341. *Deoxy-sugars. Part XXI. Synthesis of Some Derivatives of 2-Deoxy-D-galacturonic Acid.*

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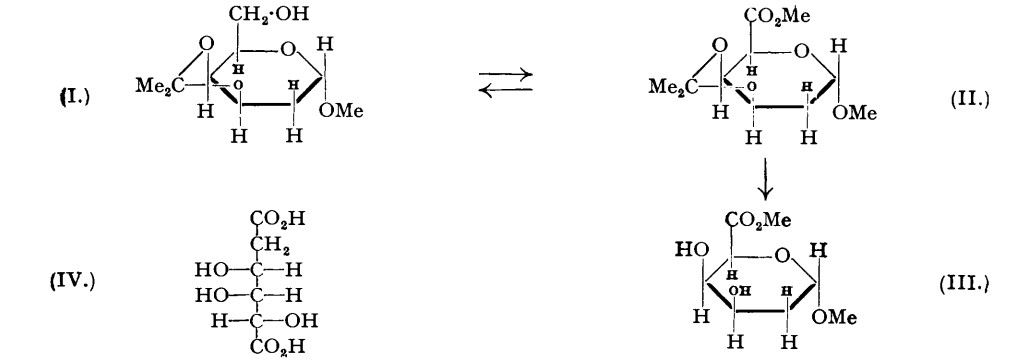
The synthesis of some derivatives of 2-deoxy-D-galacturonic acid is described. Their conversion into the monolactone of 2-deoxygalactosaccharic acid is outlined.

During work in progress in this Department on the chemistry of the hexuronic acids and particularly on the mechanism of the Tollens naphtharesorcinol diagnostic reaction for acids of this class (cf. Tollens, *Ber.*, 1908, **41**, 1788; Mayer, Block, and Chaffee, *Fed. Proc.*, 1942, **1**, 125; Hanson, Mills, and Williams, *Biochem. J.*, 1944, **38**, 274; Guerrero and Williams, *Nature*, 1948, **161**, 930; Ogata and Nozaki, *J. Pharm. Soc. Japan*, 1943, **63**, 416; 1944, **64**, 14) it became necessary to prepare hexuronic acid derivatives suitably protected at $C_{(2)}$ so that this site in the molecule would not undergo reaction. Derivatives of the hitherto unknown 2-deoxyhexuronic acids seemed suitable for this purpose. Further it is well known that hexuronic acids can undergo intramolecular changes under alkaline conditions (Smith, *J.*, 1944, 510, 577) and it was considered likely that the 2-deoxyhexuronic acid derivatives might be of particular interest in investigating these changes.

Ohle and Berend (*Ber.*, 1925, **58**, 2585) described a method whereby uronic acid derivatives could be easily prepared. They converted 1 : 2-3 : 4-di*iso*propylidene D-galactose into 1 : 2-3 : 4-di*iso*propylidene D-galacturonic acid by oxidation with alkaline potassium permanganate. Similarly Ault, Haworth, and Hirst (*J.*, 1935, 517) used the method to convert 2 : 3-*iso*propylidene α-methylmannoside into 2 : 3-*iso*propylidene α-methylmannuronoside (cf. Stacey, *J.*, 1939, 1529). Recently the preparation of 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside (I) was described (*J.*, in the press) and it was expected that this would be a suitable starting material for the preparation of derivatives of 2-deoxygalacturonic acid.

