979. *Cyclitols. Part XVII.*[1] *The Selectivity of Protecting Groups: Tetrahydropyranyl Ethers*

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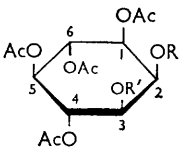
Dihydropyran reacts unselectively with axial and equatorial hydroxyl groups in partially acetylated myoinositol derivatives.

Many derivatives of inositols, such as phosphates, glycosides, and methyl ethers, occur in Nature.[2] For their syntheses, inositol derivatives are required in which some of the hydroxyl groups are protected by readily removable groups. The methods used for introducing such protecting groups can be divided into those which lead to predominantly selective reaction of equatorial hydroxyl groups, and those which show no such selectivity. Esterifications belong to the first class, 1,4,5,6-tetra-*O*-acetylmyoinositol reacts with acetyl chloride [3] and with toluene-*p*-sulphonyl chloride [1] predominantly in the 3-position. It is

[1] Part XVI, S. J. Angyal, P. T. Gilham, and G. J. Melrose, preceding Paper.
[2] S. J. Angyal and L. Anderson, *Adv. Carbohydrate Chem.*, 1959, **14**, 135.
[3] J. H. Davies and T. Malkin, *Nature*, 1959, **184**, 789.

now shown that the reaction with dihydropyran, leading to 2′-tetrahydropyranyl ethers, is completely unselective.

2,3-Dihydropyran reacts with primary, secondary, and even tertiary alcohols,[4] but there are few instances [5,6] of its use in carbohydrate chemistry. The tetrahydropyranyl ethers are valuable derivatives because they can be formed and split under mild conditions in the presence of acids; it is interesting to mention the selective removal of tetrahydropyranyl groups by acid-catalysed methanolysis with retention of isopropylidene blocking groups.[7] We have now ascertained that in partially acetylated polyols neither the formation nor the splitting of tetrahydropyranyl ethers is accompanied by acetyl migration.



(I) R = R′ = H
(II) R = R′ = C_5H_9O
(III) R = Ac; R′ = C_5H_9O
(IV) R = C_5H_9O; R′ = Ac

The readily available 1,4,5,6-tetra-*O*-acetylmyoinositol (I) [8] was used as starting material; it was hoped that preferential pyranylation in the 3 position would lead to the synthesis of the as yet elusive 1,2,4,5,6-penta-*O*-acetylmyoinositol. Reaction with dihydropyran, catalysed by hydrogen chloride, gave a mixture of di- and mono-tetrahydropyranyl ethers and starting material. The diether was readily isolated owing to its low solubility in water and was shown to be the 2,3-ditetrahydropyranyl ether (II) by its reconversion into 1,4,5,6-tetra-*O*-acetylmyoinositol. This diether is probably a mixture of diastereoisomers since formation of a tetrahydropyranyl ether from dihydropyran introduces a new asymmetric centre at C-2 of the pyranyl ring; accordingly, the melting point was not sharp.

After acetylation of the reaction mixture a monotetrahydropyranyl ether penta-acetate was isolated; the wide range of its melting point was ascribed to the presence of diastereoisomers. It was first thought that diastereoisomers of the 3-ether had been obtained because replacement of the tetrahydropyranyl by a tosyl group gave 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol [1] in low yield. However, gas chromatography of the penta-acetates, and paper chromatography after deacetylation, showed that two compounds were present of which one coincided with the 2-tetrahydropyranyl ether; the latter was readily synthesised from 1,3,4,5,6-penta-*O*-acetylmyoinositol.[9]

Since the evidence did not indicate whether the two compounds were diastereoisomers or structural isomers, a method was developed which proved to be generally useful for the analysis and characterisation of partially acetylated cyclitols. The tetrahydropyranyl groups were removed by treatment with acid (thereby removing the possibility of diastereoisomerism) and were replaced by propionyl groups. Gas chromatography then showed the presence of two compounds, one of which coincided with the penta-acetate of 2-*O*-propionylmyoinositol, synthesised from 1,3,4,5,6-penta-*O*-acetylmyoinositol; the other one must therefore be the 3-propionate. Analysis of a crude reaction mixture, by this method, indicated that approximately equal amounts of the 2- and the 3-tetrahydropyranyl ether were formed in the reaction of 1,4,5,6-tetra-*O*-acetylmyoinositol with dihydropyran.

