CCCLI.—*The Structure of Carbohydrates and their Optical Rotatory Power. Part IV. Derivatives of α- and β-Methylmannopyranoside.*

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THE direct methylation of mannose under conditions which are herein prescribed leads to the formation of a mixture of the α- and the β-form of tetramethyl methylmannopyranoside containing about 32% of the β-isomeride. Hydrolysis of this mixture yields tetramethyl mannopyranose, which is identified through the crystalline 2 : 3 : 4 : 6-tetramethyl δ-mannonolactone and the crystalline phenylhydrazide of the corresponding acid to which the lactone gives rise (Drew, Goodyear, and Haworth, J., 1927, 1243). The absence of mannofuranoside forms (Haworth and Porter, this vol., p. 649; Haworth, Hirst, and Webb, *ibid.*, p. 651) is indicated by the rate of hydrolysis of the above methylated mannosides in the presence of *N*/100-hydrochloric acid, hydrolysis proceeding only to a negligible extent. Whitnah and Milbery (*J. Amer. Chem. Soc.*, 1930, **52**, 1627) have attempted to estimate the amount of labile or γ-forms of mannosides by the agency of permanganate, a method we abandoned some years ago. α-Methylmannofuranoside and α- and β-ethylglucofuranosides are, in the pure crystalline condition, unaffected for long periods of time by neutral dilute permanganate solution in the cold, and their methylated derivatives are quite stable to this reagent.

It has been stated that mannose is an exception to the rule that a monosaccharide aldose yields a mixture of its α- and β-methylglycosides when heated with acidified methyl alcohol, and that this sugar proceeds nearly quantitatively to α-methylmannoside (C. S.

Hudson, *J. Amer. Chem. Soc.*, 1930, **52**, 1689). Contrary to this statement, we have now shown that mannose undergoes condensation by heating with 2% methyl-alcoholic hydrogen chloride with the formation of both the α- and the β-form of methylmannopyranoside, the β-form being identified as its crystalline tetra-acetate, which can be obtained in a yield of 37 g. from 100 g. of mannose. The β-derivative is also formed when mannose is condensed with methyl-alcoholic hydrogen chloride at 20° (Haworth, Hirst, and Webb, *loc. cit.*). It is identical with the compound isolated by Dale by a transformation of the condensation product of tetra-acetyl mannosidyl bromide with methyl alcohol (*J. Amer. Chem. Soc.*, 1924, **46**, 1046). This tetra-acetyl β-methylmannopyranoside is converted by alkali and methyl sulphate into crystalline *tetramethyl β-methylmannopyranoside*. The rate of hydrolysis of the latter substance is widely different from that of the furanoside form, but is comparable with that of the corresponding tetramethyl α-methylmannopyranoside. Both methylated pyranosides give rise to a mixture of α- and β-forms of tetramethyl mannopyranose, identified as the crystalline anilide. The m. p.'s of these methylated α- and β-mannopyranosides are similar, but their specific rotations are characteristically different. It has not been found possible to obtain the unsubstituted *β-methylmannopyranoside* in a crystalline form : the rotation value for the substance in aqueous solution is given. The simultaneous de-acetylation and methylation of tetra-acetyl α-methylmannopyranoside yields the crystalline tetramethyl α-methylmannopyranoside, and this substance and the β-isomeride already mentioned have been repeatedly crystallised in order to obtain the optimum values of their physical constants. A comparison of the two series of substances which have identical structures is as follows :

	α-Form.		β-Form.		
	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	
Tetra-acetyl methyl-mannopyranoside	65°	+49°	161°	−46·8°	(in chloroform)
Tetramethyl methyl-mannopyranoside	38—40	+43	36—37	−80	(in water)
		+57		−87	(in chloroform)
		+75·5		−82·5	(in ethyl alcohol)
		+77		−72	(in benzene)
Methylmanno-pyranoside	190	+79	—	−66	(in water)

The theoretical implications of these results are discussed in Part I (p. 2624).

