accompanied by Walden inversion. This rupture takes place chiefly at the bond (a) and 2 : 4 : 6-trimethyl β-methyl-*d*-idopyranoside (I) is formed.

The evidence detailed above leaves no doubt that the trimethyl methylidoside (I) and

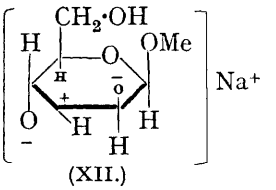
the tetramethyl methylidoside (II) are pyranoside in structure. Nevertheless in certain respects these glycosides exhibit properties which are usually more nearly associated with the furanoside type. For instance, both (I) and (II) are hydrolysable by aqueous acid with greater ease than are the corresponding β-methylglucopyranosides. Furthermore, trimethyl idose (VII) behaves as a furanose sugar inasmuch as it is converted into trimethyl methylidoside by methyl-alcoholic hydrogen chloride in the cold.



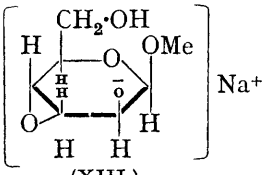
(X.)



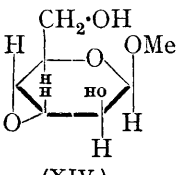
(XI.)



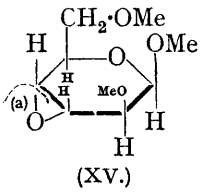
(XII.)



(XIII.)



(XIV.)



(XV.)

When tetramethyl idopyranose (III) is distilled in a vacuum, a non-reducing disaccharide of the trehalose type is formed by the union through the reducing groups of two molecules of the tetramethyl hexose. *Octamethyl di*-d-*idopyranose* (IX) is obtained in large needle-like crystals. It has $[\alpha]_D$ + 103° in water and it shows no mutarotation in aqueous solution. It is easily hydrolysed by N-acid and tetramethyl idose ($[\alpha]_D$ + 21·7° in water) is thereby regenerated. Previous examples of this type of condensation under the action of heat are known, but in these earlier examples the methylated monosaccharide is in the furanose form. Thus, distillation of trimethyl lyxofuranose yields a crystalline hexamethyl disaccharide (Bott, Hirst, and Smith, J., 1930, 665) and tetramethyl galactofuranose gives an octamethyl digalactose (Haworth, Hirst, Jones, and Woodward, J., 1938, 1575).

The isolation of a trimethoxyglutaric acid from tetramethyl idonolactone (IV) by oxidation with nitric acid affords indisputable evidence of its structure as a δ-lactone. Nevertheless the lactone shows no observable mutarotation in aqueous or in acetone–water solution. It behaves towards alkali titration in a manner characteristic of lactones, but the formation of the sodium salt thus effected is unattended by any change in the specific rotation ($[\alpha]_D$ — 32° in water). It would appear, indeed, that the lactone, the free acid, and the sodium salt of 2 : 3 : 4 : 6-tetramethyl idonic acid have the same specific rotation. The alternative explanation, namely, that the lactone ring shows an abnormal stability towards water or alkali, is contradicted by the fact that the correct value for the equivalent of the lactone is obtained by simple alkali titration.

Experimental.

The crystalline 4 : 6-dimethyl 2 : 3-anhydro-β-methylmannoside examined by Lake and Peat (*loc. cit.*) is prepared by the methylation of the product formed when 2-*p*-toluenesulphonyl β-methylglucoside is hydrolysed with sodium methoxide. The yield of the crystalline dimethyl anhydro-substance is not quantitative and it is always accompanied by a non-crystalline material which also has the composition of a dimethyl anhydromethylhexoside. The purest preparation of this syrupy material had $n_D^{21.5°}$ 1·4552 and $[\alpha]_D^{19°}$ — 21·0° in water (*c*, 2·1) (Found : C, 52·6; H, 8·1; OMe, 46·1. Calc. for $C_9H_{16}O_5$: C, 52·9; H, 7·9; OMe, 45·7%).

Hydrolysis with Sodium Methoxide.—The syrup (3·30 g.) was boiled for 20 hours with a 5% solution of sodium methoxide in dry methyl alcohol. The cooled solution was diluted with water and extracted repeatedly with chloroform. Evaporation of the dried chloroform extract gave a product which distilled at 130°/0·006 mm. as a colourless oil. The product was collected in three fractions, the total weight of distillate being 3·14 g. Fractions 2 and 3 crystallised during the distillation and fraction 1, which was more mobile, crystallised on nucleation.