Crystallisation of the ether mixture gave some pure 2-tetrahydropyranyl ether but the 3-isomer could be obtained in minute amounts only by preparative paper chromatography.

[4] H. J. E. Loewenthal, *Tetrahedron*, 1959, **6**, 269; J. F. W. McOmie, *Adv. Org. Chem., Methods and Results*, 1963, **3**, 218.
[5] H. G. Khorana, A. F. Turner, and J. P. Vizsolyi, *J. Amer. Chem. Soc.*, 1961, **83**, 686; M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *ibid.*, 1962, **84**, 430.
[6] A. N. De Belder, P. J. Garegg, B. Lindberg, G. Petropavlovskii, and O. Theander, *Acta Chem. Scand.*, 1962, **16**, 623.
[7] B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, 1963, **28**, 2132.
[8] S. J. Angyal, M. E. Tate, and S. D. Gero, *J.*, 1961, 4116.
[9] T. Posternak, *Helv. Chim. Acta*, 1941, **24**, 1045.

Hence the method is not suitable for the preparation of the 1,2,4,5,6-penta-acetate of myoinositol.

For comparison, 5-*O*-tetrahydropyranylmyoinositol and the penta-acetate of the 5-propionate were also synthesised from 1,2,3,4,6-penta-*O*-acetylmyoinositol.[10]

Experimental

Chromatography.—Descending paper chromatography at 20° on Whatman No. 1 paper with butan-1-ol–ethanol–water (40 : 11 : 19) gave the following R_{myo} values after 18 hr.: myoinositol, 1·00; 1-*O*-(2-tetrahydropyranyl), 3·18; 5-*O*-(2-tetrahydropyranyl), 3·60; 2-*O*-(2-tetrahydropyranyl), 3·76; 1,2-di-*O*-(2-tetrahydropyranyl), 4·87. In butan-1-ol–ethanol–water (6 : 1 : 1) the R_{myo} values were 6·65, 9·1, 9·25, and 8·9; in ethyl methyl ketone saturated with water the R_F values were 0·09, 0·16, 0·19, and 0·17 for the 1-, 2-, 4-, and 5-tetrahydropyranyl ethers, respectively. The substances were detected by alkaline silver nitrate.[11]

Gas chromatography was carried out as previously described.[12] The penta-acetates of tetrahydropyranyl ethers did not always give reproducible results but the 2-ether had a longer retention time at 221° than the 3-ether. The fully acetylated propionates gave the following retention times at 232°: myoinositol, 13·0; 2-*O*-propionyl, 15·1; 3-*O*-propionyl, 15·9; 2,3-di-*O*-propionyl, 17·8; 1,3-di-*O*-propionyl, 20·4 min. The last compound was obtained by propionylation of the 2,4,5,6-tetra-acetate, prepared (Dr. B. Shelton) by base-catalysed isomerisation of the 1,4,5,6-tetra-acetate.

1,3,4,5,6-*Penta*-O-*acetyl*-2-O-(2-*tetrahydropyranyl*)*myoinositol* (IV).—After standing overnight, a mixture of 1,3,4,5,6-penta-*O*-acetylmyoinositol [9] (137 mg.), dichloromethane (5 ml.), dihydropyran (0·5 ml.), and hydrogen chloride in dry dioxan (0·1 ml.; 5N) was shaken with potassium carbonate (1 g.) and then poured into an aqueous solution (10%) of sodium carbonate. The mixture was extracted with chloroform (4 × 20 ml.), and the organic layer was washed with water, dried (K_2CO_3), and evaporated at reduced pressure; the residue, on crystallisation from ethanol, gave the *tetrahydropyranyl ether* (101 mg., 60%), m. p. 183—185° (Found: C, 52·9; H, 6·25. $C_{21}H_{30}O_{12}$ requires C, 53·15; H, 6·35%).

1,2,3,4,6-*Penta*-O-*acetyl*-5-O-(2-*tetrahydropyranyl*)*myoinositol* was prepared in the same way from 1,2,3,4,6-penta-*O*-acetylmyoinositol [10] (516 mg.), dihydropyran (1 ml.), and hydrogen chloride in dry dioxan (0·5 ml.; 5N). The *compound* (429 mg., 68%), m. p. 225—226°, crystallised from ethanol (Found: C, 53·5; H, 6·4%): Deacetylation with a catalytic amount of sodium methoxide in methanol gave 5-O-(2-*tetrahydropyranyl*)*myoinositol*, m. p. 213—215°, crystals (68%) from methanol–ethyl acetate (Found: C, 49·7; H, 7·65. $C_{11}H_{20}O_7$ requires C, 50·0; H, 7·6%). Heating of the penta-acetate with 50% acetic acid for 15 min. on a steam-bath gave 1,2,3,4,6-penta-*O*-acetylmyoinositol (67%), m. p. 170—172°, not depressed on admixture with an authentic sample. The 4-tetrahydropyranyl ether was prepared in the same way but was not obtained crystalline.

