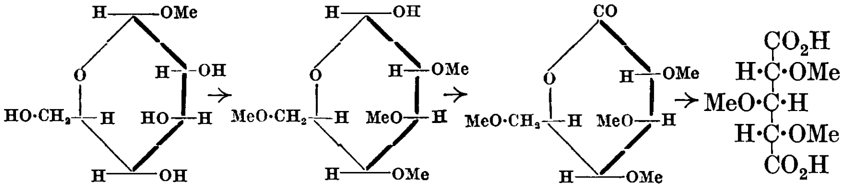
LIII.—*Synthesis of* 1-2 : 3 : 4 : 6-*Tetramethyl δ-Gluconolactone and of* 1-2 : 3 : 4 : 6-*Tetramethyl δ-Mannonolactone from* 1-2 : 3 : 5-*Trimethyl Arabofuranose.*

By Walter Norman Haworth and Stanley Peat.

The determination of the ring structure of α- and β-methylglucosides and of α-methylmannoside by one of us has hitherto been founded upon their conversion, through tetramethyl glucopyranose and tetramethyl mannopyranose, into the δ-lactones, followed by oxidation of these lactones to trimethoxyglutaric acids, *e.g.*,



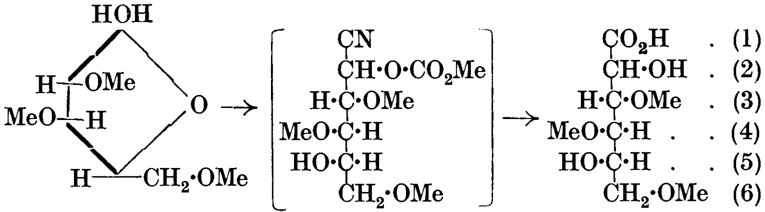
α-Methylglucoside. Tetramethyl glucopyranose. Tetramethyl δ-gluconolactone. Xylo-trimethoxyglutaric acid.

In the present work the *l*-forms of these δ-lactones have been synthetically prepared by a procedure which affords a further confirmation of their constitutional formulæ. This synthetic proof is dependent upon the constitution of the γ-form of *l*-trimethyl arabinose which has previously been determined by methods of oxidation, and the constitution assigned to it is that of trimethyl arabofuranose (I).

The usual method for ascending the sugar series from pentose to hexose involves the addition of hydrogen cyanide, followed by hydrolysis of the cyanohydrin to the related carboxylic acid, which, by ring closure, is transformed into the lactone and thence by reduction into the next higher member in the sugar series. We have modified this experimental procedure and have condensed a methylated pentose with methyl chloroformate and potassium cyanide. In a preliminary experiment the *normal* trimethyl arabopyranose was condensed with these reagents and gave a crystalline trimethyl carbomethoxy mannononitrile, and also a liquid which contained this crystalline product as well as the correspondingly substituted glucon予nitrile.

For the particular object which the authors had in view, it was necessary to utilise as the initial sugar the corresponding derivative of γ-arabinose, namely, 2 : 3 : 5-trimethyl arabofuranose (I). This has been made available by the earlier work of Baker and Haworth (J., 1925, **127**, 365). Although it would have been preferable to utilise for this purpose the *d*-sugar, which is, however, almost inaccessible, nevertheless the same theoretical conclusions could be reached by working with the natural *l*-arabinose which is readily obtainable.

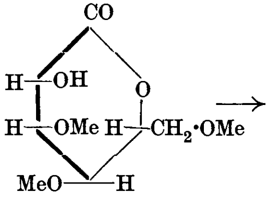
The above derivative of γ-arabinose (I) condensed easily in the cold with potassium cyanide and methyl chloroformate. The products, a crystalline substance and a liquid, are provisionally represented by the formula (II), although it is not certain whether the carbomethoxy-residue in this mixture of isomeric compounds is situated at position 2 or position 5 in the lengthened carbon chain.



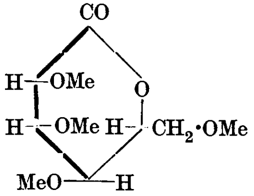
(I.) (II.) (III.)

