155. *Lactones of Mannosaccharic Acid. Part II. Synthesis of 2:3:5-Trimethyl Mannosaccharic Acid Diamide.*

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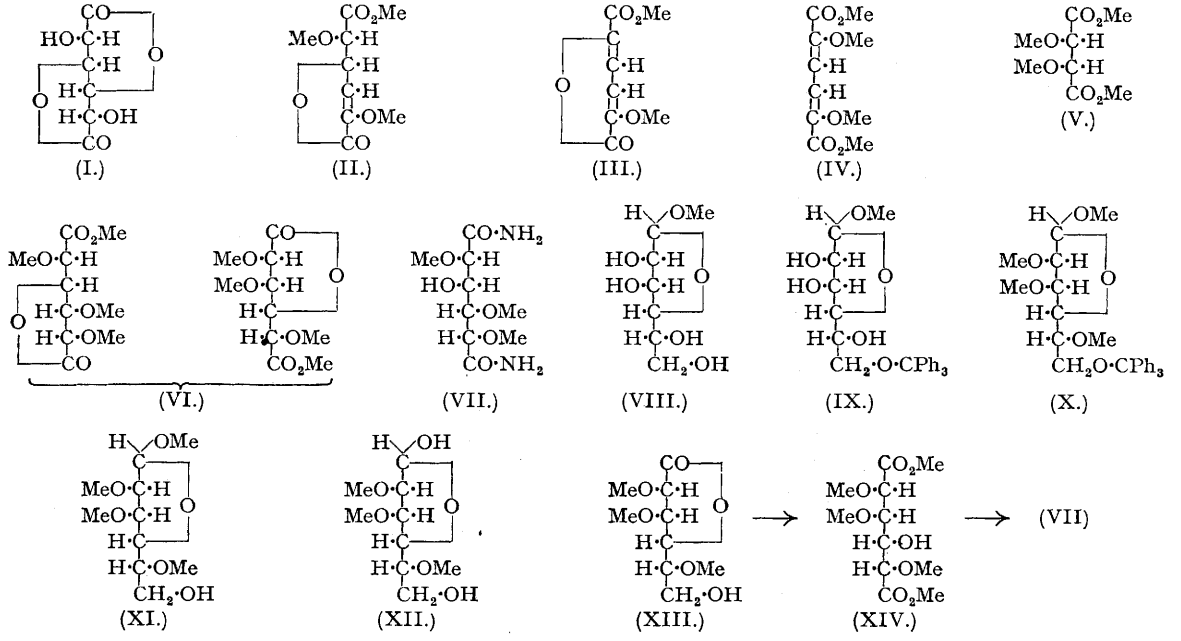
The trimethyl mannosaccharolactone methyl ester (VI), obtained previously by the action of diazomethane or the Purdie reagents upon mannosaccharodilactone (Haworth, Heslop, Salt, and Smith, this vol., p. 217), is shown by synthetic experiments to be the 2 : 3 : 5-*trimethyl* derivative. The synthesis involved the following series of reactions: α-methylmannofuranoside (VIII) ⟶ 6-*trityl* α-*methylmannofuranoside* (IX) ⟶ 6-*trityl* 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (X) ⟶ 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (XI) ⟶ 2 : 3 : 5-*trimethyl mannose* (XII) ⟶ 2 : 3 : 5-*trimethyl* γ-*mannonolactone* (XIII) ⟶ *methyl* 2 : 3 : 5-*trimethyl mannosaccharate* (XIV) ⟶ 2 : 3 : 5-*trimethyl mannosaccharic acid diamide* (VII). The last was identical with the diamide from (VI).

Methylation of mannosaccharo-1 : 4 : 3 : 6-dilactone (I) either with silver oxide and methyl iodide or with diazomethane results in the formation of 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (II) as

the main product (Haworth, Heslop, Salt, and Smith, *loc. cit.*). Four other substances were isolated, *viz.*, a new trimethyl mannosaccharolactone methyl ester (from both methods of methylation) which is the subject of this communication, methyl dimethoxyerythrosuccinate (methyl dimethyl *meso*tartrate) (V) (from the methylation with silver oxide and methyl iodide), and two unsaturated substances (by both methods of methylation).