Recrystallisation from ether–light petroleum yielded needles of a substance having m. p. 75° and $[\alpha]_D^{14°}$ — 61·0° in chloroform (*c*, 1·43) and the composition of a trimethyl methylhexoside (Found : C, 51·2; H, 8·5; OMe, 52·1. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5; OMe, 52·5%). This compound is shown below to be 2 : 4 : 6-*trimethyl* β-*methyl*-d-*idopyranoside*. The yield of crystalline material was 2·01 g.

2 : 4 : 6-*Trimethyl* d-*Idose*.—When the trimethyl methylidoside (1·60 g.) was heated at 90° with 5% sulphuric acid (60 c.c.), the following rotation changes were observed : $[\alpha]_D^{17°}$ (calc. on wt. of glycoside) — 56·3° (initial value); + 23·0° (½ hour); + 31·1° (1 hour); + 31·1° (2 hours); + 28·1° (3 hours). The cooled solution was neutralised by being made faintly alkaline with barium hydroxide solution, carbon dioxide being subsequently passed through the solution. The filtered solution was evaporated to dryness, and the product extracted with chloroform. Evaporation of the chloroform yielded a syrup showing $n_D^{22°}$ 1·4725, $[\alpha]_D^{18°}$ + 26·6° in water (*c*, 4·0) and + 8·0° in chloroform (*c*, 3·56) (Found : OMe, 41·0. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Trimethyl d-*Idono*-δ-*lactone*.—Trimethyl idose (1·20 g.) was oxidised with bromine water at room temperature and the product, isolated in the usual way, was purified by conversion into the sodium salt and removal of unoxidised material by extraction with ether. Decomposition of the sodium salt with mineral acid yielded a trimethyl hexonolactone (1·0 g.), which distilled as an oil showing $n_D^{20°}$ 1·4743, $[\alpha]_D^{17°}$ — 49·5° in chloroform (*c*, 3·46) and — 15·4° in water (*c*, 4·42) (Found : C, 48·7; H, 6·9; OMe, 41·5. Calc. for $C_9H_{16}O_6$: C, 49·1; H, 7·3; OMe, 42·3%). The substance behaved as a lactone on titration with alkali and gave an equivalent of 219 (a trimethyl hexonolactone requires equiv., 220). An aqueous solution of the lactone showed no mutarotation, although titration results showed that hydration to the trimethyl hexonic acid had occurred. It would seem that the lactone, the acid, and the sodium salt have the same specific rotation.

2 : 4 : 6-*Trimethyl* d-*Idonamide*.—Treatment of the trimethyl idonolactone (0·10 g.) with liquid ammonia gave a non-crystalline *amide* (0·08 g.), which had $[\alpha]_D^{17°}$ — 20·0° in chloroform (*c*, 1·81) (Found : OMe, 38·6. $C_9H_{19}O_6N$ requires OMe, 39·3%). The amide gave a negative Weerman reaction for α-hydroxy-amides.

Methylation of Trimethyl d-*Idono*-δ-*lactone*.—The lactone (0·25 g.) when submitted to two treatments with Purdie's reagents gave tetramethyl *d*-idono-δ-lactone (0·17 g.), m. p. 91°, identical with that prepared as described below.

Tetramethyl β-*Methyl*-d-*idopyranoside*.—2 : 4 : 6-Trimethyl β-methylidoside (0·30 g.) was methylated by three treatments with methyl iodide and dry silver oxide. The product, isolated in the usual way, distilled at 125°/0·02 mm. and showed $n_D^{21°}$ 1·4490, $[\alpha]_D^{14°}$ — 68·5° in chloroform (*c*, 3·08), — 49·0° in water (*c*, 3·23), and — 77·3° in methyl alcohol (*c*, 2·24) (Found : OMe, 61·2. Calc. for $C_{11}H_{22}O_6$: OMe, 62·0%).

Tetramethyl d-*Idopyranose*.—Tetramethyl β-methylidoside (2·30 g.) was heated at 90° with N-sulphuric acid (80 c.c.) and the hydrolysis was followed polarimetrically : $[\alpha]_D^{17°}$ — 51·0° (initial value); — 7·0° (½ hour); + 17·0° (1 hour); + 19·0° (2 hours); + 19·0° (3 hours); + 18·0° (3½ hours). After neutralisation of the cooled solution with barium hydroxide tetramethyl *d*-idopyranose (2·10 g.) was extracted by chloroform from the residue left on evaporation of the aqueous solution. It was a syrup having $n_D^{15°}$ 1·4620 and $[\alpha]_D^{14°}$ + 21·8° in methyl alcohol (*c*, 2·12). This material contained a little of the disaccharide described below.

