162. *Methylation of β-Methylglucopyranoside and αβ-Methylxylopyranosides by Thallous Hydroxide and Methyl Iodide.*

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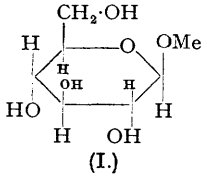
Methylation of β-methyl-*d*-glucopyranoside by the thallous hydroxide–methyl iodide process gives some of the fully methylated product, in addition to trimethyl β-methyl-*d*-glucopyranoside, when excess of thallous hydroxide is used in the formation of the thallium derivative of the sugar. The trimethyl β-methyl-*d*-glucopyranoside fraction contains all the four possible isomers (2 : 4 : 6; 2 : 3 : 6; 2 : 3 : 4; 3 : 4 : 6, with the 2 : 4 : 6 derivative preponderating), in proportions similar to those obtained by the methylation of α-methyl-*d*-glucoside by the thallous hydroxide–methyl iodide process (Barker, Hirst, and Jones, *J.*, 1938, 1695). The position of the methoxyl group on C_1 in methylglucopyranoside does not, therefore, significantly affect the orientation taken up by the thallium atoms in the formation of trithallium methyl-*d*-glucopyranoside.

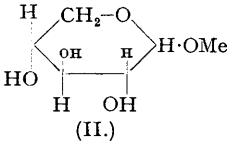
Methylation of a mixture of α- and β-methyl-*d*-xylosides by the same process gives trimethyl methyl-*d*-xyloside and dimethyl methyl-*d*-xyloside. The dimethyl methyl-*d*-xyloside is a mixture of all three possible sugars in which 2 : 4-dimethyl methyl-*d*-xyloside predominates. In view of the bulky nature of the thallium atom and the spatial position of the hydroxyl groups, these results are in agreement with expectation and similar to those obtained in the methylation of the methyl-*d*-glucopyranosides.

It has already been shown that methylation of α-methyl-*d*-glucopyranoside (I) by means of the thallous hydroxide–methyl iodide method (Menzies, *J.*, 1926, 937) gives tetramethyl α-methyl-*d*-glucopyranoside and trimethyl α-methyl-*d*-glucoside. The latter was a mixture of all four possible isomers (Barker, Hirst, and Jones, *loc. cit.*), in the proportions 2 : 4 : 6-trimethyl *d*-glucose, *ca.* 50%; 2 : 3 : 6-trimethyl *d*-glucose, *ca.* 36%; 3 : 4 : 6-trimethyl *d*-glucose, *ca.* 10%; 2 : 3 : 4-trimethyl *d*-glucose, *ca.* 4%.

The methylation of β-methyl-*d*-glucopyranoside (I) by thallous hydroxide–methyl iodide has now been shown to follow a very similar course; the trimethyl β-methylglucoside fraction contains all four isomers in the following proportions: 2 : 4 : 6, *ca.* 62%; 2 : 3 : 6, *ca.* 20%; 3 : 4 : 6, *ca.* 15%; and 2 : 3 : 4, *ca.* 3%. In both cases the amount of 2 : 4 : 6-trimethyl methylglucoside preponderated. This procedure can be utilised as a method for the preparation of the somewhat inaccessible 2 : 4 : 6-trimethyl glucose. Comparison of these figures with those obtained when the α-methylglucoside was methylated show that, within the limits of experimental error, the position of the glycoside methoxyl had little effect upon the positions taken up by the thallium atoms in the original trithallium methylglucoside.

Xylopyranose differs from glucopyranose only in the absence of a side chain on C_6. It was of interest, therefore, to determine the positions taken up by the thallium atoms in the methylation of methyl-*d*-xyloside by the thallium hydroxide method. Since preparations of pure α- or β-methyl-*d*-xyloside are not readily available and the position of the glycosidic methoxyl group in the methylglucosides had little, if any, effect on the positions occupied by the thallium atoms, a mixture of α- and β-methylxylopyranosides, containing some 42% of the α-derivative, was used in the present experiments. An examination of the structural formula of


(I.)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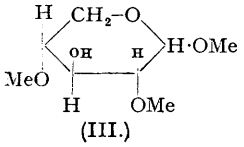
(III.)

methyl-*d*-xyloside (II) shows that the hydrogen atoms on the hydroxyl groups on C_2 and C_4 are most likely to be substituted since they are the greatest distance apart, and the thallium atoms in these positions are therefore least likely to interfere with one another. 2 : 4-Dimethyl methyl-*d*-xyloside (III) is therefore likely to be formed preferentially, and the experimental results showed that this was indeed the case. 2 : 4-Dimethyl xylose has not hitherto been prepared but the method now described renders it reasonably accessible. Proof of its structure rests on the following observations. (*a*) It is not identical with either of the known dimethyl xylopyranoses (2 : 3- and 3 : 4-). (*b*) On oxidation with bromine it yields a *pyranolactone*, the amide from which gives a negative Weerman test. Methyl groups are therefore present on C_2 and C_4.

Experimental.

