CXXI.—*Synthesis of Derivatives of γ-Xylose.*

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THIS investigation forms a part of a general study of the constitution of the normal and the γ-forms of the sugars. The isolation of derivatives of γ-fructose, γ-galactose, and γ-arabinose encouraged the view that the existence of γ-forms was a general property of the sugars (Haworth and Law, J., 1916, **109**, 1314; Haworth, Ruell, and Westgarth, J., 1924, **125**, 2468; Baker and Haworth, J., 1925, **127**, 365).

In the present paper, another example in the pentose series is described, namely, *trimethyl γ-xylose*, the structure of which has been investigated by conversion into its lactone and comparison of the properties of the latter with the corresponding lactone which we have isolated from normal trimethyl xylose.

In the case of xylose, the condensation with methyl alcohol in the cold proceeds very tardily, the *γ-methylxyloside* requiring 5 to 7 days for its formation, as contrasted with fructose, which condenses with methyl alcohol in the course of ½ hour, and galactose and arabinose, which require a period of less than a day after solution of the sugar. In following the formation of the γ-methylxyloside polarimetrically, it was observed that the condensation was accompanied by no inversion in the sign of rotation, and indeed, the final value recorded, $[\alpha]_D + 28{\cdot}8°$, differed very little from the initial value, $+ 28{\cdot}3°$, of the original xylose solution, although intermediate readings attained a maximum of $+ 37{\cdot}7°$.

γ-Methylxyloside is comparable in its properties with γ-glucosides in general, exhibiting the usual ease of hydrolysis with acids of extreme dilution, and the characteristic instability in presence of neutral permanganate. From the specimen of γ-methylxyloside, the completely methylated derivative, *trimethyl γ-methylxyloside*, was obtained as a colourless liquid, $[\alpha]_D = + 32{\cdot}0°$ in methyl alcohol. Hydrolysis of this compound was effected at 100° with either *N*/50- or *N*/100-hydrochloric acid, but for the purpose of the preparation of the corresponding free sugar *N*/15-acid may conveniently be used, the hydrolysis being complete in 4 hours. The rotation changes accompanying the hydrolysis exhibited the usual fall and rise in value, giving a time-period curve characteristic of the γ-glucosides, and indicating the presence of two stereochemical forms.

Trimethyl γ-xylose was thus isolated as a liquid containing both α- and β-forms, and its properties were compared with those of the normal trimethyl xylose prepared by Carruthers and Hirst (J., 1922, **121**, 2306).

	Trimethyl γ-xylose.	Normal trimethyl xylose.
	Syrup, b. p. 110°/0·04 mm.	Crystalline, m. p. 87—90°.
$[\alpha]_D$	$+24{\cdot}7° \longrightarrow 31{\cdot}2°$.	$+74° \longrightarrow 21°$.
Action of permanganate.	Reduces vigorously.	No action.
Acid methyl alcohol.	Combines rapidly.	Combination slow.

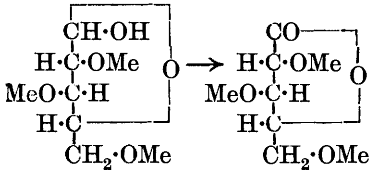
It is noteworthy that these two structurally different forms should display specific rotations of the same sign and of similar magnitude. In this respect, the two varieties of trimethyl xylose may be compared with those of tetramethyl mannose, the γ-form of which is crystalline and shows $[\alpha]_D + 48{\cdot}5°$, whereas the normal form is a liquid, showing $[\alpha]_D + 17{\cdot}2°$ (equilibrium in methyl alcohol) (Irvine and Burt, J., 1924, **125**, 1343).

With the object of deriving the constitution of trimethyl γ-xylose, the sugar was oxidised to the corresponding *lactone*, and for the purposes of comparison a similar procedure was followed also with the normal sugar. The properties of the two lactones are indicated below :

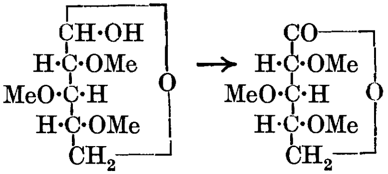
Lactone from	(*a*) Trimethyl γ-xylose.	(*b*) Normal trimethyl xylose.
	Liquid.	Crystalline, m. p. 55°.
$[\alpha]_D$ in water.	$+74{\cdot}1° \longrightarrow 61{\cdot}4°$ (Period, 21 days).	$-3{\cdot}8° \longrightarrow +20{\cdot}8°$ (Period, 8 days).

