LXXXII.—*Derivatives of γ-Xylose. A Study of Xylose-monoacetone and its Conversion into 2:3:5-Trimethyl γ-Xylonolactone.*

By Walter Norman Haworth and Charles Raymond Porter.

The lactones related to simple methylated sugars may be prepared (*a*) by direct oxidation of the methylated sugar itself or alternatively (*b*) by methylation of the lactone derived from the unsubstituted sugar by oxidation. The latter method possesses the disadvantage that during conversion of the unmethylated lactone into the methylated lactone the former may change its identity by the opening of its ring and subsequent closure to give an isomeric lactone. Certain δ-lactones pass with remarkable ease under a variety of conditions to the more stable γ-lactones (unsubstituted). It is obvious also that where the methylation of a lactone is accompanied by scission involving the formation of an ester, structural considerations rest on a precarious basis if it be assumed that the ester, on hydrolysis, necessarily passes to the same structural type of lactone as the original unmethylated one.

The first method of preparing the methylated lactones (method *a* above) is the more satisfactory, and especially so, fortunately, for the δ-lactones which are obtained with some difficulty by method (*b*). Since the purity of the lactone is dependent, however, on the homogeneity of the methylated sugar, and since there has hitherto been no satisfactory standard of purity for the γ-sugars, which may, and probably do in some cases, contain some of the methylated normal sugar, the purity of the lactones prepared by oxidation of the γ-sugars may be under suspicion. This criticism does not apply to those γ-lactones which have been obtained in a crystalline condition, and it is thus restricted to the two known cases of the liquid trimethyl γ-xylonolactone and tetramethyl γ-galactonolactone, for which special reservations were made in the provisional data given in the earlier communication (Drew, Goodyear, and Haworth, J., 1927, 1237).

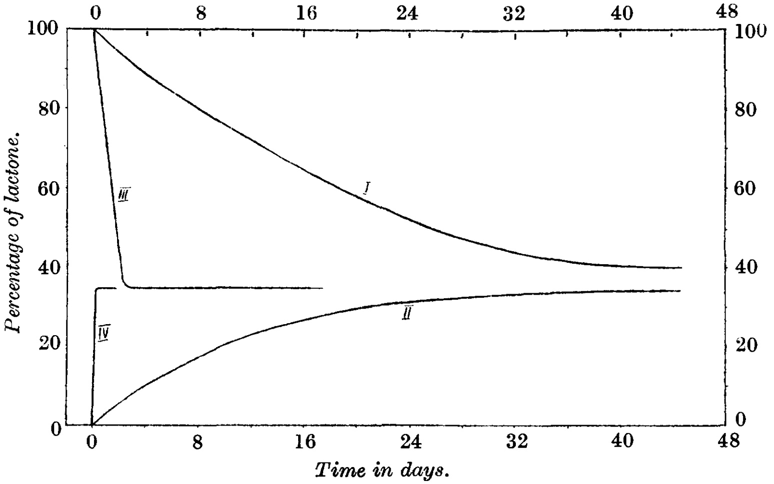
The study of the so-called γ-sugars (furanoses) is being pursued with the object of obtaining in every case structurally, and also optically, pure specimens. An obvious procedure to this end is to prepare them from homogeneous specimens of γ-lactones. In the present paper, the isolation of the highly pure trimethyl γ-xylonolactone is communicated, the procedure being that of a combination of methods (*a*) and (*b*). The satisfactory evidence of purity rests on the formation of the crystalline phenylhydrazide derivative, followed by regeneration therefrom of the lactone.