3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside (I) was prepared from α-methyl-2-deoxy-D-galactoside by treatment with acetone and zinc chloride. It was characterised as its 6-*p*-nitrobenzoate. The galactoside (I) was oxidised under appropriate conditions with a solution of potassium permanganate and aqueous potassium hydroxide, affording 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galacturonoside as its potassium salt. This was immediately treated with diazomethane in ethereal solution and gave the crystalline methyl ester (II), which could be prepared alternatively by treating the potassium salt with an excess of methyl iodide. It gave a strong naphtharesorcinol test. When (II) was kept in 1% methanolic hydrogen chloride, scission of the *iso*propylidene residue occurred and α-methyl-2-deoxy-D-galacturonoside

methyl ester (III) was obtained in crystalline form. It was readily converted into the corresponding amide by methanolic ammonia. Although both (II) and (III) readily gave the



Tollens naphtharesorcinol reaction for hexuronic acids, neither gave the brick-red colour with basic lead acetate which was described by Stacey (*loc. cit.*) as specific for galacturonic acid.

When 2-deoxy-D-galactose was oxidised with nitrogen tetroxide it yielded a crystalline derivative which elemental analysis indicated was a monolactone of 2-deoxy-D-galactosaccharic acid (IV). This was also prepared by oxidation with bromine of relatively crude 2-deoxy-D-galacturonic acid, itself prepared by acidic hydrolysis of 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galacturonoside methyl ester (II). The monolactone gave a crystalline acridine salt. It is interesting that 2-deoxy-D-galactosaccharic acid gives a monolactone, since the corresponding galactosaccharic acid cannot readily be made to undergo lactone formation. The monolactone, after treatment with dilute aqueous alkali, did not reduce hot Fehling's solution, thereby indicating that isomerisation to an unsaturated compound such as occurs with glucosaccharo-1 : 5-3 : 6-dilactone and mannosaccharodilactone (Smith *et al.*, *loc. cit.*) had not taken place.

The syntheses herein described, coupled with that of 2-deoxy-D-galactonic acid (*J.*, 1950, 671), make the main oxidation products of 2-deoxy-D-galactose available for study and use in synthetic operations. Further work on the Tollens reaction will be reported later.

Recently Lythgoe and Trippett (*J.*, 1950, 1983) elaborated a method for the identification of methylated uronic acid derivatives in which they are converted into methylated aldoses by making use of lithium aluminium hydride to effect the reduction $CO_2Me \longrightarrow CH_2{\cdot}OH$. This method was extended by Smith *et al.* (*Nature*, 1950, **166**, 1037). We had independently applied it in the present work and have been able to demonstrate that lithium aluminium hydride in ethereal solution reduces (II) to 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside (I).

Experimental.

3 : 4-iso*Propylidene α-Methyl-2-deoxy-*D*-galactopyranoside.*—α-Methyl-2-deoxy-D-galactoside (2·4 g.) was mechanically shaken for 3 days with dry acetone (50 c.c.) and zinc chloride (8 g.). The product was isolated in the manner described earlier (Overend, Foster, and Stacey, *J.*, 1951, 974). The *iso*propylidene derivative was obtained as a colourless syrup (1·5 g.), b. p. 105—110° (bath-temp.)/0·008 mm., n_D^{12} 1·4689, $[\alpha]_D^{15}$ +94·6° (*c*, 0·76 in ethanol).

This derivative (0·404 g.) and *p*-nitrobenzoyl chloride (0·315 g.) were dissolved in dry pyridine (5 ml.). After 5 hours at room temperature the solution was poured into water. The solid which separated was collected and recrystallised from aqueous methanol. The 6-p-*nitrobenzoate* had m. p. 96°, $[\alpha]_D^{18}$ +56·3° (*c*, 1·03 in methanol) (Found : C, 55·8; H, 5·5. $C_{17}H_{21}O_8N$ requires C, 55·5; H, 5·7%).

