204. *The Constitution of Pectic Acid. Part II. The Synthesis of the Methyl Ester of* 2 : 3 : 5-*Trimethyl* β-*Methylgalacturonoside.*

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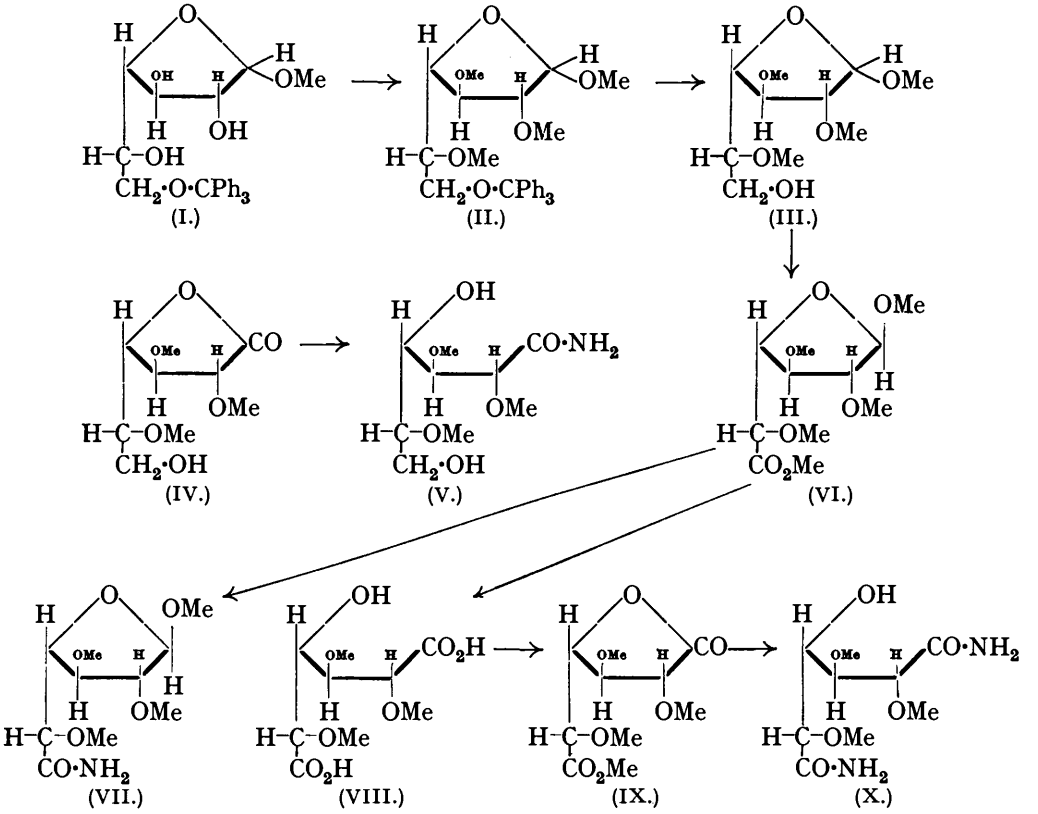
Investigations into the constitution of pectic acid have necessitated a study of methylated derivatives of galacturonic acid containing a furanose structure. One of these substances, namely, the crystalline *methyl* ester of 2 : 3 : 5-*trimethyl* β-*methylgalactofururonoside* (VI), has been synthesised from methylgalactofuranoside. The structure of (VI) has been elucidated by its transformation into the crystalline γ-lactone methyl ester of 2 : 3 : 5-trimethyl mucic acid (IX).

During the course of this work the *γ-lactone* (IV), the *amide* (V), and the *phenylhydrazide* of 2 : 3 : 5-*trimethyl galactonic acid* were isolated in the crystalline state.