The crystalline xylose-monoacetone described by Svanberg (*Ber.*, 1923, **56**, 863, 2195) gave on methylation with methyl sulphate and alkali a dimethyl xylose-monoacetone, $[\alpha]_{5780}^{15^\circ}$ $-$ 46·6°. Hydrolysis of the latter, followed by oxidation of the liberated dimethyl xylose, yielded a dimethyl γ-xylonolactone having $[\alpha]_{5780}^{21\cdot5^\circ}$ + 81·5°, changing slowly in aqueous solution to + 39° after 49 days. The crystalline phenylhydrazide (m. p. 94—95°) of the corresponding acid was prepared. Further methylation of the lactone yielded the trimethyl γ-xylonolactone, which gave a crystalline phenylhydrazide, m. p. 89—90° (yield 75%). This phenylhydrazide was also obtained from the specimen of the trimethyl γ-xylonolactone isolated by Haworth and Westgarth (J., 1926, 880) by oxidation of trimethyl γ-xylose. The constitution of the latter sugar was given by those authors as a butylene oxide (xylofuranose), and that conclusion is verified by the following experimental results. From the crystalline phenylhydrazide the purified lactone was regenerated and this was submitted to polarimetric study and its constitution was also determined by oxidation methods. The rate of conversion of the trimethyl γ-xylonolactone in aqueous solution into the corresponding trimethyl xylonic acid and also the reverse change from the acid to the lactone were calculated from the rotation figures recorded in the experimental section. The percentage of acid present in aqueous solution at any given time during the hydrolysis of the lactone is calculated from the expression $100(R - R_l)/(R_a - R_l)$ which has previously been used (Drew, Goodyear, and Haworth, *loc. cit.*; compare Levene and Simms, *J. Biol. Chem.*, 1925, **65**, 46) : R is the specific rotation of the solution at a given time and R_a and R_l are the specific rotations of the lactone in the form of acid and of the lactone respectively. It has been explained in the earlier paper (*v. supra*) that the values determined on this experimental basis are probably not strictly accurate, but they are considered sufficiently exact to be applicable to the present purpose the authors have in view, namely, to furnish a preliminary groundwork for the study of the conditions influencing the markedly different rates of hydrolysis of γ- and δ-lactones related to simple sugars.

In Fig. 1 are given the curves illustrating the percentage lactone present at any given time during the conversion of (I) trimethyl γ-lactone into the acid, and (II) the acid into the lactone. For the sake of comparison with the trimethyl δ-xylonolactone the curves III and IV are also included from the previous paper by Drew, Goodyear, and Haworth.

FIG. 1.

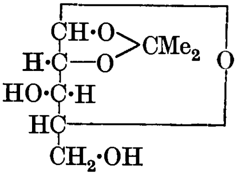
Comparative rates of hydrolysis of the isomeric trimethyl xylonolactones and the rates of the reverse change of acids into lactones.

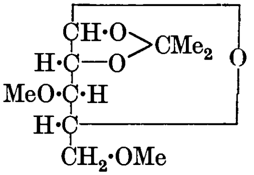


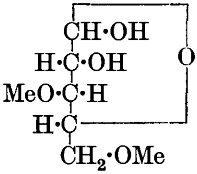
The time period during which the equilibrium γ-lactone $\rightleftharpoons$ γ-hydroxy-acid is attained must obviously be greater than 900 hours. As in previous cases the time required for the development of 25% of the xylonic acid may be more accurately ascertained, and this is seen to be 250 hours instead of the approximation of 430 hours previously suggested (Drew, Goodyear, and Haworth, *loc. cit.*). This time period is to be contrasted with the corresponding period for the isomeric δ-lactone, which is 22 hours. Equilibrium is attained very rapidly from the side δ-hydroxy-acid to δ-xylonolactone and the steepness of curve IV suggests that the reaction is being promoted either by catalysis by the organic acid itself or by the presence of the mineral salt (sodium sulphate) which is unavoidable under the experimental method adopted. The latter effect is much less marked in curve II.

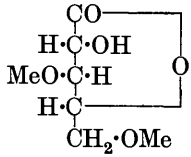
Finally, the constitution of the 2 : 3 : 5-trimethyl γ-lactone was confirmed by its oxidation to *d*-dimethoxysuccinic acid (VI), which was recognised through the crystalline methylamide, m. p. 204—205°. The latter was identical with a specimen specially prepared for this comparison by Haworth and Jones (J., 1927, 2349) from *d*-tartaric acid.