Octamethyl Di-d-*idopyranose*.—The tetramethyl idose (2·1 g.) prepared as above described was submitted to distillation at 0·008 mm. pressure. At a bath temperature of 130° a thin colourless oil distilled. After a small amount of this fraction had collected, some frothing was observed in the residue and the rate of distillation became very slow. At a bath temperature of 180° the frothing ceased and a smooth distillation of the remainder of the material took place at 180—200°. Fraction (1), b. p. 130—180° (bath temp.), 0·43 g., $n_D^{17·5°}$ 1·4619; fraction (2), b. p. 180—200° (bath temp.), 0·34 g.; fraction (3), b. p. 180—200° (bath temp.), 1·18 g. Fraction (3) crystallised during the distillation and fraction (2) partly crystallised on cooling. Crystallisation of fraction (3) from light petroleum gave *octamethyl di-idose* as fine needles, m. p. 102°, $[\alpha]_D^{19°}$ + 90·2° in chloroform, + 95·0° in methyl alcohol, and + 103° in water [Found : C, 52·5; H, 8·3; OMe, 54·3. $C_{12}H_{14}O_3(O{\cdot}CH_3)_8$ requires C, 52·8; H, 8·3; OMe, 54·5%]. The disaccharide was non-reducing to Fehling's solution, but became reducing after it was boiled with N-sulphuric acid. Fractions (1), (2), and the residue left after crystallisation of fraction (3) were combined and heated at 120°/5 mm. for 2 hours to accelerate any further conversion of the mono- into the di-saccharide. Distillation of the product of this treatment gave the following fractions : Fraction (1a), 0·30 g., $n_D^{21°}$ 1·4600, $[\alpha]_D$ + 43·6° (in methyl alcohol), OMe, 53·5%; fraction (2a), 0·10 g., n_D 1·4600; fraction (3a), 0·40 g.; fraction (4a), 0·46 g. Fractions (3a) and

(4a) were partly crystalline and, after draining on a tile, 0·10 g. of the disaccharide was isolated. The total yield of recrystallised octamethyl di-idose was 0·6 g.

The possible function of alkali in the condensation to form a disaccharide was investigated by heating tetramethyl idose (fraction 1a) with a trace of solid barium hydroxide. Decomposition occurred and no disaccharide was isolated.

Hydrolysis of Octamethyl Di-idose.—When the disaccharide (0·42 g.), dissolved in 0·1N-sulphuric acid (15 c.c.), was kept at room temperature for 15 hours, no change in rotation occurred. The solution was therefore heated on a boiling water-bath and slow hydrolysis was observed: $[\alpha]_D^{17°}$ + 101° (initial value); + 96·4° (½ hour); + 90·7° (1 hour); + 85·0° (1½ hours). The concentration of the acid was then increased to 5%, and the heating continued at 90°: $[\alpha]_D^{17°}$ + 49·3° (2 hours); + 32·8° (2½ hours); + 24·3° (3 hours); + 22·2° (3½ hours); + 20·8° (4 hours); + 20·8° (4½ hours). The slow rate of hydrolysis corresponds to that of a pyranoside. The solution was partly neutralised with sodium bicarbonate and extracted fifteen times with chloroform. Evaporation of the dried chloroform solution gave tetramethyl idose as a syrup (0·38 g.), $n_D^{19·5°}$ 1·4610, $[\alpha]_D^{15°}$ + 14·1° in methyl alcohol (*c*, 3·32) and + 21·7° in water (*c*, 1·92) (Found: OMe, 51·3%).

Hydrolysis of Tetramethyl β-*Methyl*-d-*idopyranoside.*—No change in rotation occurred when tetramethyl β-methylidoside (2·63 g.), dissolved in 0·1N-sulphuric acid, was kept at room temperature for 15 hours. Slow hydrolysis occurred, however, when the solution was heated at 90°: $[\alpha]_D^{17°}$ − 50·0° (initial value); − 42·1° (½ hour); − 37·3° (1 hour); − 32·6° (1½ hours). The acid concentration was increased to 5%, and the hydrolysis completed by heating for a further 2½ hours. The method of extraction was modified in order to minimise the tendency towards disaccharide formation. The cooled solution was partly neutralised with sodium bicarbonate and thereafter the solution, which was still acid in reaction, was extracted with chloroform (15 times). The *tetramethyl* d-*idose* so isolated was a syrup (2·45 g.), $n_D^{18°}$ 1·4614, $[\alpha]_D^{15°}$ + 14·5° in methyl alcohol (*c*, 4·15) and + 22·0° in water (*c*, 6·69) (Found: OMe, 51·5%).

