Selective *O*-Acylation of Pyranosides

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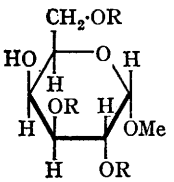
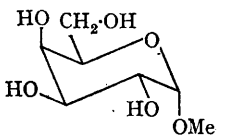
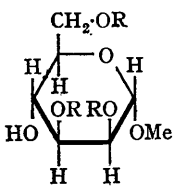
SELECTIVE esterification in the carbohydrate field has been largely confined to the preparation of derivatives esterified at the primary hydroxyl groups only, although 2,6-disubstituted derivatives of methyl α-D-glucopyranoside[1] and methyl α-D-galactopyranoside[2] have been prepared. The enhanced reactivity of the 2-hydroxyl group may be attributed to the electron-withdrawing effect of the adjacent anomeric centre, but work[3] on the selective sulphonylation of D-mannopyranose derivatives of fixed conformation has shown that steric factors can dominate the electronic effect of the anomeric centre. Since it has been established that axial hydroxyl groups are, due to steric factors, less rapidly acylated than equatorial hydroxyl groups,[4] we studied the partial acylation of pyranosides containing axial hydroxyl groups with a view to the preparation of useful synthetic intermediates.



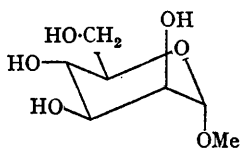
(IA); R=H
(IB); R=COPh



(II)



(IIIA); R=H
(IIIB); R=COPh



(IV)

The stable form of methyl α-D-galactopyranoside (IA) is the conformation[5] (II) in which the 4-hydroxyl group is axial. Reaction of the monohydrate of this pyranoside with 4·1 moles of benzoyl chloride in pyridine at −40° gave, in 56% yield, a crystalline tri-*O*-benzoate, m.p. 139–140·5°, $[\alpha]_D^{27}$ + 123° ($CHCl_3$). As expected, the product was identical with methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (IB), prepared by Reist *et al.*,[6] in 42% yield from methyl α-D-galactopyranoside by a four-step synthesis. The derived methanesulphonate ester underwent nucleophilic displacement by benzoate in dimethylformamide with inversion of configuration.[7] The resulting product, methyl α-D-glucopyranoside tetra-*O*-benzoate, thus provided unequivocal proof that the benzoate groups were located at the 2,3, and 6 positions.

Similarly, the stable form of methyl α-D-mannopyranoside (IIIA) is the conformation[5] (IV) in which the 2-hydroxyl group is axial. Partial benzoylation with 3·1 moles of benzoyl chloride gave, in 57% yield, a tribenzoate which crystallised as the monohydrate, m.p. 67–69°, $[\alpha]_D^{27}$ −21° (Me_2CO). The derived methanesulphonate was resistant to nucleophilic displacement by benzoate in dimethylformamide, and so other means of structural elucidation were sought.

The tribenzoate, when treated with dihydropyran, gave a crystalline diastereoisomeric mixture of the two tetrahydropyranyl ethers in 89% yield. Catalytic debenzoylation of this ether, followed by methylation (methyl iodide and silver oxide) and mild acid hydrolysis gave a methyl tri-*O*-methyl-α-D-mannopyranoside in 59% overall yield from the tetrahydropyranyl ether mixture. Acid hydrolysis of the glycoside unexpectedly gave

[1] See for example A. K. Mitra, D. H. Ball, and L. Long, jun., *J. Org. Chem.*, 1962, **27**, 160; J. M. Sugihara, *Adv. in Carbohydrate Chem.*, 1958, **8**, 1.
[2] P. A. Rao and F. Smith, *J.*, 1944, 229.
[3] G. O. Aspinall and G. Zweifel, *J.*, 1957, 2271.
[4] E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, 1957, **79**, 5986.
[5] R. E. Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499.
[6] E. J. Reist, R. R. Spencer, B. R. Baker, and L. Goodman, *Chem. and Ind.*, 1962, 1794.
[7] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, 1959, **24**, 1618.

2,3,6-tri-*O*-methyl-D-mannose, characterised as the di-*p*-nitrobenzoate, m.p. and mixed m.p. 188–190°, $[\alpha]_D^{27}$ +37° ($CHCl_3$), lit.,[8] +33°. Consequently the tribenzoate must be methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (IIIB) and not the 3,4,6-isomer as expected.

These results clearly demonstrate that the order of reactivity of the secondary hydroxyl groups of pyranosides is not solely dependant upon whether a particular group is axial or equatorial. Further investigations with a wider range of pyranosides and on the possibility of benzoyl migration are now under way.

The reactions leading to 2,3,6-tri-*O*-methyl D-mannose constitute the first synthesis of this compound from D-mannose.

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[8] P. A. Rebers and F. Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 6097.