158. *Synthesis of Uronic Acids. Part III. d-Mannuronic Acid.*

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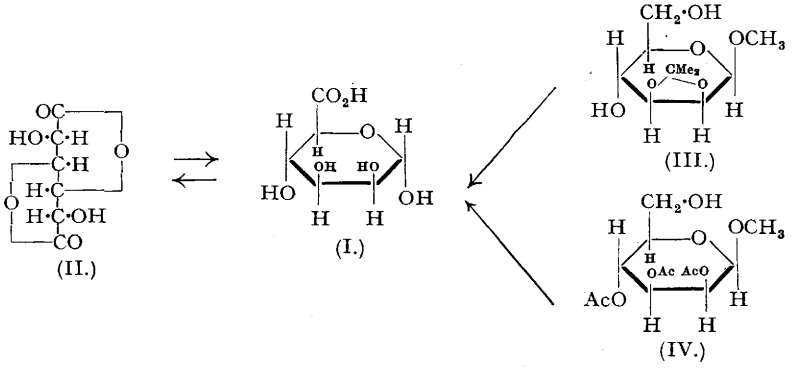
A synthesis of crystalline *β-d*-mannuronolactone in good yield from mannose is described. The stages involved are the following: mannose ⟶ α-methylmannoside ⟶ 2 : 3 : 4-triacetyl 6-trityl α-methylmannoside ⟶ 2 : 3 : 4-triacetyl α-methylmannoside ⟶ 2 : 3 : 4-*triacetyl α-methylmannuronoside* ⟶ *α-methylmannuronoside lactone* ⟶ *β-d*-mannuronolactone.

Mannuronic acid (I) is the sole identified constituent unit of the important sea-weed product alginic acid (Nelson and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 1914; 1930, **52**, 2130; Hirst, Jones, and Osman Jones, J., 1939, 1880). Two methods for its synthesis have been devised. The first (Shoeffel and Link, *J. Biol. Chem.*, 1933, **100**, 40) was based on Fischer and Piloty's method (*Ber.*, 1891, **24**, 521) and involved the reduction of mannosaccharodilactone (II) with sodium amalgam. In the second (Ault, Haworth, and Hirst, J., 1935, 517), 2 : 3-monoacetone α-methylmannoside (III) was oxidised at C_6 with alkaline potassium permanganate to give monoacetone α-methylmannuronoside, which after acid hydrolysis gave mannuronic acid in the form of its crystalline lactone.



In our hands repetition of both of these methods gave products which were difficult to crystallise, so that a third route (Stacey, J., 1939, 1529) was explored. This method utilised 2 : 3 : 4-triacetyl α-methylmannoside (IV) (cf. Watters, Hockett, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1529) as initial material which was obtained in good yield by the first three processes shown in the summary (above).

Oxidation of the triacetyl compound at C_6 was readily effected with potassium permanganate in acetone–acetic acid solution, giving syrupy 2 : 3 : 4-triacetyl α-methylmannuronic acid (characterised by conversion into *α-methylmannuronoside lactone*, m. p. 186°, $[\alpha]_D$ +80°), which was deacetylated with aqueous barium hydroxide, and then the glucosidic group was hydrolysed by N/2-sulphuric acid. The product readily crystallised in the

form of β-*d*-mannuronolactone, identical with specimens synthesised by both of the previous methods mentioned above. Further amounts were obtained by slow crystallisation of mother-liquor products after lactonisation.

Oxidation with bromine water of the syrupy mother-liquor product from the crystallisation of mannuronolactone gave mannosaccharodilactone (II) in 65% yield. In view of the fact that bromine water is known to oxidise reducing sugars only at C_1, it is clear that this syrupy product was a mixture of *d*-mannuronic acid with its lactone. Hence the yield in the conversion of (IV) into (I) was reasonably good.

Experimental

2 : 3 : 4-*Triacetyl* 6-*Trityl* α-*Methylmannoside*.—This was prepared in theoretical yield by the method of Smith, Stacey, and Wilson (this vol., p. 131) and showed $[\alpha]_D^{20°}$ +42·2° in chloroform (*c*, 1·0), m. p. 128° (cf. Watters, Hockett, and Hudson, *loc. cit.*).

2 : 3 : 4-*Triacetyl* α-*Methylmannoside*.—A solution of the 6-trityl compound in glacial acetic acid was detritylated by Helferich and Klein's method (*Annalen*, 1926, **450**, 219), and the product recrystallised from acetone–ether. It was obtained in 85% yield; m. p. 97°, $[\alpha]_D^{20°}$ +55° in chloroform (*c*, 1·0) (Found: OMe, 9·7. Calc. for $C_{13}H_{20}O_9$: OMe, 9·7%).

