388. 2 : 3 : 4-*Trimethyl Mannose.*

By W. N. Haworth, E. L. Hirst, F. Isherwood, and J. K. N. Jones.

2 : 3 : 4-Trimethyl *d*-mannose has been synthesised from 6-trityl α-methyl-*d*-mannoside by a method which leaves no doubt as to the constitution of the product. The sugar has been converted into 2 : 3 : 4-trimethyl *d*-mannonolactone, 2 : 3 : 4-*trimethyl* d-*mannonamide*, and 2 : 3 : 4-*trimethyl* d-*mannosaccharodiamide*. The properties of these compounds are recorded.

A TRIMETHYL hexose, the properties of which pointed to its being 2 : 3 : 4-trimethyl *d*-mannose, was obtained by hydrolysis of methylated mannocarolose (Haworth, Raistrick, and Stacey, *Biochem. J.*, 1935, **29**, 612) and also by hydrolysis of methylated yeast mannan (Haworth, Hirst, and Isherwood, J., 1937, 784). We have now synthesised 2 : 3 : 4-trimethyl *d*-mannose by a method which leaves no doubt concerning the positions of the substituent methyl groups and the substance so obtained differs markedly in its properties from the specimens hitherto supposed to be 2 : 3 : 4-trimethyl mannose. It follows that, in so far as the trimethyl mannose residues are concerned, there is now some uncertainty concerning the molecular structure of both methylated mannocarolose and methylated yeast mannan and further investigations are in progress on both polysaccharides.

The synthesis was effected by the following stages : (*a*) α-Methylmannopyranoside was transformed into the 6-trityl derivative, the identity of which was proved by Watters, Hockett, and Hudson (*J. Amer. Chem. Soc.*, 1939, **61**, 1529), their paper appearing while our work was in progress. (*b*) The 6-trityl derivative was methylated by the thallium method (Hirst and Jones, J., 1938, 1174), giving 6-trityl 2 : 3 : 4-trimethyl α-methylmannoside. (*c*) Removal of the trityl group by the method of Kuhn, Rudy, and Weygand (*Ber.*, 1936, **69**, 1546) gave 2 : 3 : 4-trimethyl α-methylmannoside, which on hydrolysis gave 2 : 3 : 4-trimethyl *d*-mannose. Further proof of the constitution of this trimethyl mannose was obtained by its oxidation to 2 : 3 : 4-trimethyl mannonolactone, isolated as its crystalline *monohydrate*. In this connection it is of interest that the crystalline substance, as shown by its rotation and by its ready conversion into 2 : 3 : 4-*trimethyl mannonamide*, was genuinely the lactone containing water of crystallisation and not the corresponding acid, which would, of course, have the same analytical composition.

Oxidation of the 2 : 3 : 4-trimethyl mannose with nitric acid gave 2 : 3 : 4-trimethyl mannosaccharic acid, isolated in the form of its crystalline *diamide*, which gave a strong positive Weerman reaction. It follows that there must be a hydroxyl group at C_2 or C_5 and since α-methylmannopyranoside is known to have C_5 engaged in ring formation and the hydroxyl at C_5 is incapable of undergoing methylation, it follows that the hydroxyl group revealed by the Weerman reaction is situated at C_5 and the amide must therefore have its three methoxyl groups at C_2, C_3, and C_4. This proves the constitution of the 2 : 3 : 4-trimethyl mannose. 2 : 3 : 4-Trimethyl mannosaccharodiamide displays a negative rotation in water in agreement with the Hudson rotation rule for amides, but 2 : 3 : 4-trimethyl *d*-mannonamide has a positive rotation in water and does not follow the rule (compare Harris, Hirst, and Wood, J., 1935, 1658). Further examination of the diamide (m. p. 191°) previously designated 2 : 3 : 4-trimethyl mannosaccharodiamide has revealed that this substance has a very strong lævorotation in water ($[\alpha]_D - 73°$ as compared with $- 14°$ for the genuine material) and does not give a positive Weerman reaction. It cannot therefore have been derived from a 2 : 3 : 4-trimethyl hexose.

