CCCXV.—*New Reference Compounds in the Sugar Group. The Methylamides of* d-, l-, *and* i-*Dimethoxysuccinic Acids and of* l-*Arabo- and* i-*Xylo-trimethoxyglutaric Acids.*

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Compared with other groups of organic substances, the carbohydrates have hitherto been provided with few fundamental reference compounds which can serve as final standards for the complete identification of the normal and labile forms of sugars through their oxidation derivatives.

The most readily accessible oxidation derivatives of the methylated aldoses are the lactones of the corresponding acids, and most of these lactones are crystalline and give characteristic phenylhydrazides. A lactone of the δ- or amylene-oxide series can be sharply differentiated from the corresponding member of the γ- or butylene-oxide series by reason of its different rate of hydrolysis as revealed by physical methods (Drew, Goodyear, and Haworth, this vol., p. 1237; also forthcoming paper by Carter, Haworth, and Robinson).

The ultimate basis on which the constitution of each of these lactones rests is that of the simple dibasic acids to which they give rise on oxidation. Our further study of these lactones by methods of degradative oxidation has revealed the need of a final standard of comparison of these oxidation products with the derivatives of the stereoisomeric forms of tartaric acid and of trihydroxyglutaric acid. Methylated derivatives of these acids do not lend themselves to easy recognition. Crystalline amides of some of these acids have been prepared and examined (Hirst and Purves, J., 1923, **123**, 1352; Hirst and Robertson, J., 1925, **127**, 358) and their physical properties are of some service for the purpose of identification, but inasmuch as these amides melt with decomposition at high temperatures, their utility as standard reference substances suffers by reason of the untrustworthiness of their application in mixed m. p. determinations.

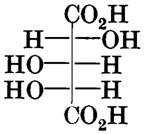
A search for new crystalline derivatives of the stereoisomeric forms of dimethoxysuccinic acid and of trimethoxyglutaric acid has led us finally to adopt as our standards the crystalline methylamides. These substances melt at a definite temperature, solidify on cooling, and then remelt at the same temperature as before, and they undergo no change either of condensation or decomposition at this elevated temperature.

Thus *l*-tartaric acid, prepared by Pasteur's method from racemic acid, was esterified to methyl *l*-tartrate, and methylation by the usual methods gave rise to *methyl* l-*dimethoxysuccinate*. The latter was converted with the aid of pure methylamine into l-*dimethoxysuccinomethylamide*. Similar methods applied to the corresponding *d*- and *i*-tartaric acids furnished the remaining stereoisomeric forms of the above methylamide. Their physical properties are tabulated below for comparison :

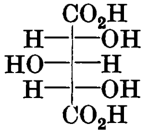
	M. p.	$[\alpha]_D$ in water.
d-Dimethoxysuccinomethylamide	205°	+132·6°
l- ,, ,, ,, ...	205	−131·8
i- ,, ,, ,, ...	210	Zero

Of the four stereoisomeric forms of trihydroxyglutaric acid, two are most frequently encountered as oxidation products in the sugar group, namely, *l*-arabotrihydroxyglutaric acid (I) and *i*-xylotrihydroxyglutaric acid (II), which are obtained, respectively, from the naturally occurring pentoses, arabinose and xylose :

(I.)



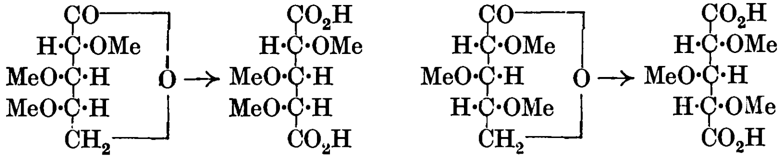
CO_2H; H—|—OH; HO—|—H; HO—|—H; CO_2H



(II.)

CO_2H; H—|—OH; HO—|—H; H—|—OH; CO_2H

Both these forms are represented in the cases which we have studied. Thus, *l*-trimethyl δ-arabonolactone (III), prepared from normal methylated arabinose, has been oxidised with nitric acid and found to give rise almost exclusively to *l*-arabotrimethoxyglutaric acid (IV). Conversion of this into the methyl ester was followed by treatment with methylamine, which gave a quantitative yield of l-*arabotrimethoxyglutaromethylamide*, m. p. 172°, $[\alpha]_D + 59{\cdot}9^\circ$. The corresponding amide was similarly prepared. Again, the oxidation of trimethyl δ-xylonolactone (V) gave an almost quantitative yield of *i*-xylotrimethoxyglutaric acid (VI), which was converted into i-*xylotrimethoxyglutaromethylamide*, m. p. 167—168°, and also into the corresponding amide.