In either event, the subsequent hydrolysis of both the nitrile and the carbomethoxy-group would give rise to the same pair of stereoisomeric forms of a 3 : 4 : 6-trimethyl hexonic acid (III), in which the hydroxyl at position 2 is directed to the right and to the left, respectively.

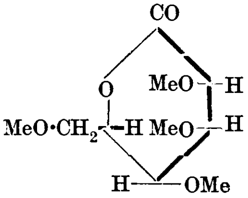
This acid product (III) was converted into the two δ-lactones by heating, and in contact with phenylhydrazine the latter gave the two stereoisomeric crystalline forms of the phenylhydrazides of the acids, which were separated by a tedious fractional crystallisation. The phenylhydrazine residue was subsequently eliminated from each of the crystalline specimens, and there were thus obtained the two trimethyl-δ-lactones (IV) and (VI). A fourth methyl group was then introduced into each of these compounds and the tetramethyl δ-lactones (V) and (VII) were isolated.



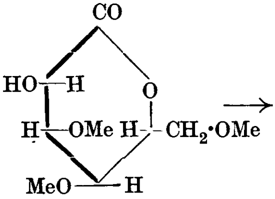
(IV.)
l-Trimethyl δ-mannonolactone.



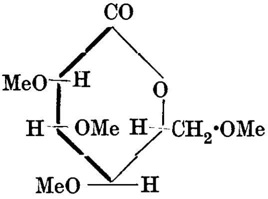
(V.)
l-Tetramethyl δ-mannonolactone.



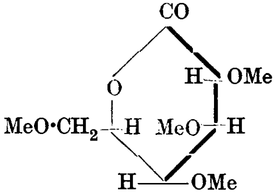
(VIII.)
d-Tetramethyl δ-mannonolactone.



(VI.)
l-Trimethyl δ-gluconolactone.



(VII.)
l-Tetramethyl δ-gluconolactone.



(IX.)
d-Tetramethyl δ-gluconolactone.

The pair of completely methylated lactones (V) and (VII) were condensed with phenylhydrazine and thereby converted into the crystalline *phenylhydrazides* of the *l*-2 : 3 : 4 : 6-*tetramethyl mannonic* and *gluconic acids*. These were found to be identical in m. p. and rotation with the enantiomorphous compounds prepared from the δ-lactones (VIII) and (IX), except that the signs of their optical rotation were opposite. The latter two are the members of the *d*-series of δ-lactones which have been fully investigated in earlier experiments and are prepared respectively from α-methylmannoside and α- and β-methylglucosides (Drew, Goodyear, and Haworth, J., 1927, 1237; Goodyear and Haworth, *ibid.*, p. 3136; Haworth, Hirst, and Miller, *ibid.*, p. 2436).

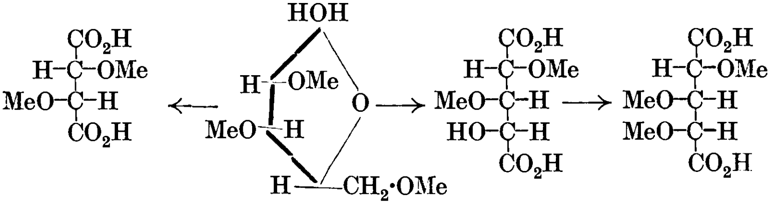
l-Series (synthetic).	*d*-Series.
Phenylhydrazide from	Phenylhydrazide from
l-2 : 3 : 4 : 6-tetramethyl δ-mannonolactone : m. p. 183—184°, $[\alpha]_{D}^{16^\circ}$ +22°.	*d*-2 : 3 : 4 : 6-tetramethyl δ-mannonolactone : m. p. 183—184°, $[\alpha]_{D}^{16^\circ}$ −22°.
l-2 : 3 : 4 : 6-tetramethyl δ-gluconolactone : m. p. 115°, $[\alpha]_{5780}^{19^\circ}$ −50°.	*d*-2 : 3 : 4 : 6-tetramethyl δ-gluconolactone : m. p. 115°, $[\alpha]_{5780}^{19^\circ}$ +50·8°.

