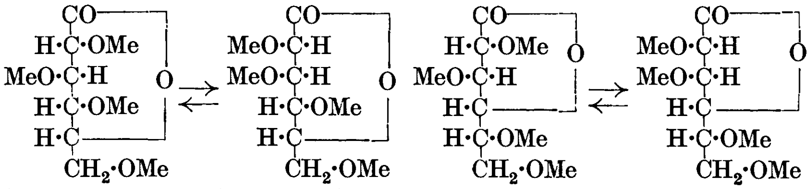
LII.—*The Conversion of Tetramethyl γ- and δ-Gluconolactones into the Corresponding Mannonolactones, and of the Trimethyl γ- and δ-Xylonolactones into the Corresponding Lyxonolactones.*

By Walter Norman Haworth and Charles William Long.

The authors have effected the epimerisation of several methylated lactones which are configurationally inter-related. Whilst the interconversion of α-hydroxy-acids is a well-recognised procedure, it has been shown that interconversion is effected just as readily when the hydroxyl groups in the hydroxy-acids are protected by methylation. Digestion with aqueous pyridine for a number of hours is sufficient to establish equilibrium between the two epimerides and the intermediate products.

One object of this investigation was to correlate a number of the methylated lactones which had already been studied in their relation to the constitution of sugars, and to supplement the evidence previously adduced of the existence of two types of ring structure. Hitherto the evidence has rested on the identification of the methoxy-dibasic acids derived from the lactones by oxidation (Haworth and Jones, J., 1927, 2349; Goodyear and Haworth, *ibid.*, p. 3136; Haworth, Hirst, and Miller, *ibid.*, p. 2436; Haworth and Porter, J., 1928, 611). The authenticity of the product depends in most cases upon a recognition of the stereochemical form of the methoxy-acid. By the inter-relationships established in the present work the evidence for the structure which has already been furnished is further strengthened. The effect is to duplicate the proofs of the ring structures of sugars and glucosides based on the original oxidation data of methylated lactones. Moreover the determination of the structure of a new methylated lactone should in future be facilitated by the adoption of this procedure, inasmuch as it may be characterised by epimerisation to a lactone of known structure.

The following interconversions have been achieved :

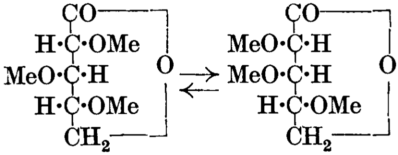


2 : 3 : 4 : 6-Tetramethyl δ-gluconolactone.

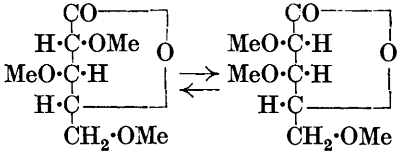
2 : 3 : 4 : 6-Tetramethyl δ-mannonolactone.

2 : 3 : 5 : 6-Tetramethyl γ-gluconolactone.

2 : 3 : 5 : 6-Tetramethyl γ-mannonolactone.



2 : 3 : 4-Trimethyl δ-xylonolactone. 2 : 3 : 4-Trimethyl δ-lyxonolactone.

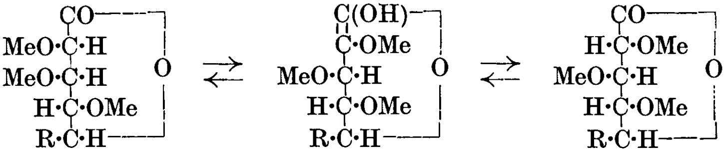


2 : 3 : 5-Trimethyl γ-xylonolactone. 2 : 3 : 5-Trimethyl γ-lyxonolactone.

In each case the resulting lactone was identified by preparing from it the crystalline phenylhydrazide of the corresponding acid, and the constants of these compounds are available for future reference.

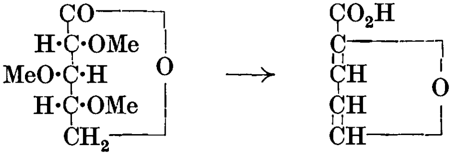
The experimental procedure differed from that adopted by E. Fischer (*Ber.*, 1890, **23**, 799) in his original work on hydroxy-acids. Whereas Fischer used quinoline or pyridine containing little water, we have used dilute aqueous pyridine, which promotes the epimerisation with extraordinary readiness even below 100°. Inasmuch as pyridine is easily eliminated from the salts by gentle heating, with the immediate formation of the methylated lactone, the removal of the organic base by means of barium hydroxide, followed by the precipitation of barium as sulphate, was obviated; as also was the use of the brucine salts for the purpose of purification, since the methylated lactones were recrystallised or distilled.

