621. *Carbonate Derivatives of Methyl* α-D-*Mannopyranoside and of* D-*Mannose.*

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Reaction of methyl α-D-mannopyranoside (I) with an excess of benzyl chloroformate and aqueous sodium hydroxide gave methyl 4,6-di-*O*-benzyloxycarbonyl-α-D-mannopyranoside 2,3-carbonate (II; R = $Ph{\cdot}CH_2$), which on catalytic hydrogenation yielded methyl α-D-mannopyranoside 2,3-carbonate (III). The latter was also prepared from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (IV) by the action of carbonyl chloride in toluene–pyridine and subsequent acid hydrolysis of the *O*-benzylidene group.

Reaction of D-mannose with benzyl chloroformate and aqueous sodium hydroxide afforded 1-*O*-benzyloxycarbonyl-α-D-mannofuranose 2,3:5,6-dicarbonate (VI).

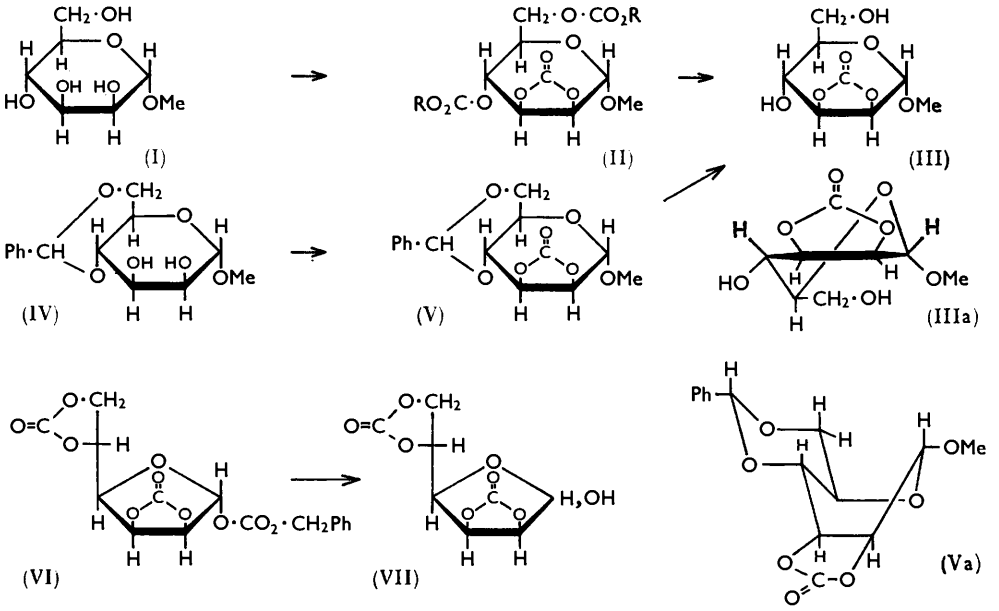
EXISTING methods for the preparation and characterisation of carbohydrate carbonates have practical difficulties which severely limit the usefulness of these derivatives as suitably protected intermediates in synthesis.[1] Three general methods of esterification have been employed, namely, carbonyl chloride in an organic base,[2] a chloroformic ester in an organic base,[3] and a chloroformic ester in aqueous alkali.[4] The application of carbonyl chloride to carbonate preparations has been restricted by the poor yields obtained, frequently lower than 5%, and the obvious practical hazards involved. Of the two more convenient methods of synthesis using chloroformic esters, the reaction in organic base is less versatile since fully substituted *O*-alkyloxycarbonyl- and *O*-aryloxycarbonyl-derivatives are usually obtained,[1] whereas the reaction in aqueous alkali can give both cyclic and open-chain carbonates.[4] The stereochemical features of this reaction have been examined with reference to methyl α-D-mannopyranoside (I) [5] and D-mannose.

Investigation of the reaction conditions showed that above 5° the yield of product was seriously impaired,[6] presumably because of the comparatively rapid alkaline hydrolysis of both the chloroformic ester and the carbohydrate carbonate. However, when a mixture of either methyl chloroformate or ethyl chloroformate and an aqueous solution of methyl-α-D-mannopyranoside (I) was treated at 0° with aqueous sodium hydroxide, smooth reactions occurred to give the crystalline methyl di-*O*-alkyloxycarbonyl-α-D-mannopyranoside carbonates. On the other hand, the use of benzyl chloroformate in this reaction gave negligible product unless an equal volume of dioxan was added, whereupon a crystalline methyl di-*O*-benzyloxycarbonyl-α-D-mannopyranoside carbonate was produced in 60—90% yield. Clearly the conditions for these esterifications are critical and vary with the nature of the chloroformic ester.

