222. *Deoxy-sugars. Part XVIII. Synthesis of an Oligosaccharide by the Thermal Condensation of αβ-Methyl-2-deoxy-*D*-galactofuranoside.*

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The nature of the product resulting from the slow distillation of αβ-methyl-2-deoxy-D-galactofuranoside has been investigated. Hydrolysis of the oligosaccharide-type material yielded 2-deoxygalactose, and methylation and hydrolysis afforded tri- and di-methyl 2-deoxygalactose.

It was noted by Deriaz *et al.* (*J.*, 1949, 2836) that on distillation of αβ-methyl-2-deoxy-L-ribofuranoside polymeric material was formed whenever superheating occurred. Similar effects were observed by Hughes, Overend, and Stacey (*J.*, 1949, 2846) with the corresponding αβ-methyl-2-deoxy-D-glucofuranoside and we now record a more extended examination of the polymeric material obtained during the purification of αβ-methyl-2-deoxy-D-galactofuranoside (Overend, Shafizadeh, and Stacey, *J.*, 1950, 671).

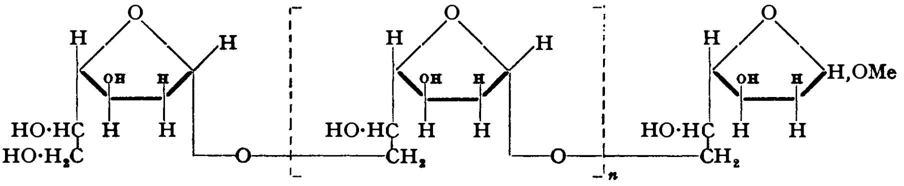
With Dr. R. E. Deriaz we examined the product from the thermal condensation of αβ-methyl-2-deoxy-L-ribofuranoside in somewhat closer detail. Thus the polymer was a hard colourless glass, very soluble in water but insoluble in the usual organic solvents. It was non-reducing to Fehling's solution until after acid hydrolysis. Determination of the molecular weight by the Rast method, and of the methoxyl content, indicated a polymer with about 5—7 pentose units. On treatment with methanolic hydrogen chloride there was a smooth conversion of the polymeric material into crystalline β-methyl-2-deoxy-L-ribopyranoside. It appeared that condensation of the methyl-2-deoxy-L-ribofuranoside had occurred by elimination of methanol. Qualitatively analogous results were obtained with the D-isomer of the deoxy-sugar. A detailed study was made on the more readily accessible αβ-methyl-2-deoxy-D-galactofuranoside, particularly as the condensation reaction leads to poor yields of the pure methylglycofuranoside.

First, it was observed that if pure αβ-methyl-2-deoxy-D-galactofuranoside was subjected to rapid distillation it was not converted easily into the glassy material. Hence impurities in the crude glycoside such as traces of colloidal silver may help to induce the condensation. With this methylglycofuranoside the important fact was established that its conversion into the hard polymeric material was accompanied by the evolution of methanol. This was collected and characterised as its *p*-nitrobenzoate and by conversion into methyl salicylate. That no more fundamental change was involved than condensation by elimination of methanol was indicated by the fact that hydrolysis of the glassy material with N-hydrochloric acid at room temperature afforded 2-deoxy-D-galactose in good yield. Moreover, it was apparent that $C_{(1)}$ of the sugar is involved in the reaction since, although there was elimination of the glycosidic methyl group, the resulting glassy material was non-reducing to Fehling's solution. That the nature of the lactol ring was unchanged during the elimination of methanol could be demonstrated by comparison of the rate of hydrolysis of the polymerised material with that of the hydrolysis of methyl-2-deoxy-D-galactopyranoside. The latter was hydrolysed by N-hydrochloric acid at room temperature only after three days, whereas the glassy material was almost completely hydrolysed in thirty minutes, and αβ-methyl-2-deoxy-D-galactofuranoside in thirty minutes.

Although it is known that a methylene group at $C_{(2)}$ of the sugar renders the glycosidic centre labile (cf. Overend and Stacey, *J. Soc. Food Agr.*, 1950, **1**, 168) (especially is this so for methyl 2-deoxyglycofuranosides) and that glycals can undergo polymerisation, it is unlikely that the loss of methanol occurred between $C_{(1)}$ and $C_{(2)}$ of the deoxy-sugar to give a furanose form of galactal which then polymerised, since at no stage did absorption of bromine occur and there was no other evidence of unsaturation. Moreover, the product did not reduce hot Fehling's solution, a property typical of glycals.

