CCCCXVI.—*The Structure of the Normal Monosaccharides. Part V. Lyxose.*

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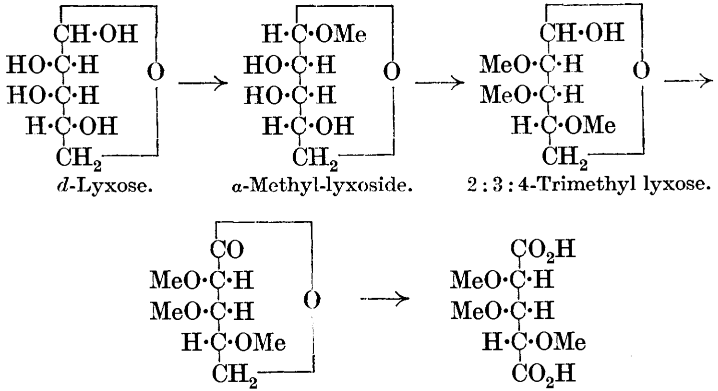
It has been shown (J., 1923, **123**, 1352 and subsequent papers) that when the normal trimethyl derivatives of xylose, arabinose, and rhamnose are oxidised by nitric acid the reaction leads in each case to the formation of a trimethoxyglutaric acid. This implies that in each of these three trimethyl pentoses the methoxyl groups are attached to the second, third, and fourth carbon atoms, and that the oxygen of the ring must be attached to the fifth carbon atom. The normal trimethyl pentoses are known to possess the same oxide ring structure as the corresponding normal methylpentosides, and it follows, therefore, that the normal forms of methylxyloside, methylarabinoside, and methylrhamnoside contain the amylene-oxide ring and belong to the pyranose group of sugar compounds.

Similar experimental methods have been now applied to determine the structure of α-methyl-lyxoside and definite proof has been obtained that this substance and its derivatives are of the pyranose type and thus conform to the general rule followed by normal sugar derivatives. Moreover, in view of the optical relationships which exist between the α-form of lyxose and α-methyl-lyxoside (Phelps and Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 503), this variety at least of the free sugar may be presumed to possess the pyranose structure. An examination of the structural relationships which exist between the α- and β-modifications of lyxose has been contributed in an earlier paper (Haworth and Hirst, this vol., p. 1221).

The normal trimethyl lyxose required for the oxidation experiments was prepared by methylating crystalline α-methyl-lyxoside with Purdie's reagents. This method of preparation ensures the formation of a *trimethyl methyl-lyxoside,* retaining the oxide ring structure of the original α-methyl-lyxoside. Other experiments showed that the same pyranose form of trimethyl methyl-lyxoside was produced by the direct methylation of lyxose with methyl sulphate. Hydrolysis of the trimethyl methyl-lyxoside gave crystalline *trimethyl lyxose,* m. p. 79°. The constitution of this substance as 2 : 3 : 4-trimethyl lyxose followed at once from a study of its oxidation by nitric acid, and also from the nature of the *trimethyl-lyxonolactone* obtained from it by the action of bromine water. The lactone, which was characterised by the preparation of the corresponding crystalline *phenylhydrazide,* m. p. 180—181°, displayed the behaviour typical of a δ-lactone. Polarimetric observations during its hydrolysis in aqueous solution showed that equilibrium was attained in about 60 hours, and that some 9% of the lactone then remained unchanged. When oxidised with nitric acid the lactone gave exclusively *d*-trimethoxyglutaric acid, which was identified both as the crystalline amide, the enantiomorph of which was originally prepared from *l*-arabinose (Hirst and Robertson, J., 1925, **127**, 358), and as the methylamide (Goodyear and Haworth, J., 1927, 3145; see also Haworth and Jones, *ibid.*, p. 2349).



d-Lyxose. α-Methyl-lyxoside. 2 : 3 : 4-Trimethyl lyxose.

Trimethyl-δ-lyxonolactone. *d*-Trimethoxyglutaric acid.

These results were in themselves sufficient to warrant the allocation of the pyranose structure to α-methyl-lyxoside, but in order to render the evidence as strong as possible, experiments were made to determine the effect of nitric acid on trimethyl methyl-lyxoside. The product of the reaction was again *d*-trimethoxyglutaric acid, the pure distilled methyl ester of which was obtained in yields corresponding to 80% of the theoretical. From the ester 88% of the theoretical quantity of pure crystalline *d*-trimethoxyglutaramide was isolated. Since the methylation of methyl-lyxoside proceeded almost quantitatively, it follows that by this method, in spite of the lengthy series of operations involved, some 70% of the calculated quantity of *d*-trimethoxyglutaramide can be obtained from methyl-lyxoside. Control experiments have shown that, under the experimental conditions adopted, nitric acid is without appreciable effect on the products of oxidation, and no product other than trimethoxyglutaric acid could be detected in the present case. In none of the numerous investigations in which this mode of oxidation has been employed has there been any sign of the migration of methoxy-groups under the influence of nitric acid, and the results obtained are both mutually consistent and in agreement with the evidence furnished by independent chemical methods of examination.