In order to satisfy steric requirements,[5] the cyclic ester group in these three derivatives of methyl α-D-mannopyranoside (I) must be attached as a six-membered 4,6-carbonate or as a five-membered 2,3-carbonate. By analogy with the structures of the corresponding *O*-isopropylidene derivatives, the cyclic carbonates have generally been assumed to be five-membered although proof of this has seldom been attempted.[1] In this connection the C=O stretching frequency in the infrared spectrum can be used to distinguish between five- and six-membered carbonate rings,[7] and application of this technique to the mannopyranoside derivatives gave evidence that the cyclic carbonates were five-membered.[8]

[1] Hough, Priddle, and Theobald, *Adv. Carbohydrate Chem.*, 1960, **15**, 91.
[2] Haworth and Porter, *J.*, 1930, 151.
[3] Zemplén and László, *Ber.*, 1915, **48**, 915.
[4] Allpress and Haworth, *J.*, 1924, **125**, 1223.
[5] Hough and Priddle, *Chem. and Ind.*, 1959, 1600.
[6] Theobald, personal communication.
[7] Hough, Priddle, Theobald, Barker, Douglas, and Spoors, *Chem. and Ind.*, 1960, 148.
[8] Hough and Priddle, *J.*, 1961, 581.

The *O*-benzyloxycarbonyl groups of the methyl di-*O*-benzyloxycarbonyl-α-D-mannopyranoside carbonate were selectively removed by catalytic hydrogenation,[9] using either Raney nickel or 10% palladium-on-charcoal as catalyst, with the formation of methyl α-D-mannopyranoside 2,3-carbonate (III). The latter was identified by comparison with an authentic specimen prepared from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (IV) by treatment with carbonyl chloride in the presence of pyridine, followed by acid hydrolysis of the 4,6-*O*-benzylidene residue in the resultant 2,3-carbonate (V). Thus, the structure of the product from the chloroformate reaction is firmly established as methyl 4,6-di-*O*-benzyloxycarbonyl-α-D-mannopyranoside 2,3-carbonate (II; R = $Ph{\cdot}CH_2$) and consequently the products from the reactions with methyl and ethyl chloroformate are assigned similar structures (II; R = Me and Et respectively). Fusion of the 2,3-carbonate ring



to the pyranoid chair conformation would be expected to bring $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ into co-planarity, and the cyclic carbonate derivative (III) would adopt a half-chair conformation (IIIa).[5] However, the *O*-benzylidene derivative (V) would tend towards a boat conformation (Va), as was suggested by molecular models and by the large difference in the molecular rotations of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (IV) ($[M]_D$ +17,900°) and its 2,3-carbonate ($[M]_D$ −5,850°).

In contrast to these pyranoside derivatives, the reaction of D-mannose with benzyl chloroformate in the presence of aqueous sodium hydroxide yielded a crystalline mono-*O*-benzyloxycarbonyl-D-mannose dicarbonate. Since catalytic hydrogenation of this compound gave the known D-mannofuranose 2,3:5,6-dicarbonate (VII),[2] the original product must be the 1-*O*-benzyloxycarbonyl derivative (VI). Comparison of the molecular rotation of the latter ($[M]_D$ +19,100°) with that of methyl α-D-mannofuranoside 2,3:5,6-dicarbonate ($[M]_{5780}$ +21,400°) [10] showed it to be the α-anomer.

Experimental

Unless otherwise stated, infrared spectra were obtained by the Nujol-mull technique. Optical rotations were measured at 24° ± 1°. M. p.s were determined on a Kofler micro-heating stage.

[9] Barker, Gillam, Lord, Douglas, and Spoors, *J.*, 1960, 3885.
[10] Haworth and Porter, *J.*, 1930, 649.

Benzyl Chloroformate.—Benzyl chloroformate was obtained in 94% yield by the dropwise addition of benzyl alcohol to excess of liquid carbonyl chloride cooled in a bath of ethanol–solid carbon dioxide. Hydrogen chloride and excess of carbonyl chloride were removed by drawing a current of dry air through the liquid. Benzyl chloroformate was characterised as its carbamate derivative.[11]