Investigations into pectic acid (see preceding paper) necessitated a closer examination of 2 : 3 : 5-trimethyl galacturonic acid and its derivatives. The synthesis of 2 : 3 : 5-trimethyl methylgalacturonoside was accomplished in the following way. When methylgalactofuranoside (Haworth, Ruell, and Westgarth, J., 1924, **125**, 2468) was allowed to react with trityl chloride, 6-*trityl methylgalactofuranoside* (I) was formed, and this on methylation with methyl sulphate and sodium hydroxide solution gave 6-*trityl* 2 : 3 : 5-*trimethyl methylgalactofuranoside* (II). Removal of the trityl group from (II) was smoothly effected with ethereal hydrogen chloride (Smith, J., 1939, 1724) and there was produced 2 : 3 : 5-*trimethyl methylgalactofuranoside* (III). Hydrolysis of the latter with dilute sulphuric acid gave 2 : 3 : 5-*trimethyl galactose*, which on oxidation with bromine furnished the crystalline 2 : 3 : 5-*trimethyl γ-galactonolactone* (IV). This lactone, which can also be

characterised as the corresponding crystalline *amide* (V) and as the crystalline *phenylhydrazide*, behaved as a typical γ-lactone in that it exhibited relatively slow mutarotation in aqueous solution.

Treatment of 2 : 3 : 5-trimethyl methylgalactofuranoside (III) with potassium permanganate in alkaline solution converted the primary alcoholic group in position 6 into a carboxyl group and there resulted 2 : 3 : 5-trimethyl methylgalactofururonoside. Esterification of this trimethyl galacturonoside with methyl-alcoholic hydrogen chloride yielded a mixture of the α- and the β-form of the *methyl* ester of 2 : 3 : 5-*trimethyl methylgalactofururonoside*, from which the β-*form* (VI) was separated by crystallisation. The crystalline β-form (VI) was transformed, when treated with methyl-alcoholic ammonia, into the corresponding *amide* (VII) of 2 : 3 : 5-trimethyl β-methylgalactofururonoside.



When either the methyl ester of 2 : 3 : 5-trimethyl galacturonoside (VI) or 2 : 3 : 5-trimethyl methylgalactofuranoside (III) was heated with nitric acid, the corresponding 2 : 3 : 5-trimethyl mucic acid (VIII) was formed: this acid was not isolated but after esterification and subsequent distillation it furnished the crystalline *γ-lactone methyl* ester (IX) of 2 : 3 : 5-*trimethyl mucic acid*, which in turn gave rise to a crystalline *diamide* (X) and a crystalline *bismethylamide*. This 2 : 3 : 5-trimethyl mucic 1 : 4-γ-lactone methyl ester is the enantiomorph of the 2 : 4 : 5-trimethyl mucic 3 : 6-γ-lactone methyl ester previously prepared from the γ-lactone methyl ester of 2 : 4-dimethyl mucic acid by methylation (Smith, *loc. cit.*). Confirmation of the furanoside structure of (III) and (VI) was provided by the observation that the diamide (X) of the trimethyl mucic acid showed a negative Weerman test for α-hydroxy-amides and consequently it follows that the three methyl groups must be in positions 2, 3, and 5.

The methyl ester of 2 : 3 : 5-trimethyl β-methylgalactofururonoside (VI), its amide (VII) and the 2 : 3 : 5-trimethyl mucic 1 : 4-γ-lactone methyl ester (IX) proved to be identical

with the corresponding substances encountered during the work on pectic acid (preceding paper).

Experimental.

6-Trityl Methylgalactofuranoside (I).—A solution of methylgalactofuranoside, prepared from galactose (30 g.) by the method of Haworth, Ruell, and Westgarth (*loc. cit.*), in dry pyridine (65 c.c.) was treated with trityl chloride (50 g.) for 4 days at room temperature. The viscous mass was warmed and poured into water, and the syrupy precipitate triturated with water to remove as much of the pyridine as possible. The last traces of pyridine were removed from the compound by washing a chloroform solution of it several times with 0·5N-sulphuric acid. The chloroform solution was washed with sodium bicarbonate solution (twice), and then with water, and finally dried over anhydrous magnesium sulphate. Removal of the solvent gave *6-trityl methylgalactofuranoside* as a pale yellow, glassy solid, $[\alpha]_D^{18°}$ — 33° in acetone (*c*, 1·2) (Found : OMe, 6·5. $C_{26}H_{28}O_6$ requires OMe, 7·1%).