A comparison of these rotation values indicates that the lactone from the γ-sugar resists hydrolysis to a much greater extent than the corresponding lactone from the normal sugar, and curves representing these changes have been given in the paper by Charlton, Haworth, and Peat (this vol., p. 93).

Since the constitution (III) allocated to normal trimethyl xylose on the basis of its oxidation to trimethoxyglutaric acid is that of a normal or δ-oxide (Hirst and Purves, J., 1923, **123**, 1352), it is evident that the structure of the derived lactone is that indicated by formula (IV). We are able to assign the structural formula (II) to the lactone from the γ-sugar for two reasons : (*a*) Its lactone ring must be situated on the right of the carbon chain on the basis of Hudson's rule, since the substance displays dextrorotation, diminishing in magnitude as the ring opens by hydrolysis to the hydroxy-acid. The lactone ring cannot engage the β-carbon acid, since in this case the lactone would be lævorotatory. (*b*) Its speed of hydrolysis in water is comparable in every respect with the series of γ-lactones examined by Charlton, Haworth, and Peat (*loc. cit.*). We therefore ascribe the constitution of a γ-lactone to this compound (II), whence it follows that the related sugar, trimethyl γ-xylose, has the constitution (I).



(I.) (II.)



(III.) (IV.)

EXPERIMENTAL.

Preparation of γ-Methylxyloside.—Polarimetric observations indicated that at 15° solutions of xylose (2%, 3·5%, and 5%) in dry, acetone-free methyl alcohol containing 1% of hydrogen chloride attained a maximum rotation after 25—30 minutes from the time of solution, this stage being succeeded by a slow diminution of rotation, and the equilibrium period seemed to be reached in about 24 hours.

The following values were obtained, for example, with a solution of this nature containing 2% of xylose :

Time (mins.)	5	10	15	20	30	53	58
$[\alpha]_D$	+28·3°	35·3°	37·2°	37·4°	37·7°	36·1°	35·9°
Time (mins.)	163	210	22½ hrs.				
$[\alpha]_D$	+30·9°	29·0°	28·8°				

With a similar solution containing, however, 5% of xylose, the following polarimetric figures were recorded :

Time (mins.)	20	26	36	52	62	72	112
$[\alpha]_D$	+37·9°	38·6°	38·8°	38·5°	37·5°	37·0°	35·3°
Time (mins.)	167	262	397				
$[\alpha]_D$	+33·5°	32·1°	30·3°				
Time (hours)	25	50	75				
$[\alpha]_D$	+29·3°	28·5°	28·2°	(Thereafter, apparently constant.)			

The evidence furnished by tests with Fehling's solution, and also by actual isolation of the product, indicated that xyloside formation was far from complete at the end of these periods.

It thus appeared that glucoside formation proceeded very slowly under these conditions, xylose differing markedly in this respect from fructose, galactose, and arabinose. Moreover, the apparent attainment of a constant rotation after 24 hours was deceptive, in that methylxyloside continued to be formed even after 5 days, although the rotation changes were negligible during this extended period.

The following experimental conditions were therefore adopted for the preparation of larger quantities of γ-methylxyloside : Dried, finely-sieved xylose (11·9 g.) was dissolved in 238 g. of pure dry methyl alcohol containing 2·27 g. of hydrogen chloride, making a 5% solution of xylose in methyl alcohol containing 1% of hydrochloric acid. The mixture was kept at room temperature until it no longer reduced Fehling's solution, this stage being reached after 7 days. The product, isolated in the usual manner, was extracted with ethyl acetate, and consisted of a viscid syrup (8 g.) containing 0·7 g. of xylose crystals, which were removed by solution of the syrup in absolute alcohol. Distillation of the syrup was effected without any decomposition, giving rise to a pale yellow, viscid product, b. p. 161·5°/0·03 mm., $[\alpha]_D = +62{\cdot}8°$ in ethyl alcohol [Found : OMe, 18·4. $C_5H_9O_4(OMe)$ requires OMe, 18·8%].

In another preparation of γ-methylxyloside, 27·5 g. of xylose gave 20·6 g. of a syrup from which 15·8 g. of the distillate were obtained, the still residue being 3·4 g. In this experiment, the solution ceased to reduce Fehling's solution after 5 days.