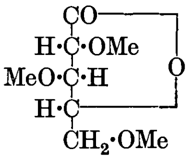
Interpretation of the experimental evidence furnished by these results leads definitely to the conclusion that the dimethyl xylonolactone (IV) employed as a source of the trimethyl γ-xylonolactone (V) was also itself a γ-lactone. Inasmuch as the dimethyl lactone (IV) originated from a dimethyl xylose, it follows that the latter was a butylene oxide or γ-sugar, that is, a xylofuranose (III), which was obtained by the hydrolysis of (II). From this it is also argued that the non-reducing xylose-monoacetone also contained a butylene-oxide ring, formulated as in (I).

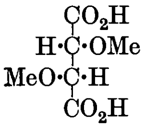

(I.)

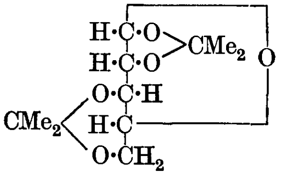

(II.)

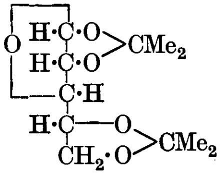

(III.)

(IV.)


(V.)



(VI.)

(VII.)


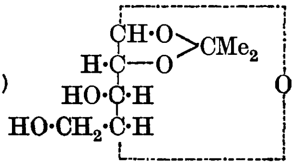

(VIII.)

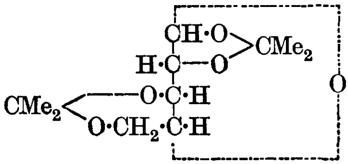
It must be conceded that no alternative interpretation of the structure of xylose-monoacetone (I) is possible in view of these experimental results. The oxide ring in this γ-sugar derivative is stabilised as effectively as in the case of γ-methylglucoside. Whether the same oxide ring structure applies also to xylose-diacetone as shown in (VII) is a case for further argument. Originally we had hoped that the present experiments would yield evidence in favour of the formula (VIII), since this presented a unique opportunity to investigate the possible existence of 1 : 3 or propylene-oxide sugars which are at present unknown, although their existence has frequently been postulated. The formula (VIII) represents the two acetone residues as connecting *cis*-hydroxyl groups attached to contiguous carbon atoms, a condition which seems to be fulfilled in all other authentic structural formulæ for sugar-acetones.

On the other hand, if xylose-diacetone exists according to the structural scheme (VIII), then the 1 : 3-oxide ring has undergone a displacement to the 1 : 4-oxide simultaneously with the removal of one acetone residue to form the monoacetone (I). This is indeed a possibility, but a careful review of the whole of the evidence leads us to the alternative decision in favour of the formulation (VII) for xylose-diacetone.

Inspection of the atom-models arranged either to represent (VII) or (VIII) indicates a marked preference for (VII) on the grounds of minimum internal strain. One of us has already directed attention to the failure of plane formulæ to represent the spatial relationship of groups at the ring-forming carbon atom intermediately situated in the chain (Drew and Haworth, J., 1926, 2303). When these are correctly represented in xylose-monoacetone and the oxygen of the oxide ring is shown to be co-planar with the first four carbon atoms of the sugar chain, it is seen (formula IX) that the 5th carbon atom of the chain is directed to the left in proximity to the hydroxyl at the 3rd carbon atom and this pair of hydroxyl groups is favourably placed to receive an acetone residue thus (formula X) :

(IX.)

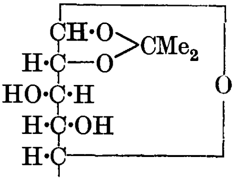




(X.)

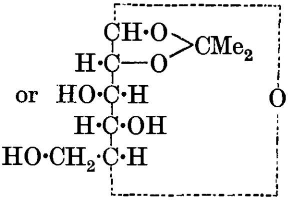
In these circumstances the internal strain is minimised and is comparable in magnitude with that associated with the union of an acetone group with *cis*-hydroxyl groups at contiguous carbon atoms.