The salient point of the present research is that the normal forms of α- and β-methylmannoside give rise on methylation and hydrolysis to one and the same tetramethyl mannose and that this yields the tetramethyl δ-mannonolactone (crystalline) which has been shown to

undergo epimerisation to tetramethyl gluconolactone. We hold, therefore, that the two methylmannosides have an identical six-atom ring structure, whereas Hudson has contended for a five-atom ring structure for the normal α-methylmannoside, and a six-atom ring structure for the normal β-methylmannoside (in the form of its acetate). Further, we have shown from the above figures that the same discrepancy in optical rotatory relationships which he has found to exist between α- and β-mannose and α- and β-methylmannoside derivatives corresponding to a deficiency of molecular rotation value of 8500 to 9000 as compared with the corresponding glucose derivatives, is also shown by the α- and β-forms of tetramethyl methylmannopyranoside described herein. On the ground of this deficiency Hudson has ascribed different rings to the mannoses and the methylmannosides, whilst he is apparently prepared to admit that one and the same structure applies to the α- and β-forms of tetramethyl methylmannoside. Although this discrepancy in molecular rotation values is shown in water by the latter pair of substances, it almost disappears when the rotations are taken in ethyl alcohol.

EXPERIMENTAL.

Tetra-acetyl β-Methylmannopyranoside.—A solution of mannose (10 g.) in 2% methyl-alcoholic hydrogen chloride (95 c.c.) was boiled for 1 hour and then kept at − 10° for several hours. After removal of the crystalline α-methylmannoside (6·1 g.) the acid was neutralised by lead carbonate and the filtered neutral solution was evaporated under diminished pressure to a mixture of syrup and crystals. Treatment with cold absolute alcohol separated the syrup from the solid α-methylmannopyranoside and on removal of the alcohol under diminished pressure crude β-methylmannopyranoside remained as a non-reducing uncrystallisable gum (3·5 g.) which still contained much of the α-isomeride. The rotation $[\alpha]_D^{18°}$ of the gum ranged from + 2° to − 25° (in ethyl alcohol), according to the proportion of the α-isomeride present.

The gum (4·5 g.) was acetylated in a mixture of pyridine (38 c.c.) and acetic anhydride (29 c.c.). After being kept for 2 days at − 5°, the solution was shaken vigorously with light petroleum (150 c.c.; b. p. 80—100°). Separation of crystalline material began at once and was complete in a few minutes. The solid was recrystallised from ethyl alcohol, giving tetra-acetyl β-methylmannopyranoside as rectangular plates (3·7 g.), m. p. 161°, $[\alpha]_D^{18°}$ − 46·8° in chloroform (*c*, 0·8) (Found: C, 50·0; H, 6·6; OMe, 8·5. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1; OMe, 8·6%). Dale (*loc. cit.*) recorded m. p. 162° and $[\alpha]_D$ − 46·8°.

β-*Methylmannopyranoside.*—When tetra-acetyl β-methylmannopyranoside (0·202 g.) was shaken with a slight excess of *N*/2-aqueous sodium hydroxide it dissolved with loss of four acetyl groups. The excess of alkali was then neutralised exactly, and the volume of the solution made up to 15 c.c. From its rotation, $\alpha_D^{21°}$ — 0·49° (l = 1), the value for β-methylmannopyranoside was approximately $[\alpha]_D^{21°}$ — 68° in water.

β-*Methylmannopyranoside* was prepared by the action of an excess of dimethylamine in methyl alcohol (75 c.c.) on tetra-acetyl β-methylmannopyranoside (4 g.) in a sealed tube at 100° for 4 hours. The alcohol and dimethylamine were removed by distillation, and the acetodimethylamide by sublimation at 110°/0·1 mm. The product (2 g.) was β-methylmannopyranoside in the form of a yellow glass which resisted crystallisation. $[\alpha]_D^{21°}$ — 66° in water (*c*, 1·05) in agreement with the above value (Found : C, 44·4; H, 7·5; OMe, 14·5. $C_7H_{14}O_6$ requires C, 44·3; H, 7·2; OMe, 15·9%).

The rate of hydrolysis of β-methylmannopyranoside in *N*/100-hydrochloric acid at 100° was extremely slow : $[\alpha]_D^{20°}$ — 64° (initial value); 59° (2 hours); 55° (4 hours); 50° (7 hours); 46° (10 hours). At this point the strength of acid was increased to *N*/10, but even under these conditions an additional 15 hours were required before hydrolysis was complete, $[\alpha]_D^{21°}$ + 15° (final constant value). The rate of hydrolysis was therefore of an entirely different order from that of α-methylmannofuranoside but comparable with that of the known methylpyranosides.