(III.) (IV.) (V.) (VI.)

The isolation of these products furnishes a proof of the constitution of the two δ-lactones (III and V), and also confirms the amylene-oxide structure of the normal forms of trimethyl arabinose and trimethyl xylose.

EXPERIMENTAL.

d-*Dimethoxysuccinomethylamide.*—Methyl *d*-dimethoxysuccinate having $[\alpha]_D^{18^\circ} + 79{\cdot}9^\circ$ in methyl alcohol ($c = 2{\cdot}04$) (compare Purdie and Barbour, J., 1901, **79**, 973) was prepared from *d*-tartaric acid. The ester was dissolved in dry methyl alcohol saturated with methylamine. The solution was kept for several days, and on concentration yielded long, colourless needles which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 205°; $[\alpha]_D^{15^\circ} + 132{\cdot}6^\circ$ in water ($c = 1{\cdot}95$); yield 90% (Found: C, 47·0; H, 7·8; N, 13·5; OMe, 29·5. $C_8H_{16}O_4N_2$ requires C, 47·05; H, 7·8; N, 13·7; OMe, 30·4%).

Methyl l-*Dimethoxysuccinate.*—A specimen of *l*-tartaric acid [m. p. 167—170°; $[\alpha]_D^{18^\circ} - 14{\cdot}6^\circ$ in water ($c = 3{\cdot}15$)] was prepared by fermentation methods from racemic acid, and esterified in the presence of methyl alcohol containing 3% of hydrogen chloride; yield 95%. The methyl *l*-tartrate was methylated by Purdie's reagents and gave a colourless liquid, b. p. 83°/0·07 mm.; $n_D^{18^\circ}$ 1·4345; $[\alpha]_D^{18^\circ} - 78{\cdot}8^\circ$ in methyl alcohol ($c = 3{\cdot}12$) (0·2340 G. required 22·9 c.c. *N*/10-sodium hydroxide. Calc.: 22·75 c.c.) (Found: C, 46·8; H, 7·0; OMe, 58·3. Calc.: C, 46·6; H, 6·8; OMe, 60·2%).

l-*Dimethoxysuccinomethylamide.*—The methyl *l*-dimethoxysuccinate was dissolved in dry methyl alcohol, saturated with methylamine, and the solution concentrated after 40 hours; a crystalline mass then filled the containing vessel. The *methylamide* was recrystallised from ethyl acetate; the long needles thus obtained melted at 205°, solidified on cooling, and remelted at the same temperature; $[\alpha]_D^{17^\circ}$ — 131·8° in water (c = 1·61); yield 82% (Found: C, 46·8; H, 7·7; N, 13·8; OMe, 28·4. $C_8H_{16}O_4N_2$ requires C, 47·05; H, 7·8; N, 13·7; OMe, 30·4%).

The crystalline l-*dimethoxysuccinamide* was also made in the usual way and isolated as colourless needles which became coloured at 250°, dark at 270°, melted at 278°, and decomposed violently at 294°, a behaviour which was identical with that exhibited by the *d*-isomeride (Found: C, 40·8; H, 6·6; N, 15·8; OMe, 33·5. $C_6H_{12}O_4N_2$ requires C, 40·9; H, 6·8; N, 15·9; OMe, 35·2%).

i-*Dimethoxysuccinomethylamide.*—*meso*Tartaric acid was esterified in presence of methyl alcohol and methylated with Purdie's reagents, giving flat plates, m. p. 68°. This specimen of methyl *i*-dimethoxysuccinate was dissolved in methyl alcohol, saturated with methylamine, and the solution kept for 3 days, during which long needles separated, further crops being obtained by concentration. The *methylamide* was recrystallised from ethyl acetate; m. p. 210°; zero rotation in water (c = 1·6); yield 97% (Found: C, 46·9; H, 8·0; N, 13·6; OMe, 29·8. $C_9H_{16}O_2N_2$ requires C, 47·1; H, 7·8; N, 13·7; OMe, 30·4%).