Evidence obtained seems to indicate that the product of the condensation reaction is not homogeneous. For example, although it was soluble in water from which solution in some cases it could be precipitated with ethanol, a property which in the sugar series indicates polymeric character, little correlation existed between molecular weight and end-group methoxyl determinations. Also no definite stages in the reaction were observed. Values for the molecular weights varied considerably from sample to sample according to the conditions used to prepare the material. Similar variable results were observed with end-group methoxyl determinations. (It was noted that the optical rotation of the material could be used as a rough guide to the molecular weight, since it became more positive the higher the molecular weight.) The molecular weight and methoxyl determinations did, however, eliminate the possibility of the material being 1 : 3-, 1 : 5-, or 1 : 6-anhydride of 2-deoxy-D-galactofuranose, or a mixture of these. From the results obtained it appears that an average of four molecules of 2-deoxy-D-galactose are joined together, although as stated considerable variation from this value was observed with some samples. In some of the deoxyribose products the almost complete absence of residual methoxyl groups could indicate substances of relatively high molecular weight.

Viscosity determinations in aqueous solution, with the viscometer described by Orthmann, Koch, and Degenfelder (*J. Amer. Leather Chem. Soc.*, 1939, **34**, 489), confirmed the oligosaccharide character of the material. In addition the material reduced lead tetra-acetate. The amount of the oxidant consumed was, for one sample, equivalent to one mole per four units of 2-deoxy-D-galactofuranose. Since this reagent is known to oxidise adjacent hydroxyl groups (Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1939, **61**, 1667) it appears that such groups occur only once every four units. This could be so if four 2-deoxy-D-galactofuranose units were joined together by 1 : 5- or 1 : 6-linkages. The material was methylated by the Freudenburg technique (*Ber.*, 1938, **71**, 2505) (*i.e.*, use of sodium in liquid ammonia, followed by methyl iodide). After four methylations no further increase in methoxyl content (36·8%) occurred. The product was purified to some extent by fractional precipitation of the impurities from chloroform solution by addition of ether. The methylated product was hydrolysed by being heated at 60° with N-hydrochloric acid for 30 minutes. The hydrolysis product was fractionally distilled and some 3 : 5 : 6-trimethyl 2-deoxy-D-galactose (cf. Overend, Shafizadeh, and Stacey, *loc. cit.*) was obtained. The residues were then converted into glycosides by treatment with 1% methanolic hydrogen chloride and subsequently distilled. After repeated fractionation, two major fractions were obtained, namely, a trimethyl and a dimethyl methyl-2-deoxy-D-galactoside. No monomethyl methyl-2-deoxy-D-galactoside was detected. The trimethyl methylglycoside probably arose from incomplete hydrolysis of the methylated product or incomplete separation of the trimethyl 2-deoxy-D-galactose. Some indication was obtained that the dimethyl methylgalactoside had the primary hydroxyl group free since it yielded a syrupy toluene-*p*-sulphonyl derivative which afforded 1 mole of sodium toluene-*p*-sulphonate when heated [140° (bath-temp.) for 30 minutes] under anhydrous conditions with acetone and sodium iodide. The rapid hydrolysis of the dimethyl methyl-2-deoxy-D-galactoside (as shown by polarimetric observation) by mild acidic reagents indicated that it was a furanose.



(I.)

The results described indicate that the hard glassy material obtained when crude αβ-methyl-2-deoxy-D-galactofuranoside is distilled slowly is mainly an oligosaccharide of low molecular weight in which the units of 2-deoxy-D-galactofuranose are most probably linked through the 1 : 6-positions as shown in (I) (other products may also be present since at all stages unidentified material was obtained). It is now well established that the methylglycosides of 2-deoxy-D-galactofuranose are very labile and it would seem that the formation of this material is a further example. This is supported by the fact that α-methyl-2-deoxy-D-galactopyranoside could be heated under similar conditions for long periods and yet be recovered unchanged. Since the methylglycofuranosides of 2-deoxyribose and 2-deoxyglucose also form similar hard glassy materials when heated, it seems that this is a fairly general reaction of 2-deoxy-sugars. It is interesting to note that recently Barker and Lock (*J.*, 1950, 23) demonstrated that the anhydride derivative of ribose first reported by Bredereck *et al.* (*Ber.*, 1940, **73**, 956) is derived from two moles of ribofuranose, and Hurd and Edwards (*J. Org. Chem.*, 1949, **14**, 680) showed that thermal dehydration of α- and β-glucose leads to the formation of products having molecular weights in the di- and tri-saccharide range.