The first of the unsaturated compounds ($C_8H_8O_5$, m. p. 212°), having an absorption band with head at λ 3070 A. (ε, 12,000) moving to 3680 A. (ε, 14,000) upon addition of alkali, was identified as 6-carbomethoxy-3-methoxy-α-pyrone (III) (Haworth, Hirst, and Jones, J., 1938, 710; Smith, *J. Soc. Chem. Ind.*, 1938, **57**, 449; Dippold, Schmidt, and Zeiser, *Ber.*, 1937, **70**, 2402); the second unsaturated substance ($C_{10}H_{14}O_6$, m. p. 140°), showing selective absorption with the head of the band at λ 3180 A. (ε, 24,000) in neutral and in alkaline solution, was not characterised, but it appeared to be a derivative of muconic acid. It may be considered to be derived from 2 : 5-dimethyl mannosaccharic acid by loss of the elements of two molecules of water from carbon atoms **2**, **3**, **4**, and **5**, and the formation of double bonds between C_2 and C_3 and between C_4 and C_5. One of the several possible geometric isomers is shown in (IV) and from the more recent work of Schmidt and Kraft (*Ber.*, 1941, **74**, 33) it is clear that the substance, m. p. 140°, has this structure.

The methyl dimethoxyerythrosuccinate probably arises as a result of oxidative cleavage of the six-carbon chain, and the trimethyl mannosaccharolactone methyl ester is formed from the dilactone by the opening of one lactone ring followed by methylation.



The disposition of the three ether methyl groups in the trimethyl mannosaccharolactone methyl ester (VI) was ascertained by the observation that the diamide (VII) derived from (VI) with methyl-alcoholic ammonia showed a negative Weerman test for α-hydroxy-amides (*Rec. Trav. chim.*, 1917, **36**, 16). Two of the methyl groups must therefore occupy positions 2 and 5. The third methyl residue may be attached either to C_3 or to C_4. Since the 2 : 3 : 5- and the 2 : 4 : 5-trimethyl derivative of mannosaccharic acid resulting from these two possibilities are identical, this lactone ester (VI), now under discussion, may be designated equally well either as 2 : 3 : 5- or as 2 : 4 : 5-trimethyl mannosaccharolactone methyl ester.

In view of the diverse nature of the reaction products obtained by the methylation of mannosaccharodilactone, it was deemed advisable to obtain further evidence in favour of the structure (VI) assigned to the trimethyl lactone methyl ester; in particular, it was important to prove that this ester (VI) was stereochemically related to mannose. The necessary evidence was forthcoming from the observation that a synthetic specimen of crystalline 2 : 3 : 5-*trimethyl mannosaccharic acid diamide* was found to be identical with the diamide (VII) prepared from the trimethyl lactone methyl ester (VI).

The synthesis of the diamide of 2 : 3 : 5-trimethyl mannosaccharic acid was performed as follows: Crystalline α-methylmannofuranoside (VIII), prepared by the method of Haworth, Hirst, and Webb (J., 1930, 651), gave 6-*trityl* α-*methylmannofuranoside* (IX) upon treatment with triphenylmethyl chloride. By means of silver oxide and methyl iodide, (IX) was converted into 6-*trityl* 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (X). When this compound was dissolved in ether containing hydrogen chloride, the trityl group was readily split off, and there was produced 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (XI). Hydrolysis of the latter was easily effected with dilute sulphuric acid, giving the corresponding 2 : 3 : 5-trimethyl mannose (XII) which, upon oxidation with bromine, yielded crystalline 2 : 3 : 5-*trimethyl* γ-*mannonolactone* (XIII), the presence of the

γ-lactone ring being indicated by the fact that an aqueous solution showed little or no mutarotation. Oxidation of the lactone (XIII) by heating with concentrated nitric acid yielded 2 : 3 : 5-trimethyl mannosaccharic acid, which was converted by methyl-alcoholic hydrogen chloride into *methyl* 2 : 3 : 5-*trimethyl mannosaccharate* (XIV). When the latter was treated with methyl-alcoholic ammonia it afforded the corresponding diamide of 2 : 3 : 5-trimethyl mannosaccharic acid, identical with (VII).