3 : 4-iso*Propylidene α-Methyl-2-deoxy-*D*-galacturonoside Methyl Ester.*—(*a*) 3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside (1·4 g.) was treated with a solution of potassium permanganate (2·8 g.) in aqueous potassium hydroxide (0·75 g. in 100 c.c. of water). The solution immediately became green, and then brown (manganese dioxide). After 20 hours at room temperature the mixture was filtered, and the filtrate neutralised with carbon dioxide and then evaporated to dryness under diminished pressure. After a preliminary extraction with ether (30 c.c.) the residue was extracted with dry ethanol. The ethanolic extract was evaporated to dryness and afforded a syrupy residue, which gave a strong Tollens naphtharesorcinol test for uronic acids. This syrup was dissolved in dry acetone (20 c.c.) and precipitated by addition of an equal volume of dry ether, as a hygroscopic amorphous powder (1·67 g.). After dissolution in water (10 c.c.) this powder was treated with 0·5N-sulphuric acid (6·24 c.c.). The acidic solution was immediately extracted with ether (5 × 60 c.c.). The extract was washed with water, dried ($MgSO_4$), and concentrated. The residue was then treated with an excess of diazomethane in ether (200 c.c.). After 2 days in a dry atmosphere the solution was filtered and the filtrate evaporated at room temperature. The solid residue was recrystallised from dry ether and 3 : 4-iso*propylidene α-methyl-2-deoxy-*D*-galacturonoside methyl ester* (0·42 g.) was obtained as colourless needles, m. p. 132—133·5°, $[\alpha]_D^{14}$ +16·8° (*c*, 0·77 in methanol) (Found : C, 53·8; H, 7·5. OMe, 25·9. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3; OMe, 25·2%). This ester gave a strong naphtharesorcinol test.

(*b*) 3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside (8·8 g.) was added to a solution of potassium permanganate (15 g.) and potassium hydroxide (9·5 g.) in water (400 c.c.). Next morning the mixture was filtered and the filtrate evaporated to dryness. The residue was washed with ether to remove unchanged material and potassium 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galacturonate was obtained by extraction with dry methanol and evaporation of the extract. It was dissolved in dry methanol (50 c.c.) and the solution heated under reflux for 3 hours with excess of methyl iodide (15 c.c.). The solvent and remaining methyl iodide were removed by evaporation and the residue was extracted by boiling under reflux with ether (4 × 50 c.c.). The residue after this extraction was re-treated with methanol and methyl iodide and the above procedure followed. This procedure was repeated twice more. The combined ethereal extracts were evaporated to dryness and the solid residue was recrystallised from dry ether; 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galacturonoside methyl ester (3·9 g.) was obtained as colourless needles, m. p. 132—133·5° alone or on admixture with the above sample.

α-Methyl-2-deoxy-D-galacturonoside Methyl Ester.—3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galacturonoside methyl ester (2·5 g.) was dissolved in 1% methanolic hydrogen chloride (25 c.c.) and set aside for 7 hours. Then the solution was neutralised with silver carbonate and filtered through a charcoal pad. The filtrate was evaporated to dryness and the syrupy residue crystallised on trituration with ethyl acetate. Repeated recrystallisation from ethyl acetate afforded *α-methyl-2-deoxy-D-galacturonoside methyl ester* (1·2 g.) as colourless needles, m. p. 111°, $[\alpha]_D^{17}$ +128° (*c*, 1·25 in methanol) (Found : C, 46·3; H 6·8. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%).

α-Methyl-2-deoxy-D-galacturonoside Amide.—α-Methyl-2-deoxy-D-galacturonoside methyl ester (0·128 g.) was dissolved in absolute methanol saturated with dry ammonia and the solution set aside for 17 hours at room temperature. Evaporation of the solvent gave a solid residue which on recrystallisation from ethyl acetate afforded the *amide* (0·086 g.) as colourless needles, m. p. 203°, $[\alpha]_D^{16}$ +105·4° (*c*, 1·1 in methanol) (Found : C, 44·02; H, 6·7. $C_7H_{13}O_5N$ requires C, 43·97; H, 6·8%).