6-Trityl 2 : 3 : 5-Trimethyl Methylgalactofuranoside (II).—The 6-trityl methylgalactofuranoside from the previous experiment was dissolved in acetone (100 c.c.) and treated with methyl sulphate (100 c.c.) and sodium hydroxide (300 c.c. of a 30% solution) at 35°. The reagents were added slowly with stirring during 1½ hours, acetone being added from time to time to replace that lost by evaporation in order to keep the trityl compound in solution. The methylation was completed by heating the solution to 60° to dispel the acetone. The trityl compound, which had separated on the surface of the hot liquid as a syrup, was removed and remethylated in the same way. After five methylations in this manner the crude material was freed from inorganic salts by dissolving it in chloroform (250 c.c.) and washing the chloroform solution several times with water. The solution was dried over anhydrous magnesium sulphate, filtered, and evaporated under diminished pressure to give a glassy solid. Four treatments of the latter with Purdie's reagents gave *6-trityl 2 : 3 : 5-trimethyl methylgalactofuranoside*, $[\alpha]_D^{15°}$ — 19° in chloroform (*c*, 1·0) (Found : OMe, 20·0. $C_{29}H_{34}O_6$ requires OMe, 25·9%). The low methoxyl content is probably due to the presence of triphenylmethyl ether.

2 : 3 : 5-Trimethyl Methylgalactofuranoside (III).—A solution of 6-trityl 2 : 3 : 5-trimethyl methylgalactofuranoside (52 g.) in ether (150 c.c.) was cooled in an ice-bath and saturated with dry hydrogen chloride. After being kept for ½ hour at 0° and for ½ hour at room temperature, the solution was evaporated under reduced pressure for a short time at room temperature to remove as much hydrogen chloride as possible. The residual ethereal solution, which still contained hydrogen chloride, was exhaustively extracted with water; the combined aqueous extracts were neutralised with lead carbonate, filtered, and evaporated under diminished pressure to give a syrup. This syrup was purified by extraction with acetone and distilled, giving *2 : 3 : 5-trimethyl methylgalactofuranoside* as a colourless, non-reducing, mobile liquid (19 g.), b. p. (bath temp.) 150°/0·05 mm., $n_D^{18°}$ 1·4510, $[\alpha]_D^{18°}$ — 55° in water (*c*, 1·2) (Found : OMe, 51·0. $C_{19}H_{26}O_6$ requires OMe, 52·5%).

2 : 3 : 5-Trimethyl γ-Galactonolactone (IV).—When a solution of 2 : 3 : 5-trimethyl methylgalactofuranoside (1·1 g.) in 0·1N-sulphuric acid was heated on the boiling water-bath, it showed $[\alpha]_D$ — 54° (initial value); — 43° (after 3 hours); — 39° (4 hours); — 27° (6 hours); — 22° (7 hours); — 15° (9 hours, constant value). The solution was neutralised with barium carbonate, filtered, and evaporated under diminished pressure to give *2 : 3 : 5-trimethyl galactose* as a liquid (0·97 g.), $[\alpha]_D^{15°}$ — 5° in water (*c*, 0·8) (Found : OMe, 44·0. $C_9H_{18}O_6$ requires OMe, 41·9%). The high methoxyl value is probably due to the presence of some methylgalactopyranoside in the starting product, methylgalactofuranoside, a portion of which would be in the form of 2 : 3 : 4-trimethyl methylgalactoside at this stage.

A solution of this syrupy 2 : 3 : 5-trimethyl galactose (0·9 g.) in water (4 c.c.) was oxidised with bromine (2 c.c.) at room temperature for 18 hours. The solution was freed from the excess of bromine by aeration, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and evaporated under diminished pressure. The lactone obtained in this way distilled as a colourless liquid, b. p. (bath temp.) 170—175°/0·01 mm., which immediately crystallised. After recrystallisation from ethyl alcohol–light petroleum the *2 : 3 : 5-trimethyl γ-galactonolactone* had m. p. 90°; $[\alpha]_D^{18°}$ — 37°, initial value in water (*c*, 0·7); — 32° (after 5 days, mutarotation still incomplete) (Found : C, 49·5; H, 7·1; OMe, 41·8. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%).