Tetramethyl d-*Idonolactone.*—Pure tetramethyl *d*-idose (1·30 g.) was oxidised with bromine water at room temperature; the non-reducing product, isolated in the usual way, crystallised spontaneously. It separated from ether–light petroleum in large colourless prisms, m. p. 91°, $[\alpha]_D^{16°}$ − 52·6° in chloroform (*c*, 1·71) and $[\alpha]_D^{13°}$ − 32·0° in water (*c*, 3·18). It had the composition of a tetramethyl hexonolactone (Found: C, 51·6; H, 7·6; OMe, 52·7. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7; OMe, 53·0%) and a molecular-weight determination by the *X*-ray method showed the lactone to be unimolecular. Titration of the substance with alkali followed the usual course of the titration of a lactone: approximately half of the alkali was neutralised immediately and thereafter the absorption of alkali at room temperature became much slower but eventually reached completion. The total alkali required represented an equivalent of 232. The equivalent of a tetramethyl hexonolactone is 234. The crystalline material is therefore a lactone and not an acid and the oxidation experiments described later show that the lactone belongs to the δ-series. Nevertheless, the lactone does not mutarotate in aqueous solution. The following experiments demonstrate this fact:

1. An aqueous solution of the lactone was kept at room temperature for 48 hours and no change in rotation occurred. Titration of the solution with alkali gave the correct equivalent and showed that both acid and lactone were present.

2. To the lactone was added one equivalent of 0·1N-sodium hydroxide solution, and the solution kept overnight. The rotation was unchanged. Phenolphthalein was then added to the solution and the resulting pink colour was discharged by the addition of one drop of 0·1N-acid. It was evident that the lactone had been converted into the corresponding sodium salt without an observable change in the optical rotation. The same result was obtained when the neutralised lactone was heated for 1 hour.

3. To investigate the possibility of a very rapid and complete hydrolysis of the lactone in aqueous solution, a solution of the lactone in acetone was prepared and to this was added an equal volume of water. The rotation of the aqueous acetone solution was observed within 1 minute of mixing. The value was $[\alpha]_D^{15°}$ − 40·9° (*c*, 2·3) and did not change overnight. After dilution with water, the solution was titrated with alkali. The correct equivalent was observed.

Attempts to convert the lactone into the corresponding amide by treatment with liquid ammonia or with methyl-alcoholic ammonia yielded only syrupy products.

The Oxidation of Tetramethyl d-*Idono*-δ-*lactone with Nitric Acid.*—The lactone (0·75 g.) was dissolved in nitric acid (*d* 1·42) (8 c.c.), and the solution heated on a water-bath. The temperature was raised during 45 minutes from 55° to 90° and maintained at that level for 1½ hours. The solution was diluted with water and evaporated at constant volume for 12 hours at 40° to

remove nitric acid. The water was then replaced by methyl alcohol during 4 hours, and the solution finally evaporated to dryness. The syrupy product was boiled for 6 hours with 2% methyl-alcoholic hydrogen chloride. The solution was neutralised and evaporated and the residue was extracted with chloroform. The extract, after removal of the solvent, was distilled

Fraction.	Weight, g.	$n_D^{19°}$.	% OMe.	$[\alpha]_D^{15°}$ in methyl alcohol.
1	0·162	1·4390	59·8	−25·1°
2	0·189	1·4417	59·5	−15·5
3	0·114	1·4440	57·5	−14·5
4	0·105	1·4500	54·3	−23·3

at (bath temp.) 118°/0·04 mm. Each fraction was separately treated at 0° for 24 hours with a saturated solution of methylamine in dry methyl alcohol. The solvent was then removed in a vacuum desiccator, and the product crystallised from ethyl acetate. From fraction (1) there was obtained *l*-dimethoxysuccinomethylamide (m. p. 205°, alone or in admixture with an authentic specimen; $[\alpha]_D^{15°}$ — 130° in water) and *i*-trimethoxyxyloglutaromethylamide (m. p. 166°, alone or in admixture with an authentic specimen; $[\alpha]_D^{15°} \pm 0°$ in water. Found: C, 48·3; H, 7·8; N, 11·2; OMe, 37·3. Calc. for $C_{10}H_{20}O_5N_2$: C, 48·35; H, 8·1; N, 11·2; OMe, 37·5%). Fractions (2) and (3) gave further quantities of *i*-trimethoxyxyloglutaromethylamide, which was also obtained in small amount from fraction (4).

The authors are grateful to Professor W. N. Haworth, F.R.S., for his interest in this work.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

[*Received, June 3rd,* 1939.]