A further comparison was established between the *l*- and *d*-forms of the tetramethyl mannonolactones themselves. Thus it was found that the synthetic *l*-2 : 3 : 4 : 6-*tetramethyl δ-mannonolactone* showed $[\alpha]_D^{18°}$ −150° (initially) ⟶ − 58° (after 150 hours), whilst the specimens of the *d*-lactone, which had previously been prepared from *d*-2 : 3 : 4 : 6-tetramethyl *d*-mannose, gave $[\alpha]_D^{18°}$ + 150° ⟶ + 63° (after 150 hours).

The synthetic *l*-forms are thus seen, by their mode of synthesis, to be constituted as six-atom ring compounds (the manno- and gluco-pyranolactones), a conclusion which verifies the structure assigned to the two *d*-compounds on the basis of their degradative oxidation to arabo-trimethoxyglutaric acid and to xylo-trimethoxyglutaric acid respectively.

This synthesis confirms the conclusions already reached in the constitutional study of γ- and normal sugars inasmuch as it is seen that these two types stand in the relation to each other as five-atom ring compounds and six-atom ring compounds. The furanose type has thus been transformed into the pyranose type by a procedure which admits only of the formation of a six-membered ring.

The starting point in the synthesis is represented by a trimethyl sugar to which a constitution has been assigned on the ground of its degradative oxidation. Thus the trimethyl arabofuranose (I) has been degraded by oxidation to give *d*-dimethoxysuccinic acid (X), which is characterised as the crystalline methylamide and amide (Haworth, Hirst, and Learner, J., 1927, 2432). The trimethyl arabofuranose has also been oxidised to hydroxydimethoxyglutaric acid (XI) which, on further methylation, passes into the *l*-arabo-trimethoxyglutaric acid (XII) (Baker and Haworth, *loc. cit.*; Haworth and Nicholson, J., 1926, 1899). The latter product has been identified through its crystalline amide :



(X.) (I.) (XI.) (XII.)

Incidentally, it may be remarked that the syntheses now recorded have furnished an alternative proof that the conclusions reached by C. S. Hudson on the ring structure of α- and β-methylglucosides are invalid (compare Haworth and Hirst, J., 1928, 1221). By the use of a statistical method involving an extension of the principle of optical superposition, Hudson concluded that α-methylglucoside contained a 1 : 4-oxide ring, and α-methylmannoside a 1 : 5-oxide ring. Although this view has been given some currency, it should finally be set aside.

EXPERIMENTAL.

I. *Condensation of* 1-2 : 3 : 4-*Trimethyl Arabopyranose with Hydrogen Cyanide and Methyl Chloroformate. Formation of* 3 : 4 : 5-*Trimethylcarbomethoxy Glucono- and Mannono-nitriles.*—This method for the ascent of the sugar series was devised for the reasons stated in the introduction.

2 : 3 : 4-Trimethyl arabinose (trimethyl arabopyranose) was prepared by methylation of the normal methylarabinosides. The trimethyl sugar (7·6 g.) was dissolved in 40 c.c. of water containing 2·7 g. of potassium cyanide and to this were added, in three portions, 3·1 c.c. of methyl chloroformate, the mixture being cooled in ice and shaken vigorously. The solution separated into two layers, and after 1 hour was extracted three times with chloroform. These extracts were washed repeatedly with water, dried, and evaporated, and yielded a viscid, colourless syrup (7·5 g.) which partly crystallised. The separated solid was obtained from ether–light petroleum (b. p. 40—60°) as colourless needles, m. p. 100—102° (Found: C, 47·6; H, 7·1; N, 5·1; OMe, 43·1. $C_{11}H_{19}O_7N$ requires C, 47·6; H, 6·9; N, 5·1; OMe, 44·8%). Both the crystalline and the syrupy product had the following properties: they reduced Fehling's solution only after boiling for 5 minutes; in solution they gave a heavy precipitate of barium carbonate on addition of barium hydroxide, and, on boiling, ammonia was evolved. In other respects also they appeared to be similar. The liquid product was a mixture of substituted *l*-glucono- and *l*-mannono-nitriles, whereas the crystalline substance was evidently one of these substances, probably the mannononitrile, which had separated by crystallisation.