Treatment of the crystalline 2 : 3 : 5-trimethyl γ-galactonolactone (50 mg.) with methyl-alcoholic ammonia for 1 day at —5° readily gave the *amide* (V) of 2 : 3 : 5-trimethyl galactonic acid, which crystallised on removal of the solvent; m. p. 152°, $[\alpha]_D^{16°}$ *ca* + 3° in water (*c*, 2·0)

(after recrystallisation from ethyl alcohol–ether) (Found : C, 45·6; H, 7·8; N, 5·8. $C_9H_{19}O_6N$ requires C, 45·6; H, 8·0; N, 5·9%).

Similarly, when the 2 : 3 : 5-trimethyl γ-galactonolactone (20 mg.) was allowed to react with phenylhydrazine (15 mg.) in boiling ether (1 c.c.) for ½ hour and for 1 hour at 70° in the absence of solvent, the corresponding crystalline *phenylhydrazide* of 2 : 3 : 5-trimethyl galactonic acid was obtained, m. p. 144°, $[\alpha]_D^{14°}$ + 18° in ethyl alcohol (*c*, 1·2) (after recrystallisation from ethyl alcohol–ether) (Found : N, 8·7. $C_{15}H_{22}O_5N_2$ requires N, 9·0%).

The Methyl Ester of 2 : 3 : 5-*Trimethyl* β-*Methylgalactofururonoside* (VI).—To a solution of 2 : 3 : 5-trimethyl methylgalactofuranoside (1·2 g.) in water (15 c.c.) was added a solution of potassium permanganate (1·8 g.) and potassium hydroxide (0·65 g.) in water (25 c.c.). Oxidation was complete after 3 days and the slight excess of potassium permanganate was then destroyed with a few drops of hydrogen peroxide. The solution was treated with a little charcoal, filtered to remove manganese dioxide, neutralised with N-sulphuric acid, treated with N-sulphuric acid (4·5 c.c.) to liberate the organic acid, and evaporated to dryness under diminished pressure at 35°. Extraction of the residue with chloroform gave 2 : 3 : 5-trimethyl methylgalacturonoside as an acidic syrup, which was dissolved in water (10 c.c.) and neutralised with 0·3N-barium hydroxide. The solution, which now contained the barium salt of the methylated uronic acid, was evaporated under reduced pressure to give a colourless glassy solid, which was extracted with ether to remove unchanged 2 : 3 : 5-trimethyl methylgalactofuranoside (0·1 g.). Treatment of the barium salt (1·5 g.) with boiling 1% methyl-alcoholic hydrogen chloride (100 c.c.) for 8 hours effected esterification. Neutralisation of the solution with silver carbonate, followed by filtration and removal of the solvent, gave the methyl ester of 2 : 3 : 5-trimethyl methylgalactofururonoside, which distilled as a colourless mobile liquid, b. p. (bath temp.) 125°/0·03 mm., $n_D^{23°}$ 1·4420, $[\alpha]_D^{18°}$ − 74° in water (*c*, 1·5) [Found : equiv., 265 (by heating with 0·02N-sodium hydroxide); OMe, 59·3%]. The distillate crystallised spontaneously and after tiling and recrystallisation from light petroleum the methyl ester of 2 : 3 : 5-trimethyl β-methylgalactofururonoside had m. p. 43° $[\alpha]_D^{14°}$ − 129° in methyl alcohol (*c*, 1·0). It was identical with that obtained from the methylated polygalacturonic acid examined in the preceding paper (Found : C, 50·1; H, 6·9; OMe, 57·8. Calc. for $C_{11}H_{20}O_7$: C, 50·0; H, 6·8; OMe, 58·7%).

Treatment of this crystalline methyl ester of 2 : 3 : 5-trimethyl β-methylgalactofururonoside with methyl-alcoholic ammonia for 2 days at −5° yielded the corresponding *amide*, m. p. 105°, $[\alpha]_D^{14°}$ − 150° in water (*c*, 1·0) (after recrystallisation from ether) (Found : C, 48·1; H, 7·6; N, 5·8; OMe, 50·2. $C_{10}H_{19}O_6N$ requires C, 48·2; H, 7·6; N, 5·6; OMe, 49·8%).