Methyl 4,6-*Di*-O-*benzyloxycarbonyl*-α-D-*mannopyranoside* 2,3-*Carbonate* (II; R = CH_2Ph).—Methyl α-D-mannopyranoside (19·4 g.) was dissolved in water (50 ml.), and to the solution was added benzyl chloroformate (100 ml., 6 mol.) previously neutralised by the addition of a little sodium hydrogen carbonate. Dioxan (100 ml.) was added and the reaction mixture was vigorously stirred at 0° whilst 3N-sodium hydroxide (200 ml.) was added dropwise during about 3 hr. Stirring was continued until the pH had fallen to a constant value. Water was then added to dissolve any precipitated sodium salts, the solution was extracted with chloroform (3 × 200 ml.), and the extracts dried ($CaSO_4$) and concentrated under reduced pressure to a thin syrup. Aromatic impurities were removed in a high vacuum at 170° (bath). The brown residue was dissolved in ethanol (charcoal) and filtered, and the clear solution concentrated to a syrup which crystallised after several months (60—90% yield in different preparations). Recrystallisation from ethanol gave *methyl* 4,6-*di*-O-*benzyloxycarbonyl*-α-D-*mannopyranoside* 2,3-*carbonate*, m. p. 111—111·5°, $[\alpha]_D$ +10·7° (*c* 1·1 in $CHCl_3$); $\nu_{max.}$ (C=O stretching) 1740, 1750, and 1830 cm.$^{-1}$ (Found: C, 59·0; H, 4·8; OMe, 6·9. $C_{24}H_{24}O_{11}$ requires C, 59·0; H, 4·9; OMe, 6·4%).

Methyl 4,6-*Di*-O-*methoxycarbonyl*-α-D-*mannopyranoside* 2,3-*Carbonate* (II; R = Me).—Methyl α-D-mannopyranoside (5 g.), in a mixture of methyl chloroformate (37 g.) and chloroform (50 ml.), was treated as above with 7·5% (w/v) sodium hydroxide (200 ml.). Evaporation of the chloroform extract gave a sticky solid (5 g.) which crystallised from chloroform–light petroleum (b. p. 40—60°) to give *methyl* 4,6-*di*-O-*methoxycarbonyl*-α-D-*mannopyranoside* 2,3-*carbonate* (2 g.), m. p. 172°, $[\alpha]_D$ +23·6° (*c* 1·1 in $CHCl_3$), and $\nu_{max.}$ (C=O stretching) 1745, 1755, and 1830 cm.$^{-1}$ (Found: C, 42·6; H, 5·0; OMe, 27·7. $C_{12}H_{16}O_{11}$ requires C, 42·8; H, 4·8; OMe, 27·7%).

Methyl 4,6-*Di*-O-*ethoxycarbonyl*-α-D-*mannopyranoside* 2,3-*Carbonate* (II; R = Et).—A mixture of methyl α-D-mannopyranoside (5 g.) and ethyl chloroformate (27 g.) was treated with 3N-sodium hydroxide (100 ml.) as above. *Methyl* 4,6-*di*-O-*ethoxycarbonyl*-α-D-*mannopyranoside* 2,3-*carbonate* was obtained as a yellow syrup (*ca.* 90% yield) which gave crystals after several months. Recrystallised from ethanol they had m. p. 117—117·5°, $[\alpha]_D$ +15·5° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ (C=O stretching) 1740, 1752, and 1832 cm.$^{-1}$ (Found: C, 45·8; H, 5·5; OAlk, 32·7. $C_{14}H_{20}O_{11}$ requires C, 46·1; H, 5·5; OAlk, 33·2%).

Methyl 4,6-O-*Benzylidene*-α-D-*mannopyranoside* 2,3-*Carbonate* (V).—A solution of carbonyl chloride (1 g.) in toluene (11·4 g.) was added dropwise to a stirred solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[12] (1 g.) in a mixture of pyridine (5 ml.) and chloroform (10 ml.), cooled in an ice-bath. After being stirred overnight, the brown solution was carefully treated with water (10 ml.), and more chloroform (25 ml.) was added. The chloroform layer was separated, dried ($CaSO_4$), and evaporated to a yellow syrup which on trituration with acetone–ether gave crystals of *methyl* 4,6-O-*benzylidene*-α-D-*mannopyranoside* 2,3-*carbonate* (1 g.). After decolorisation with activated charcoal, and recrystallisation from acetone, the crystals had m. p. 125°, $[\alpha]_D$ −19·0° (*c* 1·2 in $CHCl_3$), and $\nu_{max.}$ (C=O stretching) 1810 cm.$^{-1}$ (Found: C, 58·1; H, 5·4. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

Methyl α-D-*Mannopyranoside* 2,3-*Carbonate* (III).—(*a*) Methyl 4,6-di-*O*-benzyloxycarbonyl-α-D-mannopyranoside 2,3-carbonate (2·2 g.) was dissolved in dioxan (100 ml.), and 10% palladium–charcoal (1 g.) added. The mixture was hydrogenated at atmospheric pressure at 20° until hydrogen consumption ceased. After filtration, the solution was dried ($CaSO_4$) and evaporated to give crystals of *methyl* α-D-*mannopyranoside* 2,3-*carbonate* (1 g.). Recrystallised from acetone–ether they had m. p. 157—158°, $[\alpha]_D$ +56·9° (*c* 1·0 in $CHCl_3$), and $\nu_{max.}$ (C=O stretching) 1810 cm.$^{-1}$ (Found: C, 43·7; H, 5·7; OMe, 14·5. $C_8H_{12}O_7$ requires C, 43·7; H, 5·5; OMe, 14·1%).