The characterisation of the 2 : 3 : 5-trimethyl mannosaccharolactone methyl ester as a methylation product of mannosaccharodilactone indicates that at least one of the lactone rings in the dilactone (I) is of the γ-type (see Schmidt and Kraft, *loc. cit.*).

Experimental.

Synthesis of 2 : 3 : 5-*Trimethyl Mannosaccharic Acid Diamide.*—6-*Trityl* α-*methyl*-d-*mannofuranoside* (IX). To a solution of crystalline α-methylmannofuranoside (1·89 g.) (prepared by the method of Haworth, Hirst, and Webb, J., 1930, 651) in dry pyridine (10 c.c.), there was added triphenylmethyl chloride (2·9 g.); the mixture was warmed to 60° and then kept for 7 days at room temperature. Water (150 c.c.) was now added, and the product extracted with chloroform (150 c.c.). The chloroform solution was washed with N-sulphuric acid (five times), aqueous sodium bicarbonate (twice), and water (once). The chloroform solution was dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness under diminished pressure. The colourless glassy product, 6-*trityl* α-*methylmannofuranoside*, $[\alpha]_D^{17°}$ +40° in chloroform (*c*, 1·8), showed no tendency to crystallise (yield, 4·3 g.) (Found: OMe, 6·0. $C_{26}H_{28}O_6$ requires OMe, 7·1%).

6-*Trityl* 2 : 3 : 5-*trimethyl* α-*methylmannofuranoside* (X). The above trityl compound was methylated with silver oxide and methyl iodide in the usual manner to afford the *furanoside* (X) [Found: OMe, 21·6 (after 6 methylations); 22·3 (after 8); 22·4 (after 10). $C_{29}H_{34}O_6$ requires OMe, 25·9%] as a colourless viscous syrup having $[\alpha]_D^{16°}$ +19° in chloroform (*c*, 1·8) (yield, 4·0 g.).

2 : 3 : 5-*Trimethyl* α-*methylmannofuranoside* (XI). A solution of the 2 : 3 : 5-trimethyl compound (X) (4·0 g.) in ether (130 c.c.) was cooled in an ice-bath and saturated with hydrogen chloride. The mixture was kept for 1 hour at 0°, then allowed to acquire room temperature (1 hour), and evaporated thereat under diminished pressure to half its volume to remove as much hydrogen chloride as possible. The ethereal solution was then extracted six times with water (20 c.c.). The aqueous extracts were combined, neutralised with lead carbonate, filtered, and evaporated to dryness under reduced pressure. Extraction of the dry residue with ethyl alcohol afforded a syrup which was extracted with ether. Removal of the solvent gave a syrup (1·25 g.) which was treated with 1% methyl-alcoholic hydrogen chloride (50 c.c.) at room temperature for 17 hours in order to convert any 2 : 3 : 5-trimethyl mannose into the corresponding glycoside. Neutralisation of the mineral acid with silver carbonate, followed by filtration and removal of solvent, yielded a syrup which upon distillation gave 2 : 3 : 5-*trimethyl methylmannofuranoside* as a colourless, mobile liquid (0·8 g.), b. p. (bath temp.) 115—120°/0·03 mm., $n_D^{16°}$ 1·4580, $[\alpha]_D^{18°}$ +54° in water (*c*, 1·3) (Found: OMe, 51·9. $C_{10}H_{20}O_6$ requires OMe, 52·6%). A small fraction (0·2 g.) was obtained, b. p. (bath temp.) 120—140°/0·03 mm., $n_D^{19°}$ 1·4638, but this was not pure and so was rejected.