Tetramethyl β-*Methylmannopyranoside.*—(a) β-Methylmannopyranoside (1·65 g.) was dissolved in the minimum amount of water, acetone (15 c.c.) added, and methylation with methyl sulphate (20 c.c.) and 30% aqueous sodium hydroxide (40 c.c.) carried out at 50—55° in the usual manner. The product, after a second methylation, crystallised before distillation. It was purified by distillation under diminished pressure, giving *tetramethyl* β-*methylmannopyranoside* (1·8 g.), b. p. 110—112°/0·1 mm., $n_D^{18°}$ 1·4531 (supercooled liquid). This crystallised when cold and was recrystallised from cold light petroleum (b. p. 40—60°); it then melted at 36—37° and had $[\alpha]_D^{20°}$ — 80° in water (*c*, 1·0). A mixed m. p. determination with the material described below showed no depression.

(b) Tetra-acetyl β-methylmannopyranoside (4 g.), dissolved in acetone (30 c.c.), was treated at 50° with methyl sulphate (40 c.c.) and 30% aqueous sodium hydroxide (100 c.c.), a slightly alkaline reaction being maintained throughout. The product (2·4 g.) was treated with methyl iodide and silver oxide in the usual manner and was then distilled, giving tetramethyl β-methylmannopyranoside as a colourless mobile liquid (1·9 g.) which crystallised completely

when cold; b. p. about 90°/0·03 mm., $n_D^{17°}$ 1·4535 (supercooled liquid). Recrystallisation from a concentrated solution of the substance in light petroleum (b. p. 40—60°) in a freezing mixture gave long needles, m. p. 36—37°, $[\alpha]_D^{20°}$ — 79° in methyl alcohol (*c*, 0·52), $[\alpha]_D^{20°}$ — 80° in water (*c*, 1·0), $[\alpha]_D^{20°}$ — 87° in chloroform (*c*, 0·46), $[\alpha]_D^{20°}$ — 72° in benzene (*c*, 0·7), $[\alpha]_D^{20°}$ — 82° in ethyl alcohol (*c*, 0·4). The equilibrium rotation in 1% methyl-alcoholic hydrogen chloride was $[\alpha]_D^{20°}$ + 60°. The above rotation values remained unaltered after several successive crystallisations of the substance from light petroleum (Found: C, 52·8; H, 9·0; OMe, 60·5. $C_{11}H_{22}O_6$ requires C, 52·8; H, 8·8; OMe, 62%).

Hydrolysis. Tetramethyl β-methylmannopyranoside (0·5 g.) was hydrolysed by heating it for 6 hours at 80° with 6% hydrochloric acid: the specific rotation diminished regularly from the initial value $[\alpha]_D^{20°}$ — 78° to the constant value + 3°. After neutralisation with barium carbonate the solution was evaporated to dryness under diminished pressure and the solid residue was extracted with chloroform. Removal of the chloroform left tetramethyl mannopyranose as a viscid syrup (0·5 g.), the identity of which was proved by the preparation of its crystalline anilide. This was effected by boiling for 3 hours a solution of the syrup (0·5 g.) in alcohol (5 c.c.) containing freshly distilled aniline (0·5 c.c.). On removal of the solvent by distillation under diminished pressure a thick gum was obtained which soon crystallised. Recrystallisation from light petroleum (b. p. 80—100°) gave matted needles; these melted at 142—143°, alone or when mixed with authentic tetramethyl mannopyranose anilide prepared from the tetramethyl mannopyranose obtained by the hydrolysis of crystalline tetramethyl α-methylmannopyranoside (Irvine and McNicoll, J., 1910, **97**, 1452) (Found: C, 61·8; H, 8·3; N, 4·6; OMe, 39·3. Calc. for $C_{16}H_{25}O_5N$: C, 61·7; H, 8·0; N, 4·5; OMe, 39·9%).