(*b*) A solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside 2,3-carbonate (0·35 g.) in a mixture of acetone (8 ml.) and N-hydrochloric acid (2 ml.) was kept at room temperature for 24 hr., neutralised (Ag_2CO_3), filtered, and then evaporated to dryness under reduced pressure.

[11] Carter, Frank, and Johnson, *Org. Synth.*, 1943, **23**, 13.
[12] Schwarz, unpublished method.

The residue was extracted with boiling ether, leaving crystals of methyl α-D-mannopyranoside 2,3-carbonate (0·21 g.) which had $[\alpha]_D$ +58° (*c* 1·0 in $CHCl_3$), m. p. 158° unchanged on admixture with the sample obtained by method (*a*), and an infrared spectrum identical with the above (Found: C, 43·5; H, 5·7; OMe, 14·7%).

1-O-*Benzyloxycarbonyl*-α-D-*mannofuranose* 2,3:5,6-*Dicarbonate* (VI).—To D-mannose (9 g.) in water (20 ml.) was added sodium hydrogen carbonate (1 g.) and a solution of benzyl chloroformate (50 ml.) in dioxan (50 ml.). The mixture was cooled to 0° and 3N-sodium hydroxide (100 ml.) was added dropwise with continuous stirring. After being stirred overnight the mixture was treated with chloroform, and a sticky solid separated from the organic layer. After trituration with more chloroform, crystals of 1-O-*benzyloxycarbonyl*-α-D-*mannofuranose* 2,3:5,6-*dicarbonate* (7·8 g.) were obtained which, after recrystallisation from acetone–light petroleum (b. p. 60—80°), had m. p. 168—169·5°, $[\alpha]_D$ +52·1° (*c* 1·6 in Me_2CO), and $\nu_{max.}$ (C=O stretching) 1765, 1801, and 1845 $cm.^{-1}$ (Found: C, 52·4; H, 4·0. $C_{16}H_{14}O_{10}$ requires C, 52·4; H, 3·8%).

D-*Mannofuranose* 2,3:5,6-*Dicarbonate* (VII).—(*a*) A solution of 1-*O*-benzyloxycarbonyl-α-D-mannofuranose 2,3:5,6-dicarbonate (5 g.) in dioxan (100 ml.) was hydrogenated at 20° and atmospheric pressure, 10% palladium–charcoal (1 g.) being used as catalyst. After filtration, evaporation to dryness gave crystals of D-mannofuranose 2,3:5,6-dicarbonate (2·8 g.) which on recrystallisation from water and then from ethanol–light petroleum (b. p. 60—80°) had m. p. 119—120°, $[\alpha]_D$ +30·2° (*c* 1·4 in Me_2CO) and $\nu_{max.}$ (C=O stretching) 1770, 1800, and 1830 $cm.^{-1}$ (Found: C, 41·5; H, 3·2. Calc. for $C_8H_8O_8$: C, 41·4; H, 3·4%). Only two C=O stretching absorptions with $\nu_{max.}$ 1800 and 1820 $cm.^{-1}$ were observed (KBr disc).

(*b*) By the method of Haworth and Porter,[2] D-mannose (6 g.) was dissolved in pyridine (40 ml.), cooled to 0° and treated with a stream of carbonyl chloride for 40 min. After the addition of ice–water (200 ml.) the insoluble amorphous material (4·2 g.) was discarded and the filtrate treated with excess of barium carbonate, filtered, and extracted with ethyl acetate (3 × 200 ml.). On evaporation of the extracts a yellow syrup (1 g.) was obtained which, after trituration with ethyl methyl ketone, yielded crystals of D-mannofuranose 2,3:5,6-dicarbonate (0·25 g.). Recrystallised from ethanol–light petroleum (b. p. 60—80°) they had m. p. and mixed m. p. 119—120°, $[\alpha]_D$ +29·4° (*c* 1·3 in Me_2CO), and identical infrared spectrum with the above (Found: C, 41·4; H, 3·5%).

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