As the pyridine salts of these methoxy-acids hydrolyse readily in aqueous solution, it is evident that they are present in equilibrium with the free acids and the lactones. It has been suggested by earlier workers that epimerisation proceeds through the enolic form of the acids or salts, but it may equally be the case that the intermediate stage is represented by the enolic form of the lactones :



A comparison of the amounts of each substance occurring in the product shows that the lactone which is less easily hydrolysed by water is also the one which predominates in the epimeric mixture. Thus, in the study of the comparative rates of hydrolysis of 2 : 3 : 4 : 6-tetramethyl δ-gluconolactone and of the corresponding mannonolactone, it has already been shown (Drew, Goodyear, and Haworth, J., 1927, 1237) that the latter is considerably more stable than the former. The proportions of each found in the epimeric mixture are of the order of 5% of the former and 95% of the latter.

An unexpected result which has developed from this work is the transformation of 2 : 3 : 4-trimethyl δ-xylonolactone into furancarboxylic acid, which was isolated as the main product of the interconversion.



It is evident that aqueous pyridine is endowed with a remarkable capacity for eliminating methoxy-groups. This reaction is being investigated more closely in order to discover whether the furancarboxylic acid is preceded by a stage represented by the intermediate formation of a pyrone derivative, since there appears to be some evidence of this.

Meanwhile the above transformation throws some light on the changes which normal pentoses undergo when acted upon by dilute acid to give furfural.

EXPERIMENTAL.

The method adopted to effect the epimerisation of the methylated lactones was to dissolve 2 parts by weight of the lactone in 1 part of pyridine and 14 parts of water (compare Hedenburg and Cretcher, *J. Amer. Chem. Soc.*, 1927, **49**, 478). The solution was heated in a closed flask on a boiling water-bath during 100—120 hours. Since the solution was usually coloured at this stage, it was clarified with charcoal and diluted with much water. The water and pyridine were then removed by distillation under diminished pressure, and more water was rapidly added and again evaporated until the colourless syrupy residue was free from pyridine. Hydrolysis of the pyridine salt of the organic acid was complete after this treatment. Inasmuch as the procedure followed during the isolation of the products differed for each individual lactone, the details are briefly described in each case.

I. *Conversion of* 2 : 3 : 5 : 6-*Tetramethyl γ-Gluconolactone into* 2 : 3 : 5 : 6-*Tetramethyl γ-Mannonolactone.*—The crystalline tetramethyl gluconolactone, m. p. 26—27·5°, was digested with aqueous pyridine and yielded a syrup which crystallised rapidly. From light petroleum solution (b. p. 80—100°), it separated readily in long transparent needles, m. p. 109°. In admixture with a specimen of 2 : 3 : 5 : 6-tetramethyl γ-mannonolactone the m. p. showed no depression (Goodyear and Haworth, J., 1927, 3136) (Found : OMe, 52·3. Calc., 53·0%).

Further confirmation of the identity of the mannonolactone was obtained by preparing from it the phenylhydrazide of the corresponding acid. This separated from benzene as minute colourless prisms, m. p. 167°. A mixed m. p. determination was made with the specimen described by Goodyear and Haworth (*loc. cit.*) and showed no depression (yield, 60%).

The mother-liquors gave on evaporation a further quantity of the tetramethyl γ-mannonolactone, but the major portion of the residual syrup did not crystallise. This was digested with a proportional amount of phenylhydrazine, and the addition of benzene led to the separation of crystals of a phenylhydrazide, m. p. 134—135°. In admixture with an authentic specimen of the phenylhydrazide of 2 : 3 : 5 : 6-tetramethyl gluconic acid (m. p. 135—136°) (Haworth and Long, J., 1927, 544) there was no depression. This represented the portion of the original gluconolactone which had not been transformed.

II. *Conversion of* 2 : 3 : 5 : 6-*Tetramethyl γ-Mannonolactone into* 2 : 3 : 5 : 6-*Tetramethyl γ-Gluconolactone* (with Dr. E. H. GOODYEAR).—The procedure followed was identical with that described above under section I. About 50% of the original substance was recovered as the crystalline 2 : 3 : 5 : 6-tetramethyl γ-mannonolactone, and the mother-liquors also contained this unchanged lactone, which was isolated in the form of the phenylhydrazide of the corresponding 2 : 3 : 5 : 6-tetramethyl mannonic acid. The conversion in the direction of the gluconolactone proceeded to the extent of not more than 30%. From the mixture of the phenylhydrazides obtained after the conversion, a quantity of the crystalline phenylhydrazide (m. p. 134—135°) of 2 : 3 : 5 : 6-tetramethyl gluconic acid was isolated. The identity of this product was confirmed by mixed m. p. determination with an authentic specimen (Charlton, Haworth, and Peat, J., 1926, 89; Haworth and Peat, *ibid.*, p. 3100).