Emphasis is laid on the foregoing considerations in view of the total disagreement which exists between the conclusions now drawn from the chemical evidence and the views of Phelps and Hudson (*loc. cit.*), who assign to α-methyl-lyxoside and its derivatives a butylene-oxide formula. These authors have compared the molecular rotations of the two pairs of epimeric substances α-methyl-lyxoside and α-methylxyloside, and α-methylmannoside and α-methylglucoside. They find between each pair a difference in $[M]_D$ of about 15,500 units, which is taken to indicate the existence of similar structural relationships between the members of each pair, a conclusion with which the experimental results now presented are in complete agreement. Since, however, they regard α-methylxyloside and α-methylmannoside as 1 : 5-oxides and α-methylglucoside as a 1 : 4-oxide, it is argued that α-methyl-lyxoside must be similar in structure to α-methylglucoside and therefore a 1 : 4-oxide. In a later paper (*J. Amer. Chem. Soc.*, 1928, **50**, 2049) they reach similar conclusions from a study of the rotations of the acetylated derivatives of these four methyl-glycosides, the α-methylglucoside used for comparison being now the hypothetical 1 : 5-compound whose rotation has been calculated by Hudson. It is obvious that the validity of this mode of reasoning is dependent on the certainty with which the furanose structure can be assigned to α-methylglucoside and the pyranose structure to its hypothetical isomeride. It will be remembered that as a basis for the argument used in demonstrating the presence of a 1 : 4-ring in α-methylglucoside Hudson (*J. Amer. Chem. Soc.*, 1926, **48**, 1424, 1434) accepted the pyranose structure of α-methylxyloside and of α-methylarabinoside on the ground that it had been established experimentally by oxidation methods. It is evident, therefore, that experiments of a precisely similar nature carried out with α-methyl-lyxoside would provide a critical test of the accuracy of the optical method in assigning ring structures. These experiments have now been performed, and the results permit of no reasonable interpretation other than that α-methyl-lyxoside possesses a pyranose structure. A furanose structure was, however, deduced from the optical data and an obvious inconsistency is thus made manifest, which can be removed most simply by accepting the chemical evidence for the pyranose structure of α-methylglucoside. If this be done, the optical relationships existing between the four methylglycosides considered by Phelps and Hudson then agree with the chemical evidence in supporting the pyranose structure of all these compounds. It thus follows that the observations now recorded lend additional support to the reasons which have already been advanced (Drew and Haworth, J., 1926, 2303; Haworth and Hirst, *loc. cit.*) for doubting the validity of certain assumptions made by Hudson in deducing the furanose structure of α-methylglucoside.

EXPERIMENTAL.

Trimethyl Methyl-lyxoside.—Crystalline methyl-lyxoside (m. p. 109°) (7·2 g.) was dissolved in methyl iodide (20 c.c.) and treated with silver oxide (35 g.) in the usual manner. After the fourth successive methylation under these conditions the product was distilled, giving *trimethyl methyl-lyxoside* as a colourless mobile oil (8·7 g.), b. p. about 70°/0·02 mm., $n_{\rm D}^{14^\circ}$ 1·4460, $[\alpha]_{5461}^{20^\circ}$ + 10° in water (c = 2·61), $[\alpha]_{5461}^{20^\circ}$ + 37·3° in alcohol (c = 4·05). The substance, which possessed typical glucosidic properties, resisted all attempts to crystallise it. The absence of oxidation products in the form of lactones or esters was proved by heating a weighed portion (0·196 g.) for 30 minutes with 5 c.c. of N/10-sodium hydroxide, 5 c.c. of N/10-sulphuric acid being then required to titrate the remaining alkali. The mode of preparation and its specific rotation indicated that the trimethyl methyl-lyxoside consisted largely of the α-isomeride (Found: C, 51·8; H, 8·7; OMe, 58·8. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 60·2%).

Trimethyl Lyxose.—Trimethyl methyl-lyxoside (4·0 g.) was hydrolysed by heating it at 100° with 6% aqueous hydrochloric acid (120 c.c.). In the course of one hour the specific rotation altered from $[\alpha]_{5461}^{20^\circ}$ + 7° to a constant value $[\alpha]_{5461}^{20^\circ}$ − 19°. The hydrochloric acid was then neutralised with barium carbonate and the *trimethyl lyxose* was extracted from the solution by chloroform. The product (3·6 g.) was distilled, giving a mobile, colourless liquid, (3·3 g.), b.p. 90°/0·05 mm., $n_{\rm D}^{15^\circ}$ 1·4629. After being kept for 12 hours, the distillate became viscid and finally set to a solid glass, which crystallised when rubbed. In subsequent experiments the distillation was omitted and the trimethyl lyxose crystallised when nucleated (yield, 85%). Recrystallisation from light petroleum gave trimethyl lyxose in long needles, m. p. 79°, $[\alpha]_{\rm D}^{20^\circ}$ − 22° in water (equilibrium value; c = 2·01) (Found: C, 50·0; H, 8·4; OMe, 48·2. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3; OMe, 48·4%).