The liquid specimen of the nitrile was not very stable and showed a tendency to deteriorate on keeping.

II. *Condensation of* 1-2 : 3 : 5-*Trimethyl Arabofuranose with Hydrogen Cyanide and Methyl Chloroformate. Formation of* 1-3 : 4 : 6-*Trimethylcarbomethoxy Glucono- and Mannono-nitriles.*—This condensation was carried out in the manner described above for the trimethyl arabopyranose. γ-Methylarabinoside was methylated by methyl sulphate to the trimethyl γ-methylarabinoside, and by hydrolysis the 2 : 3 : 5-trimethyl γ-arabinose (or trimethyl arabofuranose) was isolated (Baker and Haworth, *loc. cit.*; Haworth, Hirst, and Learner, J., 1927, 2432). The latter sugar (1 mol.) was dissolved in ice-cold water containing potassium cyanide (1 mol.), methyl chloroformate (1 mol.) added in small quantities, and the mixture shaken vigorously in a stoppered bottle. After being kept for 2 hours at 5°, the solution separated into two layers, the lower layer being soluble in chloroform. The chloroform extract was washed with water, dried over magnesium sulphate, and evaporated. This gave a viscid orange syrup which did not crystallise (yield, 84% of the theoretical). Towards reagents it exhibited a behaviour similar to that of the product from trimethyl arabopyranose described under section (I).

There was indeed little doubt that the syrup was a mixture of *l*-3 : 4 : 6-trimethyl-2-carbomethoxy glucono- and mannono-nitriles. It was somewhat unstable, showing a tendency to lose hydrogen cyanide on keeping, and it was therefore hydrolysed at once to the corresponding acid.

III. l-3 : 4 : 6-*Trimethyl Gluconic and Mannonic Acids*.—The above nitrile was hydrolysed in two stages as follows. It was dissolved in ether and filtered from a small residue of white solid, and hydrogen chloride was passed into the well-cooled filtrate. The solution formed two layers and the admission of hydrogen chloride was continued until a homogeneous solution was again obtained. On removal from the cooling bath the solution deposited ammonium chloride. On the next day more hydrogen chloride was admitted and the solution was kept for 3 more days. The ether and hydrogen chloride were removed by aeration and by keeping in a vacuum over solid potassium hydroxide. The product was a mixture of a syrupy organic acid and ammonium chloride. A chloroform extract of the residue was taken, and traces of hydrogen chloride were removed from it by agitation with very little silver carbonate. Evaporation of the filtered solution gave a dark syrup and left a slight residue insoluble in ether. The ethereal solution was treated with charcoal and evaporated; the pale yellow syrup obtained crystallised but not completely. The crystals, m. p. 155°, gave analytical figures corresponding with 1-2-*carbomethoxy*-3 : 4 : 6-*trimethyl mannonic acid* (Found: C, 44·6; H, 6·9. $C_{11}H_{20}O_9$ requires C, 44·6; H, 6·8%). The crystals and syrup, which evidently still contained carbomethoxy-residue, were further hydrolysed by digestion with *N*/3-barium hydroxide, and the organic acid was recovered from the barium salt. It was now distilled under 0·05 mm. pressure from a bath heated at 150—180° and obtained in the form of its lactone. The crystalline acid similarly gave a colourless lactone on heating.

Since separation of the stereoisomeric acids or lactones could not readily be achieved by direct means, the latter were heated for a few minutes with molecular quantities of phenylhydrazine. On the addition of benzene the product crystallised at once, m. p. 111—127°.

