CLXXX.—*The Structure of Carbohydrates and their Optical Rotatory Power. Part VII. 4-Galacto-sidomannose and its Methylated Derivatives.*

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FOR similar reasons to those outlined in the introduction to the preceding paper on 4-glucosidomannose, we considered it would be helpful to the argument in which we have been previously engaged

(J., 1930, 2644) if complementary data were furnished on the behaviour of 4-galactosidomannose. We have already recorded the behaviour of its glycoside, namely, 4-galactosido-α-methylmannoside, towards emulsin and have shown that the α-methylmannoside to which it gives rise is the normal product having $[\alpha]_D + 79°$, the substance to which in all earlier papers we have ascribed the pyranoside structure.

The present outline of experiments supports this view in its entirety. We have now demonstrated that 4-galactosidomannose gives rise to 4-*galactosidomannonic acid* on oxidation, and that this product undergoes methylation and esterification without isomeric change to give *methyl octamethyl galactosidomannonate* in which the bionic junction at the 4-position remains unimpaired. As evidence of this rigidity of the grouping it is shown that the above methylated bionic ester undergoes hydrolytic cleavage with dilute mineral acid to give crystalline 2 : 3 : 5 : 6-tetramethyl γ-mannonolactone, characterised by the crystalline phenylhydrazide of the corresponding acid (Goodyear and Haworth, J., 1927, 3136) and also, as the accompanying product, 2 : 3 : 4 : 6-tetramethyl galactopyranose.

These results are in every way parallel with those recorded in the case of lactobionic acid (Haworth and Long, J., 1927, 544), which is the epimeride of 4-galactosidomannonic acid.

The methylation of 4-galactosido-α-methylmannoside gave rise to its *heptamethyl* derivative, which underwent hydrolytic cleavage with dilute mineral acid, giving crystalline 2 : 3 : 4 : 6-tetramethyl galactopyranose and also 2 : 3 : 6-trimethyl mannose, which gives a crystalline anilide. This is in every way comparable with the result obtained on hydrolysis of fully methylated lactose, which is the " epimeride " of the above biose. The variations observed from solvent to solvent in the specific rotation of heptamethyl 4-galactosido-α-methylmannoside are given.

Whilst sufficiently marked to be worthy of note and as a commentary on the undesirability of basing new structural principles on so inconstant a property, these variations are not so great as in the case of the heptamethyl 4-glucosido-α-methylmannoside. It is, however, well known that galactose derivatives give different rotation values in different solvents, as do also mannose derivatives, whilst glucose derivatives are less prone to display this inconstancy. We believe it to be probable that in the above heptamethyl 4-galactosido-α-methylmannoside variation of both the galactose and the mannose residue is apparent but that each effect is partly minimised or compensated by the other.

EXPERIMENTAL.

Methylation of 4-β-Galactosido-α-methylmannoside.—The pure substance (4·9 g.), prepared by the method previously described (*loc. cit.*), was dissolved in water (27 c.c.) and methylated at 50—55° in the presence of acetone (20 c.c.) by methyl sulphate (34 c.c.) and sodium hydroxide (28 g. in 85 c.c. of water). The product (4·9 g.) was extracted by chloroform and after a second methylation under similar conditions gave on distillation under diminished pressure *heptamethyl 4-β-galactosido-α-methylmannoside* as a colourless uncrystallisable viscid syrup (4·1 g.), b. p. about 170°/0·02 mm., $n_D^{16°}$ 1·4690, $[\alpha]_D^{20°}$ + 50° in chloroform (*c*, 1·4), + 50·5° in water (*c*, 1·3), + 53° in ethyl alcohol (*c*, 0·8), + 63° in ether (*c*, 0·8), + 41° in benzene (*c*, 0·9) (Found: C, 52·6; H, 8·5; OMe, 54·3. $C_{20}H_{38}O_{11}$ requires C, 52·9; H, 8·4; OMe, 54·6%).

Hydrolysis of Heptamethyl 4-β-Galactosido-α-methylmannoside.—This was carried out by heating the substance (3·85 g.) in 5% aqueous hydrochloric acid (56 c.c.) at 95—100° until the rotation became constant (9 hrs.). During this period the rotation increased from the initial value $[\alpha]_D^{16°}$ + 50°, passed through a maximum, and became finally + 53°. The acid was neutralised with barium carbonate and the neutral solution (A) was extracted 10 times with chloroform. Evaporation of the chloroform left a viscid syrup (1·86 g.) which, when heated with alcoholic aniline, gave tetramethyl galactopyranose anilide, m. p. 195—196°, alone or in admixture with an authentic sample. The yield of anilide was 85% of the theoretical (Found: C, 61·7; H, 8·35; N, 4·5; OMe, 39·9. Calc. for $C_{16}H_{25}O_5N$: C, 61·7; H, 8·0; N, 4·5; OMe, 39·8%). Further evidence of the identity of the syrup was provided by the fact that when kept it deposited crystalline tetramethyl α-galactose, m. p. 68—69°. A mixed m. p. determination with an authentic sample showed no depression.

The aqueous portion (A) after extraction by chloroform was evaporated to dryness under diminished pressure and the solid residue was extracted several times with boiling chloroform. The chloroform extracts yielded a colourless syrup (1·54 g.), $n_D^{16°}$ 1·4750, $[\alpha]_D^{18°}$ + 6° in water (*c*, 1), which appeared to be mainly 2 : 3 : 6-trimethyl mannopyranose (Found: OMe, 40·0. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). A portion of this syrup (0·15 g.) was heated for 4½ hours in boiling benzene (1 c.c.) containing freshly distilled aniline (0·10 c.c.). The benzene and aniline were removed by heating at 50°/0·02 mm., leaving a brown oil which set to a glass and was crystallised by trituration with a little dry ether. Recrystallisation from ether gave 2 : 3 : 6-trimethyl mannose anilide as long colourless

needles, m. p. 126—127°, alone or in admixture with the anilide of 2 : 3 : 6-trimethyl mannose which had been prepared by hydrolysis of heptamethyl 4-β-glucosido-α-methylmannoside (see preceding paper) (Found : C, 60·5; H, 7·9; N, 4·9; OMe, 31·2. Calc. for $C_{15}H_{23}O_5N$: C, 60·6; H, 7·8; N, 4·7; OMe, 31·3%).