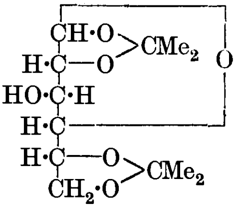
If the hydroxyl at the third carbon atom had been directed to the right instead of to the left, this type of six-ring formation with acetone could not have occurred except under exceptional strain. Adopting the conventional plane formula for oxide rings in sugars, it may be laid down as a suitable rule that where the above type of condensation with acetone is favoured the hydroxyl at a carbon within the oxide ring of the sugar must not be on the same side as the oxide ring. It is probably for this reason that glucose does not condense with acetone while existing as a pyranose, or an amylene-oxide form, since inspection of formula (XI) shows that the hydroxyl at the fourth carbon is to the right of the formula and so also is the oxide ring.



(XI.)

or





(XII.)

The formulation of glucose-diacetone on the plan of Levene, Freudenberg, and Karrer as a butylene-oxide sugar derivative or a furanose is the only scheme which leads to minimum strain in the models (formula XII). There is just as much experimental evidence for the formulation (VII) for xylose-diacetone as there is for the formulation (XII) of glucose-diacetone.

EXPERIMENTAL.

Methylation of Xylose-monoacetone.—Xylose-diacetone (13·43 g.) was dissolved in 300 c.c. of 0·2% hydrochloric acid at 17° and the hydrolysis was followed by taking polarimetric readings in a 2-dcm. tube. The rotation was α + 0·56° (after 10 mins.), falling to a constant value, α − 1·28° (after 100 mins.). The solution was neutralised with barium carbonate, filtered, evaporated at 35° and gave xylose-monoacetone (Svanberg, *loc. cit.*). The substance was now methylated with methyl sulphate and sodium hydroxide in the usual way, first at 35—45° and finally at 60—70°. The product was extracted with chloroform, again methylated, and distilled, b. p. 75—78°/0·07 mm. (yield, 10 g.). The dimethyl xylose-monoacetone showed $[\alpha]_{5780}^{15°}$ − 46·6°; $n_D^{15°}$ 1·4455.

Dimethyl γ-Xylonolactone.—This was prepared by the combined hydrolysis and oxidation of dimethyl xylose-monoacetone. The latter (5·6 g.) was heated at 85° with 2·7% hydrobromic acid (65 c.c.) for an hour. Bromine (6 c.c.) was then gradually admitted to the solution, which was kept at 75°. (Bromination of some of the liberated acetone occurred.) After 15 hours the solution was neutralised with lead carbonate, and treated with silver oxide, followed by hydrogen sulphide in the usual way, and the organic acid was isolated as the lactone, which distilled at 105—106°/0·08 mm. Yield, 3·55 g. of distilled lactone. The dimethyl xylonolactone showed $n_D^{15°}$ 1·4643; $[\alpha]_{5780}^{21·5°}$ + 81·5° (after 3 mins.), 85·1° (after 1 day), 83·2° (2 days), 66·9° (7 days), 54·5° (14 days), 44·1° (21 days), 39·6° (40 days), 39° (49 days) (Found : C, 47·1; H, 6·9; OMe, 32·7. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8; OMe, 35·2%).

Phenylhydrazide. The dimethyl γ-xylonolactone and phenylhydrazine in molecular proportion were mixed in dry ether, the solvent was evaporated, the mixture heated during an hour on the water-bath and cooled, and the solid product triturated with ether and finally recrystallised from benzene. It was obtained as rosettes of needles, m. p. 94—95°, soluble in chloroform, less so in ether or water, and insoluble in light petroleum (Found : C, 55·1; H, 7·1; N, 10·15; OMe, 19·5. $C_{13}H_{20}O_5N_2$ requires C, 54·9; H, 7·0; N, 9·9; OMe, 21·8%).