EXPERIMENTAL.

(1) 6-*Trityl* α-*Methyl*-d-*mannoside* (compare Watters, Hockett, and Hudson, *loc. cit.*).—α-Methyl-*d*-mannoside (11·4 g.) was dissolved in dry pyridine (100 c.c.) containing trityl chloride (20 g.) and kept at 25° during 20 hours. The yellow solution was poured on ice and stirred until the oil had solidified. The solid (16·2 g.) was washed by decantation, ground to a powder, and dried over phosphoric oxide. It was very difficult to remove the last traces of pyridine from the solid. Trityl α-methyl-*d*-mannoside, m. p. 100°, $[\alpha]_D^{20°} + 20°$ (*c*, 1·1 in chloroform), is very soluble in alcohol, ether, acetone, nitrobenzene and benzene, and insoluble in light petroleum and water. In agreement with Watters, Hockett, and Hudson (*loc. cit.*) it gave a calcium chloride derivative, m. p. 110° after recrystallisation from alcohol.

(2) 6-*Trityl* 2 : 3 : 4-*Trimethyl* α-*Methyl*-d-*mannoside*.—The crude solid (above) was dissolved in benzene containing thallous ethoxide (5 equivs.), the solvent removed at 40°/12 mm., and the residual solid dried in a desiccator, powdered, and boiled with methyl iodide until the solid no longer had an alkaline reaction. Methyl iodide was then boiled off, and the residue extracted with acetone. Concentration of the acetone gave a syrup, which was methylated with Purdie's reagents. The 6-trityl trimethyl α-methyl-*d*-mannoside (16·8 g.) was isolated in the usual manner as a syrup which crystallised immediately. The solid was not recrystallised owing to difficulties arising from its great solubility in all the common organic solvents except light petroleum. M. p. 106—110° (crude material); $[\alpha]_D^{20°} + 33°$ (*c*, 1·04 in chloroform); OMe, 19·3%.

(3) 2 : 3 : 4-*Trimethyl* α-*Methyl*-d-*mannoside*.—The trityl trimethyl α-methyl-*d*-mannoside

(12·0 g.) was hydrolysed by boiling a solution in glacial acetic acid (100 c.c.) under reflux with gradual addition of water (40 c.c.) (method of Kuhn, Rudy, and Weygand, *Ber.*, 1936, **69**, 1546). The cooled solution was filtered from triphenylcarbinol and evaporated to a syrup, which was extracted with ether; the extract was concentrated to a syrup (7·40 g.), which was distilled in a vacuum, giving 2 : 3 : 4-*trimethyl α-methyl-*d*-mannoside* (6·62 g.), b. p. (bath temp.) 150°/0·005 mm., $n_D^{20°}$ 1·4605, $[\alpha]_D^{20°}$ + 38° (*c*, 3·9 in N-hydrochloric acid) (Found: OMe, 51·6. $C_{10}H_{20}O_6$ requires OMe, 52·6%). The colourless syrup (6·5 g.) was dissolved in 2N-hydrochloric acid (30 c.c.) and heated at 90° for 3 hours, the rotation then becoming constant at + 1°. The solution was neutralised with silver carbonate, filtered, and evaporated to a syrup. This was extracted with acetone, and the solution filtered from colloidal silver and concentrated, giving 2 : 3 : 4-trimethyl *d*-mannose (6·10 g.). $n_D^{18°}$ 1·4715, $n_D^{20°}$ 1·4705, $[\alpha]_D^{20°}$ + 2° (*c*, 5·9 in water). The sugar did not crystallise and gave no crystalline anilide or phenylhydrazone.