The γ-Lactone Methyl Ester of 2 : 3 : 5-*Trimethyl Mucic Acid* (IX).—(a) *From* 2 : 3 : 5-*trimethyl methylgalactofuranoside.* A solution of 2 : 3 : 5-trimethyl methylgalactofuranoside (1·5 g.) in concentrated nitric acid (10 c.c., *d* 1·42) was heated for ½ hour at 50° and, when the initial vigorous reaction had ceased, for 2 hours at 80°. The solution was diluted with water and freed from nitric acid by distillation under diminished pressure, a process which was facilitated by the simultaneous addition and distillation of water and finally of methyl alcohol. The acidic syrup was dried by heating in a vacuum and then esterified by boiling with 1% methyl-alcoholic hydrogen chloride (100 c.c.) for 6 hours. The solution was cooled, neutralised with silver carbonate, filtered, and evaporated under diminished pressure to a syrup. Distillation of this syrup gave the *γ-lactone methyl ester* of 2 : 3 : 5-*trimethyl mucic acid* as a colourless liquid (1·3 g.), b. p. (bath temp.) 160°/0·01 mm., $n_D^{20°}$ 1·4500, which crystallised spontaneously. After recrystallisation from ether it had m. p. 62°, $[\alpha]_D^{16°}$ − 84° (initial value in water, *c* 1·0) (Found : C, 48·7; H, 6·1; OMe, 49·8; equiv., 130. $C_{10}H_{16}O_7$ requires C, 48·4; H, 6·4; OMe, 50·0%; equiv., 124).

(b) *From the methyl ester of* 2 : 3 : 5-*trimethyl* β-*methylgalactofururonoside.* A solution of the crystalline methyl ester of 2 : 3 : 5-trimethyl methylgalacturonoside (150 mg.) in nitric acid (4 c.c., *d* 1·42) was heated for ½ hour at 50° and for 1½ hours at 90°. The 2 : 3 : 5-trimethyl mucic acid thus produced was converted as in (a) into the crystalline γ-lactone methyl ester, which had m. p. 62° alone or in admixture with a specimen prepared from 2 : 3 : 5-trimethyl methylgalactofuranoside (Found : OMe, 49·5%).

When the γ-lactone methyl ester of 2 : 3 : 5-trimethyl mucic acid was treated with methyl-alcoholic ammonia for 3 days at −5°, an amide was obtained which crystallised on removal of the solvent. After recrystallisation from water the *diamide* (X) of 2 : 3 : 5-trimethyl mucic acid had m. p. 255° (decomp.). This amide gave a negative Weerman test (Found : OMe, 36·0. $C_9H_{18}O_6N_2$ requires OMe, 37·2%).

In another experiment the interaction of the ester-lactone with ammonia was arrested before the formation of the diamide of 2 : 3 : 5-trimethyl mucic acid was complete and on removal of

the solvent there was obtained the *amide* of 2 : 3 : 5-*trimethyl mucic acid monomethyl* ester, m. p. 173° (after recrystallisation from ethyl alcohol). This monoamide showed a negative Weerman reaction (Found : N, 5·4; OMe, 47·1. $C_{10}H_{19}O_7N$ requires N, 5·3; OMe, 46·8%).

Treatment of the γ-lactone methyl ester of 2 : 3 : 5-trimethyl mucic acid with methyl-alcoholic methylamine at room temperature for 2 days gave the *bismethylamide* of 2 : 3 : 5-trimethyl mucic acid, in excellent yield, m. p. 232°; $[\alpha]_D^{17°}$ — 22° in water (*c*, 1·8) (after recrystallisation from ethyl alcohol) (Found : C, 47·6; H, 7·8; N, 10·1; OMe, 32·5. $C_{11}H_{22}O_6N_2$ requires C, 47·5; H, 7·9; N, 10·1; OMe, 33·4%).

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