Oxidation of Trimethyl δ-Xylonolactone.—A specimen of this lactone, m. p. 55° (Haworth and Westgarth, J., 1926, 886) was oxidised with nitric acid (d 1·42) by heating the solution in a water-bath at 70—75° for ¾ hour, and thereafter for 3 hours at 90—95°. The removal of the nitric acid was effected in the usual way and the syrupy oxidation product collected, esterified with dry methyl alcohol containing 4% hydrogen chloride, the solution neutralised with silver carbonate, and the solvent evaporated. The liquid product was dissolved in ether, dried, and distilled; b. p. 102—104°/0·09 mm.; n_D 1·4402; the yield was quantitative. That this product was methyl *i*-trimethoxyglutarate was shown by conversion into the crystalline amide (yield over 60%); the crystals turned slightly brown at 195° and melted quickly at 195—198° to a blue liquid. The rotation was zero. Comparison with an authentic specimen of *i*-xylotrimethoxyglutaramide proved its identity.

i-*Trimethoxyglutaromethylamide.* — The above ester was dissolved in methyl alcohol, saturated with methylamine, and kept for 15 hours; crystals then separated, and further crops were obtained by concentration of the solution. The *methylamide* crystallised from ethyl acetate in silky needles, m. p. 167—168°, solidifying and then remelting at 167° (yield 85%). The rotation was zero (Found: C, 48·4; H, 8·4; N, 10·85; OMe, 36·3. $C_{10}H_{20}O_5N_2$ requires C, 48·35; H, 8·1; N, 11·2; OMe, 36·4%).

Oxidation of Trimethyl δ-Arabonolactone.—This lactone (m. p. 45°; $[\alpha]_D^{21°}$ + 179·5° in water) was prepared from crystalline trimethyl β-methylarabinoside as described by Drew and Haworth (this vol., p. 778). The lactone (5 g.) was dissolved in 40 c.c. of nitric acid (*d* 1·42), and the solution heated on the water-bath. The oxidation commenced at 90°, and during a period of 5 hours the evolution of brown fumes was continuous; the reaction then ceased. The nitric acid was removed by dilution with water followed by continuous distillation of the dilute acid at 40°/15 mm.; methyl alcohol was added to, and distilled from, the residue, and the resulting syrup was digested with a solution containing 80 c.c. of methyl-alcoholic hydrogen chloride (3%). Thereafter, the mineral acid was removed by neutralisation with silver carbonate, and the product, a pale yellow syrup (5·8 g.), was distilled, b. p. 105°/0·14 mm.; $n_D^{15°}$ 1·4365; yield 5·25 g. The methyl trimethoxyglutarate showed $[\alpha]_D^{20°}$ + 37·6° in water ($c = 2·52$) and $[\alpha]_D^{18°}$ + 41·2° in methyl alcohol ($c = 1·31$) (Found: C, 47·6; H, 7·3; OMe, 58·35. Calc.: C, 48·0; H, 7·2; OMe, 62·0%). This product (0·5 g.) was dissolved in dry methyl alcohol (6 c.c.), and the solution saturated with dry ammonia. On keeping, a crystalline amide separated, (yield 0·4 g.), m. p. 228—229°. Recrystallisation from methyl alcohol raised the m. p. to 230° (decomp.) (Found: C, 43·7; H, 7·2; N, 13·0; OMe, 40·6%).

l-*Arabotrimethoxyglutaromethylamide.*—Another specimen (0·46 g.) of the preceding ester was dissolved in methyl alcohol (6 c.c.) and saturated with methylamine. After keeping for 3 days at the ordinary temperature the solution was concentrated under diminished pressure and gave crystals (yield 0·45 g.) of the *methylamide.* Recrystallisation from ethyl acetate gave radiating needles (m. p. 172°), solidifying on cooling and remelting at the same temperature; $[\alpha]_D^{18°}$ + 59·9° in water ($c = 1$) (Found: C, 48·3; H, 8·2; N, 10·9; OMe, 35·6. $C_{10}H_{20}O_5N_2$ requires C, 48·35; H, 8·1; N, 11·2; OMe, 36·4%).

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