(4) 2 : 3 : 4-*Trimethyl* d-*Mannonolactone and the Corresponding Amide.*—Under the usual conditions, with bromine in dilute aqueous solution, the sugar underwent very slow oxidation to the corresponding lactone. On the other hand the reaction proceeded quickly and conveniently in concentrated solution. Accordingly the sugar (6·0 g.) was dissolved in water (10 c.c.), and bromine (10 c.c.) added; the mixture became hot and the bromine boiled. After 5 minutes, all the bromine had dissolved, giving a dark brown solution. After a further 14 hours at 40°, the excess of bromine was removed by aeration, and the solution worked up in the usual manner, giving the syrupy lactone (5·9 g.), $n_D^{20°}$ 1·4730, which was then esterified by boiling with 3% methyl-alcoholic hydrogen chloride (50 c.c.). When the ester was heated at 160°/0·005 mm., methyl alcohol was eliminated and the distillate consisted of 2 : 3 : 4-trimethyl *d*-mannonolactone (5·52 g.), b. p. 160° (bath temp.)/0·005 mm., $n_D^{20°}$ 1·4750. Trituration with moist ether gave crystalline 2 : 3 : 4-*trimethyl* d-*mannonolactone monohydrate*, m. p. 73°. $[\alpha]_D^{20°}$ + 138° (*c*, 2·25 in water after 5 mins.); 136° (2 hrs.); 134° (3¾ hrs.); 132° (4¾ hrs.); 131° (5½ hrs.); 125° (9¾ hrs.); 109° (22¾ hrs.); 106° (25 hrs.); 102° (29½ hrs.); 90° (46 hrs.); 87° (53 hrs.); 84° (71 hrs.); 83° (77 hrs.); 81° (95 hrs., constant) (Found: C, 45·3; H, 7·3; OMe, 40·0; equiv., 238. $C_9H_{16}O_6,H_2O$ requires C, 45·4; H, 7·7; OMe, 39·1%; equiv., 238).

The lactone on solution in liquid ammonia gave crystalline 2 : 3 : 4-*trimethyl* d-*mannonamide*, m. p. 143° (depressed to 105° on admixture with 3 : 4 : 6-trimethyl *d*-mannonamide). The amide gave a negative Weerman test and had $[\alpha]_D^{20°}$ + 5° (*c*, 0·8 in water) (Found: C, 45·6; H, 8·0; N, 5·9. $C_9H_{19}O_6N$ requires C, 45·6; H, 8·1; N, 5·9%).

(5) 2 : 3 : 4-*Trimethyl* d-*Mannosaccharamide.*—2 : 3 : 4-Trimethyl *d*-mannose (0·40 g.) was oxidised under the usual conditions with nitric acid (10 c.c., *d* 1·42), and the product worked up in the usual manner to give a syrup (0·35 g.), which was esterified with 2% methyl-alcoholic hydrogen chloride (20 c.c.). The resulting ester (0·34 g.), $n_D^{17°}$ 1·4480, was distilled in a vacuum, b. p. 140°(bath temp.)/0·001 mm. (0·30 g.). With methyl-alcoholic ammonia this ester gave in good yield 2 : 3 : 4-*trimethyl* d-*mannosaccharodiamide*, m. p. 228° (decomp.), $[\alpha]_D^{20°}$ − 17° (*c*, 0·46 in methyl alcohol), − 14° (*c*, 1·7 in water). The amide gave a strong positive Weerman test (Found: C, 43·2; H, 7·3; N, 11·0; OMe, 36·8. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%). The m. p. of the new amide on admixture with the amide previously described as 2 : 3 : 4-trimethyl mannosaccharodiamide (Haworth, Hirst, and Isherwood, *loc. cit.*) was depressed to 200° (not sharp).

The authors thank the Colston Research Society and Imperial Chemical Industries Ltd. for grants.

THE UNIVERSITY, BIRMINGHAM.
THE UNIVERSITY, BRISTOL.

[*Received, October 4th,* 1939.]