EXPERIMENTAL.

*Experiments with 2-Deoxy-*D*-ribose* [with R. E. DERIAZ].—2-Deoxy-D-ribose (0·26 g.) was dissolved in 0·1% methanolic hydrogen chloride (5 c.c.) at 23°. The ensuing reaction was followed polarimetrically and after 12 minutes silver carbonate and silver oxide were added to arrest the reaction. The solution was filtered through a charcoal pad and then concentrated under diminished pressure. The syrupy residue was non-reducing to Fehling's solution and was αβ-methyl-2-deoxy-D-ribofuranoside (cf. Deriaz *et al., loc. cit.*). On rapid heating, distillation resulted [b. p. 115—120° (bath-temp.)/0·4 mm.], but on slow heating polymerisation occurred and a hard glassy substance was formed. The glassy solid (1·214 g.) was dissolved in 1% methanolic hydrogen chloride. After 0·5 hour the specific rotation of the solution was constant. The solution was neutralised with barium carbonate and filtered. After removal of the solvent by evaporation at 40°, the residue was extracted with benzene. Evaporation of the benzene at 40° gave β-methyl-2-deoxy-D-ribopyranoside (0·36 g.), m. p. 83·5° alone or on admixture with an authentic specimen.

*2-Deoxy-*D*-galactose.*—2-Deoxy-D-galactose, prepared by the method already reported (Overend, Shafizadeh, and Stacey, *J.*, 1950, 671), showed m. p. 110° and $[\alpha]_D^{20}$ +57° ± 2° (equilibrium, *c*, 1·0 in water).

*αβ-Methyl-2-deoxy-*D*-galactofuranoside.*—To 2-deoxy-D-galactose (3·8 g.) in methanol solution (100 c.c.), 4·5% methanolic hydrogen chloride (1 c.c.) was added. The reaction was followed polarimetrically and at the maximum lævorotation the solution was neutralised with silver carbonate. The glycoside (3·5 g.) was isolated in the usual manner. It showed n_D^{21} 1·4828 and $[\alpha]_D^{17}$ −68° (*c*, 0·67 in methanol) (Found : OMe, 17·7. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). On rapid distillation of this crude material a colourless syrup was obtained, b. p. 180° (bath-temp.)/0·001 mm., $[\alpha]_D^{17}$ −75° (Found : OMe, 17·6%).

*α-Methyl-2-deoxy-*D*-galactopyranoside.*—This was prepared according to Overend, Shafizadeh, and Stacey (*loc. cit.*), and had m. p. 112—113°, $[\alpha]_D^{18}$ +164° (*c*, 0·38 in methanol) (Found: OMe, 17·8. Calc. for $C_7H_{14}O_5$: OMe, 17·4%).

Formation of the Polymer.—αβ-Methyl-2-deoxy-D-galactofuranoside (5 g.) was heated at 230° (bath-temp.)/12 mm. for 15 minutes. A colourless mobile liquid was evolved and collected in a trap cooled with liquid air. This mobile liquid was identified as methanol and further characterised as its *p*-nitrobenzoate, m. p. 96° alone or on admixture with an authentic specimen. The residue was further heated at 210—230°/12 mm. for 2·5 hours and then any unchanged material or anhydride was removed by distillation [up to 235° (bath-temp.)/0·01 mm.]. The polymer was a brittle glass, soluble in water, but less so in ethanol. The above example is a typical procedure, although it should be recorded that the degree of polymerisation obtained is greater for lower pressures. The optical rotation became increasingly positive the greater the degree of polymerisation. For the largest polymer obtained $[\alpha]_D^{18}$ was +11·4° (*c*, 1·73 in water). Molecular-weight determinations (cryoscopic) on several samples indicated that the polymers ranged on an average from 4 to 8 units. Methoxyl determinations supported the molecular-weight data although in general they tend to give slightly lower values. Thus a polymer with molecular weight 650 (corresponding to 4—5 units) showed OMe, 3·4%. This polymer was not precipitated by ethanol (2 vols.), but more highly polymerised specimens showing traces only of methoxyl content could be precipitated from aqueous solution by addition of one volume of ethanol. When dried, this precipitate was a pale yellow hygroscopic powder, non-reducing to Fehling's solution.

