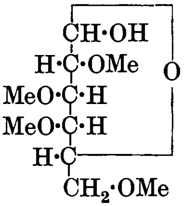
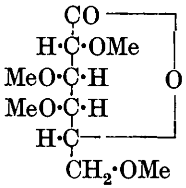
CCCXXIV.—*The Ring Structure in Normal Galactose. Oxidation of Tetramethyl δ-Galactonolactone.*

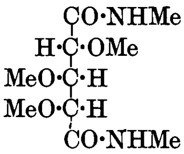
By Walter Norman Haworth, Edmund Langley Hirst, and David Idris Jones.

The form of galactose present in α- and β-methylgalactosides, lactose, raffinose, and melibiose is recognisable as the form which appears in crystalline tetramethyl galactose (Haworth and Long, this vol., p. 544; Charlton, Haworth, and Hickinbottom, *ibid.*, p. 1527; compare Schlubach and Moog, *Ber.*, 1923, **56**, 1957). This compound is readily characterised by its physical properties and by its crystalline anilide. Its oxidation to tetramethyl δ-galactonolactone has also been described (Haworth, Ruell, and Westgarth, J., 1924, **125**, 2468). In the present series of experiments, this lactone has again been examined and the characteristic crystalline *phenylhydrazide* (m. p. 135—137°) of the corresponding tetramethyl galactonic acid has been prepared. From the latter compound the lactone can readily be regenerated and the purified product obtained in this way has properties which are indistinguishable from those previously recorded. The oxidation of this lactone was conducted with nitric acid (*d* 1·42), and from this treatment a liquid product resulted which was isolated in the form of the methyl ester. That this consisted almost entirely of methyl *l*-arabotrimethoxyglutarate was shown by its conversion into the crystalline amide and methylamide. The degradative oxidation of the original sugar was thus carried out in two stages, involving first the oxidation to the lactone by bromine water, and secondly its conversion into a dibasic acid; and this mode of procedure in stages possesses the distinct advantage that the final product is essentially homogeneous, whereas this is not the case when the sugar is oxidised direct with nitric acid (compare Hirst, J., 1926, 350). Only a trace of *d*-dimethoxysuccinic acid, which was isolated as the diamide, was found to be present in the oxidation product. The absence of any trace of tetramethoxymucic acid excludes the possibility of a 1 : 6-oxide linking. The *l*-arabotrimethoxyglutaramide was recognised by its rotation $[\alpha]_D + 50°$ in water, and by its decomposition on heating at 230°. Direct comparison with an authentic specimen prepared from arabinose (Hirst and Robertson, J., 1925, **127**, 358) indicated its identity. When the ester was treated with methylamine in methyl-alcoholic solution, the crystalline l-*arabotrimethoxyglutaromethylamide* (III) separated as needles, m. p. 173°; $[\alpha]_D^{18°} + 59{\cdot}9°$. Comparison with an authentic specimen prepared by an alternative method, *viz.*, from pure methyl *l*-arabotrimethoxyglutarate obtained from normal trimethyl arabinose, proved its identity (Haworth and Jones, this vol., p. 2349). Since the crystalline methylamide has a definite m. p. (without decomposition) the comparison could in this case be made by means of a mixed m.-p. determination, a procedure which cannot be followed with equal certainty with the crystalline amide.

These results prove the constitution of the tetramethyl δ-galactonolactone, and lead by inference to the conclusion that crystalline tetramethyl galactose possesses an amylene-oxide structure, as was previously suggested on other grounds (Pryde, J., 1923, **123**, 1808; Haworth, Ruell, and Westgarth, *loc. cit.*). This sugar should now be definitely indexed as 2 : 3 : 4 : 6-tetramethyl galactose (I), and the derived lactone as 2 : 3 : 4 : 6-tetramethyl galactonolactone (II). By inference, it is concluded that free galactose possesses the amylene-oxide structure, since there appear to be no reasonable grounds for postulating a difference in ring structure between galactose and α- and β-methylgalactosides (compare Drew and Haworth, J., 1926, 2303).