Methylation.—β-Methylglucoside (m. p. 105°; $[\alpha]_D^{20°}$ −34° in water, *c*, 1·0) (24·7 g.) was dissolved in water (15 c.c. and added to a solution of 1·6N-thallous hydroxide (600 c.c.) which had been concentrated to a small volume (about 100 c.c.). The precipitate was filtered off, washed, dried, and then digested with boiling methyl iodide (for further details see Barker, Hirst, and Jones, *loc. cit.*). A syrup (24·3 g.), $n_D^{20°}$ 1·4462, was isolated and distilled in a vacuum giving the following fractions:

Fraction I. Tetramethyl β-methylglucoside (14·32 g.) (Found: OMe, 60·8%).
Fraction II. Mixed methylated methylglucosides (2·86 g.) (Found: OMe, 57·7%).
Fraction III. Trimethyl β-methylglucoside (5·19 g.) (Found: OMe, 51·2%).
Residue. 1·39 g.

Fraction III crystallised. A portion (3·69 g.) was recrystallised from light petroleum (b. p. 40—60°) and gave 2 : 4 : 6-trimethyl β-methylglucoside (1·32 g.), m. p. 66°; mixed m. p. with an authentic specimen, 67°. The residual syrup (2·12 g.) was hydrolysed with 8% hydrochloric acid and the sugar (*A*) (1·62 g.) was isolated in the usual manner.

Estimation of 2 : 3 : 6-*Trimethyl Glucose in the Syrup* (*A*).—A portion of the syrup dissolved in 1% methyl alcoholic hydrogen chloride showed $[\alpha]_D^{20°}$ +72° (initial value); +69° (½ hour); 66° (1 hour); 61° (2 hours); 55° (3 hours); 51° (4 hours); 46° (6 hours); 43° (7·5 hours); 40° (9 hours); 38° (constant value, 24 hours). Under similar conditions 2 : 3 : 6-trimethyl *d*-glucose shows a change from $[\alpha]_D^{20°}$ +73° to −31°; this gives 32% as the amount of 2 : 3 : 6-trimethyl *d*-glucose present in the syrup (*A*). (Calc. on the weight of Fraction III, 20%.)

Estimation of 3 : 4 : 6-*Trimethyl* d-*Glucose*.—A portion of the syrup (*A*) was oxidised with bromine water and the resultant mixture of lactones isolated in the usual manner after distillation. (Yield 83%; Found: OMe, 41·5; equiv. wt., 217. Calc. for $C_9H_{16}O_6$: OMe, 42·3%; equiv. wt., 220.) The lactones were converted into the amides by solution in liquid ammonia. The mixed amides (51 mg.) gave, on treatment with sodium hypochlorite followed by semicarbazide, the hydrazodicarbonamide (2·4 mg.), which, assuming a 40% yield in the reaction (see Hirst and Jones, *J.*, 1938, 496), implies the presence of 24% of 3 : 4 : 6-trimethyl *d*-glucose in syrup *A*, or 15% calculated on Fraction III.

Estimation of 2 : 3 : 4-*Trimethyl* d-*Glucose*.—This estimation was carried out by the method used previously. The mixed glucosides (1·35 g.) gave silver iodide (0·047 g.), after the *p*-toluenesulphonyl derivatives had been heated with sodium iodide, equivalent to the presence of 3% of the 2 : 3 : 4-isomer. From the above mentioned evidence the yields of the various isomerides were as follows:

2 : 4 : 6-Trimethyl β-methyl-*d*-glucoside (isolated as crystalline glucoside) (*ca.* 36%).
2 : 3 : 6-Trimethyl β-methyl-*d*-glucoside (*ca.* 20%).
2 : 3 : 4-Trimethyl β-methyl-*d*-glucoside (*ca.* 3%).
3 : 4 : 6-Trimethyl β-methyl-*d*-glucoside (*ca.* 15%).

The remainder (*ca.* 26%) consisted of 2 : 4 : 6-trimethyl β-methylglucoside which failed to crystallise and was not directly estimated.

The Action of Thallium Hydroxide on Methyl-d-*xyloside*.—Xylose was boiled under reflux with methyl alcoholic hydrogen chloride and the resulting mixture of methylxylopyranosides isolated in the usual manner and purified by distillation in a vacuum. B. p. 180°/0·01 mm. (bath temp.); $[\alpha]_D^{19°}$ +62° in water. The mixed xylosides (36·9 g.) were evaporated to dryness with 1·54N-thallous hydroxide (2·5 equivalents) under reduced pressure and in a stream of carbon dioxide-free air. The yellow thallium derivative thus obtained was dried, powdered, and converted into a mixture of methylated xylosides by boiling under reflux with excess of methyl iodide.

The methylated xylosides (40·6 g.) isolated in the usual manner were fractionally distilled giving:

Fraction I. Trimethyl methyl-*d*-xylosides (13·72 g.) (Found: OMe, 62·0%).
Fraction II. Dimethyl methyl-*d*-xylosides (20·0 g.) (Found: OMe, 48·3%).
Fraction III. Still residue, 6·90 g.