The trimethyl mannose (1·2 g.) was methylated 3 times by methyl iodide and silver oxide, giving a mobile liquid (1·1 g.) which was distilled under diminished pressure. The main fraction (0·93 g.), b. p. about 95°/0·02 mm., $n_D^{16°}$ 1·4492, crystallised when cooled in the refrigerator. The solid material after being drained on porous earthenware had m. p. 35—36°, $[\alpha]_D^{20°}$ — 80° in water (*c*, 1·0), and was recognised as tetramethyl β-methylmannopyranoside. A mixed m. p. determination showed no depression. The liquid which drained away from the tetramethyl β-methylmannopyranoside was heated on the water-bath with 6% hydrochloric acid until the rotation remained constant ($[\alpha]_D^{18°}$ + 19°; 5 hrs.). The product (yield, 75%) was isolated in the usual way and gave, when heated with alcoholic aniline, tetramethyl mannopyranose anilide, m. p. 143°.

Oxidation of 2 : 3 : 6-trimethyl mannose for 45 hours at 40° with bromine water yielded 2 : 3 : 6-trimethyl mannonolactone as an uncrystallisable liquid, $[\alpha]_D^{15°}$ + 66°, initial value in water (*c*, 1·2) (yield, 94%). On methylation with methyl iodide and silver oxide this substance gave in good yield tetramethyl γ-mannonolactone, m. p. 108—109°.

Methylation of 4-β-*Galactosidomannonic Acid.*—Pure 4-β-galactosido-α-mannose (10 g.) (Haworth, Hirst, Plant, and Reynolds, *loc. cit.*) was oxidised by bromine water in the presence of barium benzoate (Hudson and Isbell, *J. Amer. Chem. Soc.*, 1929, **51**, 2225). The 4-β-galactosidomannonic acid was isolated as its amorphous *calcium* salt, which was precipitated when a concentrated aqueous solution of the salt was poured into a large excess of absolute alcohol (Found : Ca, 5·2. $C_{24}H_{42}O_{24}Ca$ requires Ca, 5·3%). The calcium salt (7·2 g.), dissolved in water (32 c.c.) containing a little acetone, was methylated at 50—55° with methyl sulphate (64 c.c.) and 30% aqueous sodium hydroxide (160 c.c.). After 1 hour at 80°, the mixture was cooled to 0° and almost neutralised with sulphuric acid. The slightly alkaline liquor was evaporated to small bulk and then treated with methyl sulphate (64 c.c.) and alkali at 50—55° in the manner just described. This solution was cooled to 0°, acidified with sulphuric acid, filtered, and thoroughly extracted with chloroform (A). The filtered solid was extracted with slightly alkaline 60% alcohol at 80°. The material in the alcoholic extract was added to the aqueous portion, which was rendered alkaline and evaporated to small bulk. The mixture of solid and syrup was then

remethylated. Chloroform extracts were made as before and combined with (A), giving the methylated bionic acid as a viscid gum (3·9 g.). This material was subjected to three successive methylations by methyl iodide and silver oxide. At this stage a pale yellow syrup (3·2 g.) was obtained, b. p. about 180°/0·02 mm., $n_D^{16°}$ 1·4660 (Found : OMe, 53. $C_{21}H_{40}O_{12}$ requires OMe, 57·6%). This material consisted largely of methyl octamethyl 4-galactosidomannonate in spite of the low methoxyl value, which could not easily be raised by further methylation. The failure to effect complete methylation is probably attributable to the presence of some methylated 4-galactosidomannonolactone.

Hydrolysis of the methylated product (2·2 g.) by 5% hydrochloric acid at 95° required 12 hours, during which the rotation rose from the initial value $[\alpha]_D^{18°}$ + 13° to + 80°. The solution (A) was neutralised with barium carbonate and extracted with chloroform. The chloroform extract was concentrated until its volume was 10 c.c. and shaken three times with an equal volume of 3*N*-aqueous sodium carbonate (B) in order to remove any tetramethyl mannonolactone which had been dissolved in the chloroform. Evaporation of the chloroform left tetramethyl galactopyranose as a colourless viscid liquid (0·9 g.). When heated with alcoholic aniline, it gave in excellent yield tetramethyl galactopyranose anilide, m. p. 195°. This m. p. was not depressed when the substance was mixed with an authentic sample.

The aqueous portion (A) was acidified with hydrochloric acid and evaporated to dryness at 40° under diminished pressure. Water was added and evaporated, this operation being repeated until no mineral acid remained. The last traces of water were removed by the addition of benzene, followed by evaporation. The residual solid material was extracted with boiling ether. The aqueous sodium carbonate extracts (B) were treated in the same way. The combined ethereal extracts gave on evaporation a viscid syrup (0·81 g.), which was heated at 100° for 30 minutes to complete the lactonisation. It crystallised slowly when kept at room temperature and after trituration with dry ether, followed by recrystallisation from light petroleum (b. p. 80—100°), gave tetramethyl γ-mannonolactone as long needles, m. p. 108°, alone or in admixture with an authentic sample. $[\alpha]_D^{18°}$ + 63°, in water (*c*, 1·2).

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