Oxidation of 2 : 3 : 4-*Triacetyl* α-*Methylmannoside*.—The foregoing compound (10 g.) was dissolved in glacial acetic acid (100 c.c.), potassium permanganate (2·5 g.) in acetone (100 c.c.) and water (25 c.c.) was added, and the mixture gently stirred at room temperature. More permanganate (8 g.) was added in small quantities over a period of 2 days. Acetone (100 c.c.) and ether (200 c.c.) were added to the mixture, and the precipitate of manganese dioxide separated (centrifuge) and washed well with acetone–ether. The combined supernatant liquors were evaporated under diminished pressure to a brown syrup, which was dissolved in chloroform (100 c.c.) and washed with dilute sulphuric acid and then with water. The chloroform solution was dried over anhydrous magnesium sulphate, and the solvent removed, giving mainly 2 : 3 : 4-*triacetyl* α-*methylmannuronoside* as a thick yellow syrup (7·8 g.), $[\alpha]_D^{20°}$ +41° in chloroform (*c*, 1·05) (Found: OMe, 9·0. $C_{13}H_{18}O_{10}$ requires OMe, 9·3%). The syrup gave a strongly positive naphtharesorcin test for uronic acid.

α-*Methylmannuronoside Lactone*.—(*a*) 2 : 3 : 4-Triacetyl α-methylmannuronoside (1·0 g.) was dissolved in methyl alcohol (30 c.c.) containing anhydrous hydrochloric acid (1%), and the solution boiled for 3 hours ($[\alpha]_D^{20°}$ +52° ⟶ +38°), neutralised with silver carbonate, filtered, and concentrated. The residual syrup (0·6 g.) was dissolved in ether, the solution filtered, and the solvent again removed. The product (0·5 g.) slowly crystallised. After being kept for several weeks it was stirred with a small amount of absolute methyl alcohol and the solution filtered. The residual α-*methylmannuronoside lactone*, recrystallised from methyl alcohol, had m. p. 186°, $[\alpha]_D^{20°}$ +80° (*c*, 1·1 in water) (Found: C, 43·9; H, 5·3; OMe, 16·7. $C_7H_{10}O_6$ requires C, 44·2; H, 5·3; OMe, 16·3%).

(*b*) 2 : 3 : 4-Triacetyl α-methylmannuronoside (3·8 g.) was dissolved in acetone (30 c.c.), and saturated aqueous barium hydroxide added until the solution was alkaline to phenolphthalein. It was kept for six hours at room temperature, and the barium then removed by quantitative addition of N-sulphuric acid. Evaporation of the solvents gave α-methylmannuronoside as a colourless, viscid syrup (2·1 g.), $[\alpha]_D^{20°}$ +70° in water (*c*, 1·0) (Found: OMe, 16·0%).

β-d-*Mannuronolactone*.—The mannuronoside syrup (2·1 g.) was dissolved in N/2-sulphuric acid (250 c.c.), the solution heated at 100° for 3½ hours ($[\alpha]_D^{20°}$ +74° ⟶ +17°; equilibrium value), neutralised with aqueous barium hydroxide, and the precipitate of barium sulphate removed (centrifuge) and washed well with water. The supernatant liquors were evaporated under diminished pressure to 50 c.c., and the barium mannuronate precipitated as a white powder by addition of ethyl alcohol (4 vols.). The barium salt was converted into the lead salt, from which mannuronic acid was obtained in solution by means of hydrogen sulphide. Removal of solvent gave mannuronic acid as a colourless syrup (1·5 g.), strongly acid to Congo-red indicator. After intensive drying at 70° in a vacuum, the syrup was dissolved in a small amount of ethyl alcohol and ether was added. Crystallisation was rapid and the product, recrystallised from ethyl alcohol containing glacial acetic acid, had m. p. and mixed m. p. 143—144° with specimens of mannuronolactone supplied by Professor K. P. Link and by Professor W. N. Haworth, F.R.S.; $[\alpha]_D^{21°}$ +50° ⟶ +94° in 30 minutes (Found: C, 41·2; H, 4·7. Calc. for $C_6H_8O_6$: C, 40·9; H, 4·6%).

Mannosaccharodilactone.—Evaporation of the mother-liquors from the crystallisation of mannuronolactone gave syrupy products from which mannuronolactone slowly crystallised as broad plates. A syrupy sample (0·20 g.) was oxidised in the usual way with bromine water at 40° over a period of three days, and from the solution mannosaccharodilactone (0·14 g.) (m. p. 190°, decomp.), identical with an authentic specimen, was isolated.

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