Hydrolysis of the Polymeric Material.—The polymer (0·537 g.) was dissolved in N-hydrochloric acid (10 c.c.) and the solution was kept at room temperature. The reaction, followed polarimetrically, was complete in 30 minutes. The solution was neutralised with silver oxide and filtered through a charcoal pad. The filtrate was evaporated to dryness and afforded a thick syrup which crystallised. Recrystallisation from methanol afford 2-deoxy-D-galactose (0·325 g.), m. p. 110°, $[\alpha]_D^{20}$ +58° (equilibrium, *c*, 1·0 in water).

*Attempt to polymerise α-Methyl-2-deoxy-*D*-galactopyranoside.*—α-Methyl-2-deoxy-D-galactopyranoside (1 g.) was heated under diminished pressure. At 170° (bath-temp.)/0·01 mm. it began to reflux and no methanol was evolved. After 45 minutes at this temperature the starting material was recovered unchanged.

Methylation of the Polymer.—The polymer (powder form) (3 g.) was smoothly methylated by dissolving it in liquid ammonia (250 c.c.) and adding excess of sodium (1·5 g.) in small pieces, followed by methyl iodide (15% excess, 12 g.). The procedure was repeated 4 times, and then the liquid ammonia was allowed to evaporate and the residue was extracted repeatedly with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. The syrupy residue was dissolved in chloroform (15 c.c.) and ether (30 c.c.) was added. A tarry material separated and was removed. Evaporation of the solvent gave a syrupy material (2·3 g.), insoluble in water and non-reducing to Fehling's solution, $[\alpha]_D^{19}$ ±0° (*c*, 1·3 in ethanol) (Found : OMe, 36·8%).

Hydrolysis of the Methylated Product.—The purified methylated polymer (2·32 g.) and N-hydrochloric acid (15 c.c.) were heated to 60° for 0·5 hour and then left for 20 hours at room temperature. The solution was neutralised with silver carbonate and filtered through a charcoal pad, and the filtrate was evaporated to dryness under diminished pressure. A pale brown mobile syrup (2·0 g.) was obtained, which reduced Fehling's solution.

Fractionation of the Hydrolysis Product.—The syrupy material was distilled and the distillate was mainly a trimethyl 2-deoxy-D-galactofuranoside (see table, fraction *A*) which was purified by successive redistillation. The still residues were combined and treated with 1% methanolic hydrogen chloride (15 c.c.) for 5 hours to effect glycosidation. The solution was neutralised with silver carbonate and filtered through a charcoal pad, and the filtrate evaporated to dryness. The syrupy residue was fractionally distilled (see table) and the fractions obtained were further purified by repeated redistillation. This process yielded three main fractions, namely, trimethyl 2-deoxy-D-galactose (*A*), trimethyl methyl-2-deoxygalactoside (*B*) (Found: C, 54·3: H, 9·4. Calc. for $C_{10}H_{20}O_5$: C, 54·6; H, 9·1%), dimethyl methyl-2-deoxygalactoside (*C*), and some residues which were hard tarry materials after heating at 140°/0·02 mm. No monomethyl methyl-2-deoxy-D-galactoside was detected.

Fractionation products.

Fraction.	OMe, %. Found.	OMe, %. Calc.	n_D.	B. p./mm.	Weight (mg.).	Ref.
A, Trimethyl 2-deoxy-D-galactose	46·7	45·1	1·4460	90°/0·3	200	1
B, Trimethyl methyl-2-deoxygalactoside	53·5	56·3	1·4420	83°/0·01	310	2
C, Dimethyl methyl-2-deoxygalactoside	44·9	45·1	1·4561	110°/0·05	606	—
D, Residue from redistillations of *C*	—	—	—	—	82	—
Tarry still residue	—	—	—	—	252	—

[1] Overend, Shafizadeh, and Stacey (*loc. cit.*) give b. p. 105—110° (bath-temp.)/0·001 mm. for 3 : 5 : 6-trimethyl 2-deoxygalactofuranose. [2] *Idem, ibid.*, quote b. p. 130—135° (bath-temp.)/12 mm., n_D^{21} 1·4421, for 3 : 5 : 6-trimethyl $\alpha\beta$-methyl-2-deoxygalactofuranoside.

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