Phenylhydrazide of the Acid corresponding to Trimethyl γ-Xylonolactone.—The above dimethyl xylonolactone was twice methylated by Purdie's reagents, and gave a colourless liquid, b. p. 84°/0·1 mm., $n_D^{15·5°}$ 1·4472, which was the crude trimethyl γ-xylonolactone (Found : C, 50·2; H, 7·4; OMe, 49·0. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 49·0%). The *phenylhydrazide* was prepared in a similar way to that described above, and gave (75% of the theoretical yield) rosettes of needles, m. p. 89—90°, crystallised from benzene. The same substance was also prepared from a specimen of the trimethyl γ-xylonolactone prepared by Haworth and Westgarth (*loc. cit.*) from trimethyl γ-xylose, but the yield in this case was not so high (Found: C, 56·2; H, 7·3; N, 9·8; OMe, 27·7. $C_{14}H_{22}O_5N_2$ requires C, 56·4; H, 7·4; N, 9·4; OMe, 31·2%).

Regeneration of the Purified Trimethyl γ-Xylonolactone from the above Crystalline Phenylhydrazide.—The phenylhydrazide (m. p. 89—90°) of the acid corresponding to this lactone was hydrolysed with a slight excess of *N*/10-hydrochloric acid at 90°, the solution evaporated at 35° under diminished pressure, and the residue dried. The lactone obtained was dissolved in dry ether containing a little chloroform, the solution treated with charcoal, and the trimethyl xylonolactone distilled, b. p. 82°/0·06 mm.; $n_D^{17°}$ 1·4464.

The rate of hydrolysis of the lactone was studied by the polarimetric method, aqueous solutions being used. The rate of conversion of the free trimethyl xylonic acid into the lactone was similarly studied; for this purpose the lactone was hydrolysed by the addition of the equivalent amount of sodium hydroxide, and to this aqueous solution of the sodium salt the equivalent of dilute hydrochloric acid was admitted to liberate the free acid in solution. Polarimetric readings were taken immediately and over a period of 43 days.

	Conversion of lactone into acid (c = 1·998).		Conversion of acid into lactone (c = 0·856) (calc. as lactone).	
Time (days).	$[\alpha]_{5780}^{17^\circ}$.	$[\alpha]_{5461}^{17^\circ}$.	$[\alpha]_{5780}^{17^\circ}$.	$[\alpha]_{5461}^{17^\circ}$.
0	+108°	+118°	+42·5°	+46°
1	110	120	40	45·5
2	108	117	40	42·5
7	98	108	49	52
9	95·5	104·5	52	55·5
14	88·5	96	55	58·5
19	81·5	88·5	58	61·5
26	75	80	62	66
29	73	78·5	61·5	66
33	70	75·5	62	68
40	67·5	73	62·5	67
43	67·5	72·5	62·5	68

Oxidation of Trimethyl γ-Xylonolactone.—The above lactone was oxidised by heating at 95—100° for 8 hours with nitric acid (*d* 1·42). The cooled solution was diluted with water and evaporated under diminished pressure during successive additions of water. This treatment was followed by the repeated addition of methyl alcohol and evaporation of this solvent. The syrupy residue was esterified by digestion with methyl-alcoholic hydrogen chloride (3%), and the ester isolated by neutralisation with silver carbonate, filtration, evaporation, and extraction with ether. The residue remaining after evaporation of the ether was distilled under 0·15 mm. from a bath heated at 117—120°. The colourless distillate showed $n_D^{14^\circ}$ 1·4429, and amounted to rather more than one-fourth of the weight of the original lactone. It appeared to be the methyl ester of a dibasic methoxy-acid, and was characterised by the following experiment.

The ester was dissolved in dry methyl alcohol, cooled in ice and saturated with dry methylamine. After being kept for a day, the solution was evaporated in a vacuum and yielded a crystalline product which, purified from ethyl acetate, had m. p. 204—205°. A mixture of the crystals with an authentic specimen of *d*-dimethoxysuccinomethylamide prepared from *d*-tartaric acid (Haworth and Jones, *loc. cit.*) showed no depression. There can therefore be no doubt that the trimethyl γ-xylonolactone yielded on oxidation as the only product recognisable by these methods, *d*-dimethoxysuccinic acid.

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