Monolactone of 2-Deoxy-D-galactosaccharic Acid.—(*a*) 2-Deoxy-D-galactose (1·5 g.) was treated with dry nitrogen tetroxide (3 c.c.) at 0° in a dry atmosphere. After 18 hours the nitrous gases were removed by evaporation under diminished pressure initially at room temperature and then at 50°. The residual syrup was dissolved in ethyl acetate, and the solution was re-evaporated. This procedure was repeated several times to ensure complete removal of nitrous gases. The syrup finally obtained, which was non-reducing towards hot Fehling's solution, was dissolved in water (15 c.c.) and treated with excess of silver oxide. Filtration and evaporation of the filtrate afforded material which was washed with absolute ethanol to remove syrupy products. The dry material was then dissolved in water (20 c.c.) and the solution filtered through a charcoal pad. Thereafter hydrogen sulphide was passed through the filtrate and the precipitate separated. After re-evaporation the dry residue was extracted with acetone. Removal of the solvent afforded a syrup which crystallised on trituration with ether. Recrystallisation from acetone–ether afforded the *monolactone* (150 mg.), m. p. 155—157° (indefinite), $[\alpha]_D^{21}$ −43·4° (constant for 6 days) (*c*, 1·15 in water) (Found : C, 40·8; H, 4·6. $C_6H_8O_6$ requires C, 40·9; H, 4·5%).

(*b*) 3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galacturonoside methyl ester (0·5 g.) in 0·01% hydrochloric acid (20 c.c.) was heated at 100° for an hour (after this time the optical rotation was constant). Silver carbonate was added to effect neutralisation. After filtration the filtrate was treated with hydrogen sulphide and refiltered. Evaporation of the filtrate to dryness, followed by extraction of the residue with absolute methanol and concentration of the extract, afforded a syrup (0·24 g.) which could not be induced to crystallise. It was strongly reducing towards Fehling's reagent. The syrup was dissolved in water (5 c.c.) and bromine (0·5 c.c.) was added. After 4 days, excess of bromine was removed by aeration and the solution was neutralised by addition of silver oxide. The precipitate was removed and the filtrate evaporated to dryness. The residue was heated under reflux with methanol (15 c.c.) and then filtered. The precipitate was washed with absolute methanol followed by ether and was then redissolved in water (2 c.c.). Hydrogen sulphide was passed through the solution which was then filtered through a charcoal pad. The lactone (0·05 g.), isolated from the filtrate in the manner already described, had m. p. 155—157° alone or on admixture with the sample prepared by the previous method.

The monolactone (59 mg.) and acridine (60 mg.) in dry methanol (1·0 c.c.) were heated at 60° for 5 minutes. Thereafter ether was added. A precipitate formed and was collected. Recrystallisation from methanol–ether afforded the *monoacridine* salt (75 mg.), m. p. 148°, $[\alpha]_D^{19.5}$ −25·3° (*c*, 2·1 in methanol) (Found : C, 63·9; H, 4·9. $C_6H_8O_6,C_{13}H_9N$ requires C, 64·2; H, 4·8%).

Reduction of 3 : 4-iso*Propylidene α-Methyl-2-deoxy-D-galacturonoside Methyl Ester with Lithium Aluminium Hydride.*—3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galacturonoside methyl ester (1 g.) and finely powdered lithium aluminium hydride (1·2 g.) in dry ether (200 c.c.) were heated under reflux for 5 hours. After the solution had been cooled, water (10 c.c.) was added, followed by excess of 5N-hydrochloric acid (15 c.c.). The mixture was vigorously agitated and then immediately neutralised by the addition of sodium hydrogen carbonate. The ethereal layer was separated and the aqueous residue further extracted with ether (3 × 150 c.c.). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated under diminished pressure. The syrupy residue was distilled as a colourless syrup (0·2 g.), b. p. 105—110° (bath-temp.)/0·05 mm., n^{15} 1·4685 (Found : C, 54·4; H, 8·1; OMe, 15·0. Calc. for $C_{10}H_{18}O_5$: C, 55·0; H, 8·3; OMe, 14·3%). It was 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactopyranoside.

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