By repeated fractional crystallisation from benzene the stereoisomeric phenylhydrazides of the 3 : 4 : 6-trimethyl gluconic and mannonic acids were separated. The less soluble *phenylhydrazide* (A), m. p. 137—139°, was shown to be the mannono-compound. The corresponding glucono-compound (B) melted, though not sharply, at 125° and probably still retained a trace of (A) [Found for (A) : C, 54·7 ; H, 7·5 ; N, 8·8 ; OMe, 28·6. $C_{15}H_{24}O_6N_2$ requires C, 54·8 ; H, 7·7 ; N, 8·5 ; OMe, 28·35%]. The phenylhydrazide (A) was hydrolysed at 90° with *N*/10-hydrochloric acid (in slight excess), the water evaporated at 35°, and the residue dried. Evaporation of the dry ethereal extract from this product yielded a viscid syrup which crystallised in hard colourless prisms, m. p. 96—97°, from ether (Found : C, 49·1 ; H, 7·5 ; OMe, 41·8. $C_9H_{16}O_6$ requires C, 49·1 ; H, 7·5 ; OMe, 42·3%). Further experiments proved this compound to be l-3 : 4 : 6-*trimethyl* δ-*mannonolactone*. It showed the following polarimetric values in water (*c* = 1·88).

Hours ...	0	⅓	1½	5	9	22	34	74
$[\alpha]_D$	−167°	165°	161·8°	155·2°	147·2°	126·5°	119°	112·8° (constant)

An attempt was made to reduce this lactone to the sugar with sodium amalgam, but the slowness of the reaction would have required the use of more material than was available, and this part of the work was postponed.

IV. l-2 : 3 : 4 : 6-*Tetramethyl* δ-*Mannonolactone*.—The methylation of the crystalline 3 : 4 : 6-trimethyl mannonolactone was achieved by using silver oxide and methyl iodide which had been specially dried. The product, which had partly crystallised (Found : OMe, 50·8%), distilled as a colourless oil. This was heated with phenylhydrazine (equal mols.) along with a little ether, and as soon as the ether evaporated the residue crystallised to a hard cake, which was purified to give needles, m. p. 183—184° (Found : C, 55·75 ; H, 7·55. Calc. : C, 56·1 ; H, 7·6%). This *l*-phenylhydrazide showed $[\alpha]_D^{16°}$ +22° (*c* = 1·37 in chloroform), whereas the corresponding *d*-isomeride prepared by Haworth and Long (preceding paper) showed −22° (*c* = 1·37).

The above phenylhydrazide was hydrolysed and the tetramethyl mannonic acid converted into the lactone, which was distilled under 0·06 mm. from a bath at 145—150°. The liquid lactone crystallised to a low-melting solid (the *d*-isomeride has m. p. 23—25°) and showed, in water, $[\alpha]_D^{18}$ −150° (¼ hour), −95·6° (28 hours), −69·4° (98 hours), −58·2° (150 hours) constant. The *d*-2 : 3 : 4 : 6-tetramethyl δ-mannonolactone prepared by Drew, Goodyear, and Haworth (*loc. cit.*) showed $[\alpha]_D^{18°}$ $+150° \longrightarrow +63°$ (after 146 hours).

The slightly impure phenylhydrazide (B, above) of 3 : 4 : 6-trimethyl gluconic acid was hydrolysed in the usual manner with *N*/10-hydrochloric acid. After extraction the liberated organic acid was heated at 100°, and its ethereal solution treated with charcoal and evaporated. The resulting lactone showed $[\alpha]_D$ −90° changing to −27° in aqueous solution after 30 hours ($c = 1{\cdot}6$).

The trimethyl lactone was now methylated by Purdie's reagents, and the liquid tetramethyl lactone was distilled from a bath at 115°/0·5 mm. The distillate was a colourless liquid. This was digested with phenylhydrazine and gave almost immediately colourless crystals which were purified first from benzene and then from ether. A small quantity of the above *l*-2 : 3 : 4 : 6-tetramethyl mannonophenylhydrazide separated, m. p. 183—184°, and this was followed by the separation from the solution of the *l*-2 : 3 : 4 : 6-*tetramethyl gluconophenylhydrazide*, m. p. 115° (Found for the latter : C, 55·8; H, 7·5; OMe, 36·3. $C_{16}H_{26}O_6N_2$ requires C, 56·1; H, 7·6; OMe, 36·3%).

The phenylhydrazide of *l*-2 : 3 : 4 : 6-tetramethyl gluconic acid showed $[\alpha]_{5780}^{19^\circ}$ −50° in ethyl alcohol, which compares with the value $[\alpha]_{5780}^{19^\circ}$ +50·8° obtained for the corresponding *d*-enantiomorph.

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