Methylation of Mannose by Methyl Sulphate.—Mannose (30 g.) was treated in the usual way with methyl sulphate (120 c.c.) and 30% aqueous sodium hydroxide (300 c.c.), the temperature being kept below 35° until reducing properties had disappeared. Methylation was completed by the use of silver oxide and methyl iodide, giving a mixture of the α- and β-forms of tetramethyl methylmannopyranoside as a colourless syrup (23 g.), b. p. about 95°/0·14 mm., $[\alpha]_D^{21°}$ + 22° in methyl alcohol (*c*, 1·4), $[\alpha]_D^{21°}$ + 59°, equilibrium value in 5% methyl-alcoholic hydrogen chloride. Since the α- and β-forms of tetramethyl methylmannopyranoside have respectively $[\alpha]_D$ + 71° (Irvine and Moodie, J., 1905, **87**, 1462) and — 79° (see above), the methylated product contained about 32% of tetramethyl β-methylmannopyranoside (Found: OMe, 59·8%).

The absence of furanose derivatives was shown by the negligible rate of hydrolysis in $N/100$-hydrochloric acid at 90°. Hydrolysis was carried out by heating for 7½ hours at 95° with 6% hydrochloric acid. During this time the rise and fall in rotation characteristic of a mixture of α- and β-glycosides was observed, the final value being $[\alpha]_D^{20°}$ + 4°. Tetramethyl mannopyranose was obtained as a viscid oil, b. p. about 115°/0·03 mm., $n_D^{15°}$ 1·4631, $[\alpha]_D^{19°}$ + 28° in methyl alcohol (*c*, 1·1) (Found: C, 50·5; H, 8·8; OMe, 51·5%). This was transformed by the method of Drew, Goodyear, and Haworth (*loc. cit.*) into 2 : 3 : 4 : 6-tetramethyl δ-mannonolactone, which was isolated as crystalline material having properties identical with those already recorded. The lactone, dissolved in water, required 120 hours to attain the equilibrium value $[\alpha]_{5461}^{15°}$ + 70°: this remained unchanged for a further 400 hours, and the proportion of γ-lactone present was therefore negligible. The crystalline phenylhydrazide was also identical with that described in the earlier paper.

(With ROBERT STUART TIPSON.)

Simultaneous Deacetylation and Methylation of Tetra-acetyl α-Methylmannopyranoside.—Tetra-acetyl α-methylmannopyranoside, m. p. 65°, $[\alpha]_D^{18°}$ + 49° in chloroform, was prepared by Dale's method (*loc. cit.*). A solution of it (10 g.) in acetone (30 c.c.), rendered slightly alkaline by the addition of dilute sodium hydroxide solution, was kept at 55—60° during the gradual simultaneous addition of methyl sulphate (26 c.c.) and 30% aqueous sodium hydroxide (62 c.c.), care being taken to avoid the development either of acidity or of excessive alkalinity at any stage during the reaction. The product was isolated in the usual manner and methylation was completed by treatment with methyl iodide and silver oxide. This gave a colourless liquid, b. p. about 105°/0·02 mm., which crystallised when cold as irregular prisms, m. p. 38—40° (after recrystallisation) alone or when mixed with authentic tetramethyl α-methylmannopyranoside prepared by the direct methylation of α-methylmannopyranoside, $[\alpha]_D^{18°}$ + 43° in water (*c*, 0·8). Yield, almost quantitative.

Methylation of α-Methylmannopyranoside.—α-Methylmannopyranoside was twice methylated in the usual way by methyl sulphate and sodium hydroxide. The product was a colourless liquid, b. p. about 105°/0·02 mm., which crystallised completely when cold (yield, 90%). Recrystallisation from cold (− 10°) light petroleum gave tetramethyl α-methylmannopyranoside, m. p. 38—40°, $[\alpha]_D^{18°}$ + 42° in water (*c*, 1·3) (compare Drew, Goodyear, and Haworth, *loc. cit.*; Irvine and Moodie, *loc. cit.*). After one more crystallisation the rotation was + 43° and this value remained unaltered after four successive crystallisations. The following rotations were also

observed : $[\alpha]_D^{20^\circ}$ + 57° in chloroform (*c*, 1·1), + 77° in benzene (*c*, 0·8). The substance gave on hydrolysis tetramethylmannopyranose, which was identified in the form of its crystalline anilide.

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