2 : 3 : 5-*Trimethyl* γ-d-*mannonolactone* (XIII). A solution of the foregoing compound (XI) (0·74 g., first fraction) in 0·1N-sulphuric acid (40 c.c.) was heated on the boiling water-bath; the specific rotation changed in 80 minutes from +52° (initial value) to +28° (equilibrium value). After a further hour's heating the solution was neutralised with barium carbonate, heated with a little charcoal until the barium sulphate had settled, and then filtered, the residue being well washed with boiling water. The filtrate was evaporated to dryness under reduced pressure, giving syrupy 2 : 3 : 5-trimethyl mannose (0·63 g.), which reduced Fehling's solution.

This syrup (0·62 g.) was dissolved in water (20 c.c.) and oxidised with bromine (1 c.c.) at room temperature for 3 days. The excess of bromine was removed by aeration, the solution neutralised with silver oxide, treated with a little charcoal, filtered before and after treatment with hydrogen sulphide, and then evaporated under reduced pressure to dryness. The syrupy product was purified by extraction with acetone–ether and then lactonised by heating in a vacuum for 3 hours at 70—80°. On keeping, the lactone (0·3 g.) crystallised spontaneously. After purification by distillation, followed by recrystallisation from ethyl alcohol–light petroleum, the 2 : 3 : 5-*trimethyl* γ-*mannonolactone* had m. p. 118°, $[\alpha]_D^{18°}$ +67° (initial value) in water (*c*, 1·0) changing in 22 days to +63·5° (mutarotation still incomplete). The sodium salt, prepared by heating the lactone with a slight excess of sodium hydroxide solution, showed $[\alpha]_D^{18°}$ −27°, and upon acidification the solution had $[\alpha]_D^{18°}$ −31°. The lactone is soluble in water, ethyl and methyl alcohol, acetone, and ethyl acetate, sparingly soluble in ether, and insoluble in light petroleum (Found: C, 49·0; H, 7·5; OMe, 41·6. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%).

Treatment of the pure crystalline lactone (20 mg.) with methyl-alcoholic ammonia (2 c.c.) for 2 days at − 5° gave the *amide* of 2 : 3 : 5-trimethyl mannonic acid, which crystallised upon removal of the solvent; m. p. 162°, $[\alpha]_D^{18°}$ − 28° in water (*c*, 1·0) (after recrystallisation from ethyl alcohol or ethyl alcohol–acetone) (Found: OMe, 38·2. $C_9H_{19}O_6N$ requires OMe, 39·3%).

2 : 3 : 5-*Trimethyl mannosaccharic acid diamide* (VII). A solution of the lactone (0·3 g.) in nitric acid (5 c.c.; *d* 1·42) was heated on the water-bath for 1 hour at 50° and for 5 hours at 85—95° The solution was diluted with water and freed from nitric acid by distillation under diminished pressure, water and then methyl alcohol in the final stages being added to complete the removal. The syrupy acid residue was dried by heating in a vacuum and then esterified by boiling with 1% methyl-alcoholic hydrogen chloride (50 c.c.) for 8 hours. The solution was neutralised with silver carbonate, filtered, and evaporated to dryness under diminished pressure. Distillation of the syrupy residue gave *methyl* 2 : 3 : 5-*trimethyl mannosaccharate* (XIV) (0·2 g.), b. p. (bath temp.) 160°/0·07 mm., $n_D^{17°}$ 1·4465, $[\alpha]_D^{15°}$ −21° in methyl alcohol (*c*, 0·8) (Found: OMe, 54·1. $C_{11}H_{20}O_8$ requires OMe, 55·4%).

This ester (XIV) (0·1 g.) was treated with methyl-alcoholic ammonia for 4 days at −5°. By this time most of the *diamide* of 2 : 3 : 5-trimethyl mannosaccharic acid had crystallised. The crystals were washed by decantation with methyl alcohol and then purified by recrystallisation from water; m. p. 258° (decomp.), $[\alpha]_D^{18°}$ −39° in water (*c*, 0·6). This diamide gave no depression of m. p. when mixed with the diamide of 2 : 3 : 5-trimethyl mannosaccharic acid obtained from mannosaccharodilactone. A Weerman test upon this synthetic amide (20 mg.) was negative (Found: C, 43·3; H, 7·35; N, 11·25; OMe, 37·7. $C_9H_{18}O_6N_2$ requires C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%).

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