III. *Conversion of* 2 : 3 : 4 : 6-*Tetramethyl δ-Gluconolactone into* 2 : 3 : 4 : 6-*Tetramethyl δ-Mannonolactone.*—After treatment of the methylated δ-gluconolactone with aqueous pyridine the syrupy product was heated with phenylhydrazine during $\frac{1}{4}$ hour, and gave a 90% yield of a crystalline substance which, purified from benzene, was identified as the phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl mannonic acid, m. p. 184—185° (Found: C, 56·0; H, 7·8; N, 8·4; OMe, 35·6. Calc.: C, 56·1; H, 7·6; N, 8·2; OMe, 36·3%). This gave no depression in admixture with an authentic specimen prepared by Drew, Goodyear, and Haworth (*loc. cit.*). The mother-liquors gave a 5% yield of the phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl gluconic acid, m. p. 115°.

IV. *Conversion of* 2 : 3 : 4 : 6-*Tetramethyl δ-Mannonolactone into* 2 : 3 : 4 : 6-*Tetramethyl δ-Gluconolactone.*—The product from the pyridine treatment was not crystalline, and was heated for 1 minute with phenylhydrazine. A crystalline phenylhydrazide separated, m. p. 184—185°. This was identified as the phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl mannonic acid. The mother-liquors evidently contained the conversion product in the form of the free lactone. These were evaporated and the residue was heated for ½ hour with phenylhydrazine. Crystals again separated, which were purified from ether; m. p. 184°. The major portion of this product was thus the phenylhydrazide from the unchanged δ-mannonolactone. The concentrated mother-liquors, dissolved in ether, deposited another crystalline product, which was purified by recrystallisation (ether) and had m. p. 113—114°. This was identified as the phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl gluconic acid by mixed m. p. determination with a specimen prepared by Haworth, Hirst, and Miller (J., 1927, 2436). The conversion in the direction of δ-mannono- to δ-glucono-lactone was not more than 8%.

V. *Conversion of* 2 : 3 : 4-*Trimethyl δ-Xylonolactone into* 2 : 3 : 4-*Trimethyl δ-Lyxonolactone.*—The conversion followed the usual course, except that the syrupy product deposited a crystalline substance, which was identified as a furancarboxylic acid, m. p. 131—132° (Found : C, 53·5; H, 3·4%), formed (yield, 63%) through a secondary reaction involving the elimination of methyl alcohol. The remaining syrup was heated with phenylhydrazine containing a little dry ether, and on evaporation of the solvent the corresponding phenylhydrazide crystallised. This was purified from benzene and yielded colourless needles, m. p. 180—181° (Found : C, 56·1; H, 7·3; OMe, 30·6; N, 9·7. Calc. for $C_{14}H_{22}O_5N_2$: C, 56·4; H, 7·4; OMe, 31·2; N, 9·4%). This was identified as the phenylhydrazide of 2 : 3 : 4-trimethyl lyxonic acid—a substance recently prepared from trimethyl lyxose (Hirst and Smith, J., 1928, 3147). A mixed m. p. determination of the phenylhydrazide prepared by the latter method gave no depression. In admixture with a specimen of the *phenylhydrazide* of 2 : 3 : 4-trimethyl δ-xylonic acid, m. p. 137—138·5° (Found : C, 56·5; N, 7·45; OMe, 30·9; N, 9·45. $C_{14}H_{22}O_5N_2$ requires C, 56·4; H, 7·4; OMe, 31·2; N, 9·4%), which was prepared for this comparison from the initial material, the m. p. was depressed.

VI. *Conversion of* 2 : 3 : 5-*Trimethyl γ-Xylonolactone into* 2 : 3 : 5-*Trimethyl γ-Lyxonolactone.*—Trimethyl γ-xylonolactone (1 g.) was heated with aqueous pyridine and gave, on concentration of the solution, a coloured syrup. Part of this (0·6 g.) was soluble in ether and gave a *phenylhydrazide* (m. p. 142°) in minute hexagonal prisms (Found : C, 56·25; H, 7·35. $C_{14}H_{22}O_5N_2$ requires C, 56·4; H, 7·4%).

The conversion into the lyxonolactone had proceeded to the extent of 60% of the total quantity of methylated xylonolactone originally taken.

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UNIVERSITY OF BIRMINGHAM,
EDGBASTON.

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