Methylation of γ-Methylxyloside.—Methylation of this product was carried out with methyl sulphate and sodium hydroxide, care being taken to prevent development of acidity during the operation. The first eighth of each reagent was added at 40°, the second at 55°, and the remainder at the usual temperature of 70°. The quantities used were: γ-methylxyloside, 6·3 g.; methyl sulphate, 16·3 c.c.; sodium hydroxide, 15·5 g. in 31 c.c. of water. This yielded a pale liquid product which was remethylated with methyl iodide and silver oxide. The liquid product weighed 3·5 g. and had b. p. 78°/0·03 mm., n_D = 1·4407. A small quantity of crystals was also collected.

The distilled liquid was colourless and immediately reduced neutral permanganate in the cold, but showed no reduction of Fehling's solution even on vigorous boiling [Found: C, 51·35; H, 8·4; OMe, 56·3. $C_5H_6O(OMe)_4$ requires C, 52·4; H, 8·7; OMe, 60·2%. $C_5H_7O_2(OMe)_3$ requires C, 50·0; H, 8·3; OMe, 48·3%].

These figures indicated that the xylose compound contained between three and four methoxyl groups.

The material was mixed with a further 11·2 g. which had been methylated to the same stage, and the whole (14·4 g.) was remethylated six times by Purdie's reagents. On distillation the first few drops were rejected, and a yield of 10·05 g. of the main fraction, b. p. 82·5—84·5°/0·03 mm., was obtained. In order to ensure a better fractionation, this product was re-distilled in the vacuum of the water-pump and then had b. p. 110—114°/14 mm. (Found: C, 52·2; H, 8·8; OMe, 59·0. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 60·2%). $[\alpha]_D = +32·0°$ in methyl alcohol (c = 0·7975); n_D 1·4387.

The sugar derivative was therefore a fully-methylated pentoside, and was essentially trimethyl γ-methylxyloside.

Preliminary Hydrolysis.—Preliminary experiments were instituted with the view of determining the ease of hydrolysis of trimethyl γ-methylxyloside with acid of varying dilutions. For this purpose hydrochloric acid (*a*) *N*/100; (*b*) *N*/50; (*c*) *N*/15 was employed at 100° and the following polarimetric data were recorded:

(*a*) Time (mins.) ...	5	25	55	85	120	150	210	275
$[\alpha]_D$	+37·9°	17·2°	16·3°	19·7°	22·0°	24·1°	28·6°	33·2°

(*b*) Time (mins.) ...	3	27	57	89	109
$[\alpha]_D$	+33·9°	18·2°	24·2°	24·2°	26·4°

(*c*) Time (mins.) ...	0	30	60	150	240	360
$[\alpha]_D$	+35·6°	28·8°	34·2°	36·9°	38·3°	37·8°

To the solution (*c*) sufficient concentrated hydrochloric acid was added to increase the *N*/15-acid to 1% strength, and this solution was kept at 100° for an hour, after which the specific rotation diminished from + 37·8° to 35·1°. By increasing the acid concentration to 5% and boiling the solution for a further period of 1½ hours the rotation fell to +29·9°. It was evident, therefore, that if any of the normal form of trimethyl methylxyloside was present in the original product, this quantity was extremely small, since normal trimethyl xylose has a lower specific rotation ($[\alpha]_D$+21°) and is formed from its glucoside by hydrolysis with 5% hydrochloric acid at 100°.

Isolation of Trimethyl γ-Xylose.—Trimethyl γ-methylxyloside (4·5 g.) was dissolved in 100 c.c of *N*/15-hydrochloric acid and heated under reflux on a boiling-water bath as in the above control experiment. The hydrolysis was arrested after 5 hours, when a constant rotation was reached. The solution was then neutralised with barium carbonate, filtered, and evaporated at 40°/12 mm. to a syrup. This was dissolved in chloroform, filtered from inorganic salt and evaporated, and the residual product (3·8 g.) was distilled.

Fraction 1. B. p. 96·5°/0·06 mm., 1·3 g., n_D = 1·4509.
,, 2. B. p. 110°/0·04 mm., 2·3 g., n_D = 1·4539.

The first fraction contained some unchanged xyloside, and any of the normal form of trimethyl methylxyloside which might be present would be collected in this fraction of lower boiling point since it would be unaffected by the *N*/15-acid.

The second fraction, consisting of trimethyl γ-xylose (Found: C, 49·5; H, 8·5; OMe, 47·2. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3; OMe, 48·4%), was a colourless liquid which reduced Fehling's solution very actively, and also neutral permanganate in the cold. $[\alpha]_D$ in water, + 24·7° ⟶ 29·5° after 40 hours. After catalysis, the final equilibrium value was + 31·2°.