(I.)


(II.)



$$\begin{array}{c} CO{\cdot}NHMe \\ H{\cdot}C{\cdot}OMe \\ MeO{\cdot}C{\cdot}H \\ MeO{\cdot}C{\cdot}H \\ CO{\cdot}NHMe \end{array}$$

(III.)

EXPERIMENTAL.

Preparation of Tetramethyl Galactose.—Octamethyl lactose (Haworth and Leitch, J., 1918, **113**, 198) was hydrolysed in the usual manner with aqueous hydrochloric acid, the neutralised solution being thereafter extracted with chloroform to remove the tetramethyl galactose. The crude tetramethyl galactose so obtained was purified by conversion into the crystalline anilide (m. p. 192°), which is easily obtainable in a very pure state (Irvine and McNicoll, J., 1910, **97**, 1454). Hydrolysis of the anilide with 5% aqueous hydrochloric acid (Haworth, Ruell, and Westgarth, J., 1924, **125**, 2473), followed by distillation of the product, now gave a pure specimen of tetramethyl galactose in the form of a syrup containing both the α- and β-modifications of the sugar; $n_D^{13°}$ 1·4682; $[\alpha]_D^{15°}$ + 118° in water ($c = 1·9$; equilibrium value). A small quantity of this syrup dissolved in ether yielded crystals when rubbed with a glass rod during the evaporation of the solvent. When nucleated with this crystalline material, the main bulk crystallised readily to give in good yield solid tetramethyl galactose, m. p. 71—72° after recrystallisation from light petroleum (compare Schlubach and Moog, *loc. cit.*).

Preparation of Tetramethyl δ-Galactonolactone.—For comparative purposes three methods were employed for the preparation of this lactone. In the first, the directions given by Haworth, Ruell, and Westgarth were followed, the liquid tetramethyl galactose mentioned above being used; the resulting lactone was a liquid whose physical constants were in exact agreement with those previously recorded. The second method involved the preparation of the lactone from crystalline tetramethyl galactose, the experimental conditions being otherwise unchanged. The product (b. p. with bath temperature 163—166°/0·18 mm.; $n_D^{14°}$ 1·4606) was a liquid which could not be induced to crystallise (0·1603 G. required 6·9 c.c. of *N*/10-sodium hydroxide for neutralisation. Calc. : 6·85 c.c.).

A polarimetric study of its behaviour in aqueous solution showed $[\alpha]_D$ + 157° approx. (initial value by extrapolation); $[\alpha]_D$ + 26·2° (equilibrium value after 14 hours). The values of $[\alpha]_D$ plotted against time gave a curve indistinguishable from that already recorded by Haworth, Ruell, and Westgarth (*loc. cit.*) and by Drew, Goodyear, and Haworth (this vol., p. 1237). The third method for preparing the lactone in a highly pure condition lay in the regeneration of the compound from the crystalline phenylhydrazide of the corresponding 2 : 3 : 4 : 6-tetramethyl galactonic acid. The lactone (1·9 g.) prepared from the liquid tetramethyl galactose (α + β forms) was mixed with the theoretical amount of freshly distilled phenylhydrazine and sufficient ether to form a homogeneous solution. The mixture was heated on the water-bath for 30 minutes and a solid mass remained. This was broken up, rubbed with ether, and filtered, giving a white, crystalline solid (2·55 g.; m. p. 135—137°), which was the pure *phenylhydrazide* of tetramethyl galactonic acid. Recrystallisation from ether or benzene failed to raise the m. p. (Found : C, 56·25; H, 7·5; N, 8·5; OMe, 32·4. $C_{16}H_{26}O_6N_2$ requires C, 56·1; H, 7·6; N, 8·2; OMe, 36·3%). The phenylhydrazide (1·9 g.) was treated with a slight excess of *N*/10-aqueous hydrochloric acid (60 c.c.) and heated at 100° for 3 hours. This gave a pale yellow solution, which was evaporated to dryness under diminished pressure, the residue being finally dried for 2 hours at 100°/12 mm. The lactone was then extracted by dry chloroform containing a little ether, and after removal of the solvent and thorough drying, it was finally purified by distillation to give a colourless liquid (1·09 g.), $n_D^{13°}$ 1·4609; $[\alpha]_D$ + 156° (initial value). Equilibrium value after 14 hours +26·1°. 0·3139 G. required for neutralisation 13·6 c.c. of *N*/10-sodium hydroxide (Calc. : 13·4 c.c.).