Fraction II (20·0 g.) was heated at 100° with 8% hydrochloric acid for 70 minutes; the solution was cooled, neutralised with barium carbonate, filtered, and evaporated to dryness. The dimethyl *d*-xylose was taken up in ether and was obtained as a syrup (16·9 g.) which partly crystallised. Trituration with acetone–light petroleum (b. p. 40—60°) gave β-2 : 4-*dimethyl* d-*xylose* (3·0 g.), m. p. 108° (Found: C, 47·2; H, 7·9; OMe, 34·8. $C_7H_{14}O_5$ requires C, 47·1; H, 7·9; OMe, 34·5%). In aqueous solution the sugar showed mutarotation as follows: $[\alpha]_D^{20°}$ −30° (initial value); −16° (7 mins.); −8° (10 mins.); −1° (15 mins.); +4° (20 mins.); 9° (25 mins.); 13° (30 mins.); 15° (40 mins.); 19° (55 mins.); 22° (constant value, 24 hours).

On boiling with alcoholic aniline, the sugar gave 2 : 4-*dimethyl* d-*xylose anilide*, m. p. 170°; $[\alpha]_D^{20°}$ −82° (in dioxan) (Found: C, 61·4; H, 7·7; N, 5·5; OMe, 23·3. $C_{13}H_{19}O_4N$ requires C, 61·8; H, 7·5; N, 5·8; OMe, 24·5%). Oxidation of the sugar (1 g.) with bromine (1 c.c.) in water (6 c.c.) at 50° for 4 hours gave 2 : 4-*dimethyl* d-*xylonic acid* isolated, in the usual manner, as a syrup which on distillation in a vacuum gave 2 : 4-*dimethyl* d-*xylopyranolactone*, $n_D^{20°}$ 1·4768; $[\alpha]_D^{20°}$ +23° (in chloroform). The lactone mutarotated in water at a rate characteristic of a pyranolactone, $[\alpha]_D^{20°}$ −15° (initial value); −13° (1 hour); −11° (2 hours); −9° (3 hours); −6° (5 hours); +19° (23 hours); +28° (45 hours); +30° (constant value). (Found: C, 47·7; H, 7·0; OMe, 34·8; equiv. wt., 176. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 35·2%; equiv. wt., 176).

The amide, prepared from the lactone by dissolving it in liquid ammonia and allowing excess ammonia to evaporate, was a syrup which gave a negative Weerman reaction proving the presence of a methoxyl group on C_2.

Examination of the Syrup Remaining after Removal of Crystalline 2 : 4-*Dimethyl* d-*Xylose*.—The mixed lactones were prepared fom the syrupy sugars by the usual method (yield, 80%) (Found: OMe, 35·0; equiv. wt., 173. Calc. for $C_7H_{12}O_5$: OMe, 35·2%; equiv. wt., 176). $[\alpha]_D^{20°}$ +17° ⟶ + 47° (48 hours, constant value).

Reaction of the mixed lactones with liquid ammonia gave a non-crystalline mixture of amides which gave a positive Weerman reaction. The mixed amides (73 mg.) were treated with sodium hypochlorite followed by the addition of semicarbazide after the removal of excess of hypochlorite. The precipitated hydrazodicarbonamide was filtered off, dried, and weighed (yield, 7·6 mg.). This corresponds to the presence of some 8% of 3 : 4-dimethyl *d*-xylose in Fraction II (above) assuming a yield of 40% of the theoretical in the yield of hydrazodicarbonamide.

2 : 3-Dimethyl *d*-xylonolactone mutarotates in water from $[\alpha]_D^{20°}$ +97° ⟶ + 86° (48 hours), 2 : 4-dimethyl *d*-xylonolactone from $[\alpha]_D^{20°}$ −15° ⟶ + 30° (equilibrium value), and the 3 : 4-isomer from $[\alpha]_D^{20°}$ −56° ⟶ − 34° (48 hours) ⟶ −27° (equilibrium value) (James and Smith, *J.*, 1945, 744) in 65 hours. These rotational figures (equilibrium values) taken in conjunction with the estimated yield of 3 : 4-dimethyl *d*-xylose (from the yield of hydrazodicarbonamide) indicate the presence of some 39% of 2 : 3-dimethyl *d*-xylose in the syrup or of 32% of the sugar in Fraction II.

These results indicate that the dimethyl methylxyloside fraction contains the following sugars in the approximate percentages indicated:

2 : 4-Dimethyl *d*-xylose. Isolated as crystals (*ca.* 18%).
2 : 4-Dimethyl *d*-xylose. Non-crystalline, by difference (*ca.* 43%).
3 : 4-Dimethyl *d*-xylose. From yield of hydrazodicarbonamide in Weerman test (*ca.* 7%).
2 : 3-Dimethyl *d*-xylose. From lactone formation (*ca.* 32%).

In view of the uncertainty concerning the optical rotatory power of 3 : 4-dimethyl *d*-xylonolactone (cf. Mullen and Percival, *J.*, 1940, 1504) the percentages given above are regarded as approximate only and the proportion of the 2 : 4-isomeride may be some 8% higher than that stated. The general position, however, remains unaltered.

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