Oxidation of Trimethyl γ-Xylose with Bromine Water. Isolation of Trimethyl γ-Xylonolactone.—Trimethyl γ-xylose (1·5 g.) was dissolved in 12 c.c. of water, and 1 c.c. of bromine added gradually with shaking. The solution was then heated for 6½ hours at 30—35°. After keeping in the cold for 60 hours, it slightly reduced Fehling's solution. A further ½ c.c. of bromine was accordingly added and the oxidation completed by again heating for 9 hours at 35—40° and keeping over-night at room temperature. Excess of bromine was then removed by aeration, and the solution concentrated under diminished pressure. Hydrobromic acid was removed by the usual treatment, and the solution evaporated at 40°. The residual syrup was dissolved in dry ether and filtered several times to remove traces of inorganic matter. In this way, 1·3 g. of a pale yellow liquid were obtained, which was submitted to fractionation in a high vacuum. Nearly the whole distilled at about 105°/0·04 mm., and showed n_D 1·4465 (Found: C, 50·7; H, 7·6; OMe, 47·4. Calc. for $C_8H_{14}O_5$, C, 50·5; H, 7·4; OMe, 48·9%).

On titration, the compound behaved as a lactone: 0·1060 g. required, on heating, 5·4 c.c. of *N*/10-sodium hydroxide (Calc. for $C_8H_{14}O_5$, 5·6 c.c.). The compound behaved in aqueous solution as a typical γ-lactone; there was a slow change in the value of the specific rotation due to the opening of the lactone ring, with formation of an acid of lower rotatory power. The following rotations were observed in aqueous solution ($c = 1·1062$): $[\alpha]_D + 74·1°$ after 5 minutes, 71·8° after 64 hours, 69·6° after 7 days, 61·4° after 21 days.

The experimental evidence stated above has led to the conclusion that the oxidation product was trimethoxy-γ-xylonolactone, and a 1 : 4 or butylene-oxide structure has thus been assigned to the derivatives of γ-xylose.

Preparation of Trimethyl δ-Xylonolactone from the Normal Form of Trimethyl Methylxyloside.—A simultaneous hydrolysis and oxidation of crystalline trimethyl β-methylxyloside (m. p. 48—49°) was carried out as follows (compare Pryde, Hirst, and Humphries, J., 1925, **127**, 348): A solution of the normal form of the xyloside (1·5 g.) in 16·6 c.c. of 3% aqueous hydrobromic acid was heated at 85° for an hour and cooled to 75°. Bromine was then added (0·7 c.c.) over a period of 4 hours at the rate of 7 drops every half-hour. The solution stood at room temperature for 24 hours and then a further 1 c.c. of bromine was added at 75° over a period of 4 hours at the rate of 10 drops every half-hour. The liquid still reduced Fehling's solution after cooling and keeping over-night. More bromine (0·5 c.c.) was introduced over a period of 6 hours at the same temperature as before. On keeping over-night, the oxidation was found to be complete, and the product was isolated in the usual way. The yellow liquid thus obtained (1·13 g.) crystallised on the addition of ether. It was considered advisable, however, to distil the product in order to decompose any free acid that might be present. The product having been heated on a bath at 100—110°/0·05 mm. for 1¼ hours, the bath temperature was raised to 145—150°; the product then distilled smoothly at 115—120°/0·05 mm. as a colourless liquid which solidified, and the crystalline mass was drained on porous tile (m. p. 52—53°). It recrystallised from light petroleum (sparingly soluble) in very long needles melting sharply at 55°. A further recrystallisation produced no change in the melting point. The recrystallised material resembled glass wool in appearance, and analysis proved it to be trimethoxyxylonolactone, which must be the δ-lactone, since the normal trimethyl xylose gives rise on oxidation to trimethoxyglutaric acid (Hirst and Purves, *loc. cit.*) (Found : C, 50·8; H, 7·5; OMe, 48·9. Calc. for $C_8H_{14}O_5$, C, 50·5; H, 7·4; OMe, 48·9%). On titration the compound behaved as a lactone : 0·1025 g. required, on heating, 5·15 c.c. of *N*/10-sodium hydroxide (Calc. for $C_8H_{14}O_5$, 5·39 c.c.). The hydrolysis of the lactone in aqueous solution at room temperature ($c = 1·3289$) was followed polarimetrically : $[\alpha]_D^{15^\circ}$ −3·8° after 4 minutes, + 2·3° after 1½ hours, + 3·0° 4 hrs., + 6·9° 23 hrs., + 15·8° 4 days, + 19·5° 6 days, + 20·8° 8 days.

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