The mutarotation of normal trimethyl lyxose was rapid in aqueous solution, the equilibrium value being reached in less than 30 minutes at 21°. The following table gives the details of a typical experiment (c = 2·01).

Time (mins.)	1·5	3·3	4·3	6·0	7·8	10·0
$[\alpha]_{\rm D}^{21^\circ}$	−11·9°	13·4°	14·4°	14·9°	15·9°	17·4°
Time (mins.)	11·8	15	20	28	250	
$[\alpha]_{\rm D}^{21^\circ}$	17·8°	19·4°	21°	21·8°	21·8°	

From these figures the initial rotation was calculated to be $[\alpha]_{\rm D}^{21}$ − 10°, and the mean value for $k_1 + k_2$ was found to be 0·045 (t in mins.). Observations were made of the specific rotation in methyl alcohol containing 1% of hydrogen chloride before and after heating the solution. The values were respectively $[\alpha]_{\rm D}^{20^\circ}$ − 7·1° (c = 0·77) and $[\alpha]_{\rm D}^{20^\circ}$ + 21° (c = 0·83). In the latter case the concentration is that of the trimethyl methyl-lyxoside formed during the reaction and the observation gives the specific rotation of the equilibrium mixture of the α- and β-isomerides of normal trimethyl methyl-lyxoside.

Methylation of Lyxose with Methyl Sulphate.—Lyxose (10 g.), dissolved in the least possible amount of water, was treated with methyl sulphate (76 c.c.) and 50% aqueous sodium hydroxide solution (140 c.c.), the usual precautions being taken. The product (12 g.) was then subjected to two successive methylations with methyl iodide and silver oxide. On distillation, trimethyl methyl-lyxoside was obtained as a colourless oil (10·6 g.), b. p. about 70°/0·02 mm., $n_D^{14°}$ 1·4471, $[\alpha]_D^{20°}$ − 6° in methyl alcohol (c = 1·44). After being heated with methyl alcohol containing 1% of hydrogen chloride, the trimethyl methyl-lyxoside gave as the equilibrium value $[\alpha]_D^{20°}$ + 20·6°. The trimethyl methyl-lyxoside prepared in this manner therefore contained excess of the β-isomeride, and gave the same equilibrium value for the specific rotation as normal trimethyl methyl-lyxoside (Found: OMe, 58·8. Calc.: OMe, 60·2%). Further evidence confirming the absence of the furanose isomeride was obtained in the following way. During hydrolysis with 6% aqueous hydrochloric acid, the rotation of the solution changed to $[\alpha]_D^{20°}$ − 22° (calculated as trimethyl lyxose), which is very near to the value recorded for normal trimethyl lyxose, and the yield of crystalline trimethyl lyxose, m. p. 79°, isolated after hydrolysis was 90% of the theoretical.

Trimethyl-lyxonolactone.—A solution of trimethyl lyxose (9 g.) in water (60 c.c.) was treated with bromine (8—10 c.c.), the bromine being added gradually and the temperature maintained at 35° until the reducing properties of the solution had disappeared. This required several days, after which the excess of bromine was removed by aëration. The solution was then neutralised with silver oxide and filtered and the dissolved silver was removed as silver chloride by addition of the exact quantity of hydrochloric acid, the end-point being determined with the aid of Congo-paper. The water was then removed under diminished pressure. The residual syrup was heated at 100°/12 mm. for some hours to complete lactonisation and was then distilled, giving *trimethyl-δ-lyxonolactone* as a liquid, b. p. 105°/0·02 mm., $n_D^{18°}$ 1·4620 (yield, 8·0 g.). $[\alpha]_D^{19°}$ + 35·5° (initial value); $[\alpha]_D^{19°}$ − 9·3° (equilibrium value), both in water (c = 1·2) (Found: C, 50·3; H, 7·4; OMe, 49·1. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 48·9%). 0·1232 G. of the substance required 7·0 c.c. of N/10-sodium hydroxide for neutralisation (calc., 6·9 c.c.).