Oxidation of Tetramethyl δ-Galactonolactone with Nitric Acid.—The lactone used was a specially purified specimen ($n_D^{13°}$ 1·4606) which conformed exactly in its polarimetric behaviour to the standards accepted for the pure lactone. A solution containing 5 g. of lactone in 40 c.c. of nitric acid (*d* 1·42) was gently warmed for ½ hour at 50—60°, whereupon oxidation commenced. The reaction continued slowly and smoothly as the temperature was gradually raised to 90°, and appeared to be complete after 6 hours at this temperature. Throughout the subsequent dilution, removal of the nitric acid and water by distillation under diminished pressure, and esterification of the oxidation products with methyl alcohol, the usual methods were employed, details of which have already been published. The esterified product was obtained as a clear, mobile liquid weighing 4·33 g. This was neutral to litmus and without action on Fehling's solution. Distillation gave (I) 3·6 g., b. p. 95°/0·08 mm., $n_D^{15°}$ 1·4359, $[\alpha]_D^{20°}$ + 44·7° in water ($c = 1·2$); (II) 0·56 g., b. p. 110°/0·18 mm., $n_D^{15°}$ 1·4369, $[\alpha]_D^{20°}$ + 33·8° in water ($c = 2$). The first fraction agreed in physical properties with methyl *l*-arabotrimethoxyglutarate (Hirst and Robertson, *loc. cit.*) and analysis showed it to be very nearly pure (Found : C, 47·6; H, 7·3; OMe, 58·8. Calc. for $C_{10}H_{18}O_7$: C, 48·0; H, 7·2; OMe, 62·0%).

Confirmation was obtained by the formation of the corresponding amide. The ester (0·97 g.) dissolved in methyl-alcoholic ammonia (10 c.c.) gave after 15 hours a first crop of crystals in the form of needles, m. p. 270—278° (decomp.), which appeared to be a mixture of *d*-dimethoxyglutaramide and *l*-arabotrimethoxyglutaramide (Found : C, 41·6; H, 7·15; N, 14·0; OMe, 33·4%). The main crop, which crystallised in the course of a few days, weighed 0·55 g. (yield 63% of theory). Recrystallised from methyl alcohol, this material decomposed at 230° with evidence of melting beginning at 228°, and it was shown to be *l*-arabotrimethoxyglutaramide by comparison with an authentic specimen; $[\alpha]_D$ + 50·2° in water (c = 1·14) (Found: C, 43·2; H, 7·2; N, 12·4; OMe, 40·1. Calc.: C, 43·6; H, 7·3; N, 12·7; OMe, 42·2%).

The corresponding methylamide was prepared by dissolving the ester (0·46 g.) in methyl alcohol (6·0 c.c.) saturated with methylamine, and allowing the solution to remain at room temperature for 4 days. After removal of the solvent in a vacuum desiccator, the resulting solid mass was recrystallised from ethyl acetate, giving needles; m. p. 172°, alone or mixed with an authentic specimen of the methylamide (Haworth and Jones, *loc. cit.*) prepared from pure methyl *l*-arabotrimethoxyglutarate; yield 0·4 g.; $[\alpha]_D^{18°}$ + 59·9° (Found: C, 48·3; H, 8·2; N, 10·9; OMe, 35·55. Calc.: C, 48·35; H, 8·1; N, 11·2; OMe, 36·4%).

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