The lactone, although analytically pure, could not be made to crystallise. When, however, it was heated on the water-bath with the exact quantity of phenylhydrazine dissolved in a little ether, it readily formed the crystalline phenylhydrazide of the corresponding acid. The solid product (yield 80%), after being washed with ether, was found to be the pure *phenylhydrazide* of 2 : 3 : 4-trimethyl-lyxonic acid, m. p. 180—181°, remaining unaltered after two recrystallisations from benzene (Found : C, 56·5; H, 7·7; N, 9·6; OMe, 30·9. $C_{14}H_{22}O_5N_2$ requires C, 56·3; H, 7·4; N, 9·4; OMe, 31·2%).

Attempts to obtain the lactone in a crystalline condition by regenerating it from the crystalline phenylhydrazide yielded material identical with that described above.

Hydrolysis of the lactone. The velocity of hydrolysis in aqueous solution was determined by polarimetric observation, the mean value for $k_1 + k_2$ being 0·027 at 19° (*t* in hours). Equilibrium was reached in about 3 days at 19°. The rotation of the corresponding acid was obtained in the following manner. A weighed amount of the lactone was dissolved in excess of standard sodium hydroxide solution. The exact amount of sulphuric acid equivalent to the alkali was added, and the rotation was observed immediately; $[\alpha]_D^{19°}$ — 13·4° (calc. as lactone). The proportion of lactone present at equilibrium was therefore 9·1%.

t (hrs.).	$[\alpha]_D^{19°}$.	% Lactone.	*t* (hrs.).	$[\alpha]_D^{19°}$.	% Lactone.
0	+35·5°	100	51·5	−7·7°	12·4
18·0	5·1	38·3	66·5	9·3	9·1
27·8	− 0·8	26·4	90·5	9·3	9·1
42·5	6·1	15·6	200	9·3	9·1

Oxidation of Trimethyl-lyxonolactone.—A solution of the lactone (1·6 g.) in nitric acid (*d* 1·42; 25 c.c.) was heated gently on the water-bath until the vigorous reaction had ended, and then for 1½ hours at 90°. The nitric acid was removed by distillation under diminished pressure, and the syrupy residue boiled for 5 hours with 3% methyl-alcoholic hydrogen chloride (25 c.c.). The solution, after being neutralised with silver oxide, was evaporated to a syrup, which gave on distillation methyl trimethoxyglutarate (1·6 g., or 76% of the theoretical), b. p. about 100°/0·1 mm., $n_D^{21°}$ 1·4353, $[\alpha]_D^{20°}$ — 39° in methyl alcohol ($c = 0·4$), $[\alpha]_D^{20}$ — 31° in water ($c = 1·51$) (Found : OMe, 59·0; CO_2Me, by titration, 46·2. Calc.: OMe, 62·0; CO_2Me, 47·2%). Treatment of the ester with methyl-alcoholic ammonia gave trimethoxyglutaramide, m. p. 230° (decomp.), $[\alpha]_D^{20°}$ — 49° in water ($c = 0·7$). Methyl-alcoholic methylamine gave similarly the methylamide, m. p. 171—172° alone or when mixed with a specimen of the methylamide of the trimethoxyglutaric acid obtainable from tetramethyl-δ-mannonolactone (Goodyear and Haworth, *loc. cit.*). The high yields of pure amide and methylamide (in each case, more than 70% of the theoretical) served to prove the homogeneity of the liquid ester.

Additional oxidation experiments were performed in order to determine the largest possible yields of crystalline trimethoxyglutaramide obtainable from α-methyl-lyxoside. For this purpose trimethyl methyl-lyxoside (prepared as above from α-methyl-lyxoside) was heated with nitric acid (*d* 1·42) under conditions exactly similar to those given above for the oxidation of the trimethyl-lyxonolactone. In this way 1·6 g. of trimethyl methyl-lyxoside gave 1·7 g. of distilled methyl trimethoxyglutarate, $n_D^{20°}$ 1·4355, $[\alpha]_D^{20°}$ – 34° in water (c = 1·3).

The values now recorded of $[\alpha]_D^{20°}$ for methyl trimethoxyglutarate are regarded as more nearly correct than those given in earlier papers (compare Hirst and Robertson, *loc. cit.*; McOwan, J., 1926, 1747). Dilute nitric acid was used in the previous work and it is probable that the ester then obtained contained a little trimethyl-δ-arabonolactone, insufficient in amount to affect the analyses but sufficient, owing to the exceedingly large rotation of the lactone, to affect the observed rotation value. That no racemisation or structural change has occurred in the present experiment is proved by the fact that nearly theoretical yields (88%) of the crystalline amide, m. p. 230° (decomp.), were obtained when the ester was treated with methyl-alcoholic ammonia. The specific rotation of this amide, $[\alpha]_D^{20°}$ – 49° in water (c = 0·9), agreed exactly with the observations previously recorded. The overall yield of amide from α-methyl-lyxoside was therefore 70%. The corresponding methylamide, m. p. 171—172°, was also prepared from the ester (yield 80%).

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