1,3,4,5,6-*Penta*-O-*acetyl*-2-O-*propionylmyoinositol.*—After standing overnight, a mixture of 1,3,4,5,6-penta-*O*-acetylmyoinositol (1·02 mg.), dry pyridine (3 ml.), and propionic anhydride (2 ml.) was poured into ice–water. After 2 hr. the separated crystals were filtered and recrystallised from ethanol, to give the *propionate* (127 mg., 94%), m. p. 175—177° (Found: C, 51·0; H, 5·75. $C_{19}H_{26}O_{12}$ requires C, 51·1; H, 5·85%).

In the same way, 1,2,3,4,6-*penta*-O-*acetyl*-5-O-*propionylmyoinositol* and 1,4,5,6-*tetra*-O-*acetyl*-2,3-*di*-O-*propionylmyoinositol* were prepared from the 1,2,3,4,6-penta-acetate and the 1,4,5,6-tetra-acetate, respectively. The propionate, m. p. 171—172°, was obtained in 92% yield (Found: C, 50·8; H, 5·85%), and the dipropionate, m. p. 143—145°, in 68% yield (Found: C, 52·25; H, 6·15. $C_{20}H_{28}O_{12}$ requires C, 52·15; H, 6·15%).

Reaction of Dihydropyran with 1,4,5,6-*Tetra*-O-*acetylmyoinositol.*—(*a*) After standing overnight, a mixture of 1,4,5,6-tetra-*O*-acetylmyoinositol [8] (2·78 g.), dichloromethane (20 ml.), dihydropyran (1·01 g.), and hydrogen chloride in dry dioxan (0·3 ml.; 5N) was shaken with potassium carbonate (1 g.) and then poured into an aqueous solution (10%) of sodium carbonate. The mixture was extracted with chloroform (5 × 40 ml.), and the organic layer was washed with water, dried (K_2CO_3), and evaporated *in vacuo*; the residue was dissolved in anhydrous methanol

[10] S. J. Angyal and M. E. Tate, *J.*, 1961, 4122.
[11] E. F. L. J. Anet and T. M. Reynolds, *Nature*, 1954, **174**, 930.
[12] Z. S. Krzeminski and S. J. Angyal, *J.*, 1962, 3251.

(6 ml.) and a catalytic amount of sodium was added. Next day the mixture was evaporated and the residue was chromatographed on a column of cellulose powder (500 g.) with acetone–water (4 : 1). Fractions (40 ml.) were examined by paper chromatography in acetone–water (4 : 1).

Fractions 1—7 contained inositol-free material (350 mg.) which did not show up with the silver nitrate reagent. Fractions 7—12 gave 1,2-*di*-O-(2-*tetrahydropyranyl*)*myoinositol* (500 mg.; 18%), R_F 0·90, which crystallised from ethanol as colourless needles, m. p. 183—185°, after shrinking at 153—158° (Found: C, 54·4; H, 8·0. $C_{16}H_{28}O_8$ requires C, 55·15; H, 8·1%).

Fractions 12—19 contained a mixture of mono- and di-ethers. Fractions 19—50 gave a spot at R_F 0·69 and on evaporation gave mono-(2-tetrahydropyranyl)myoinositols (987 mg., 47%). Part of this material was chromatographed on Whatman 3 MM paper in butan-1-ol–ethanol–water (40 : 11 : 19) for 48 hr.; the slower moving material was eluted with acetone–water (4 : 1) and was found to be homogeneous (R_{myo} 3·18; retention time on g.l.c., after removal of the tetrahydropyranyl group and propionylation, 15·9 min.).

(*b*) Another similar reaction mixture was evaporated to dryness under reduced pressure and the yellow residue was extracted with boiling water (90 ml.); the undissolved material (1·0 g., 12%) was recrystallised from ethanol, to yield 1,4,5,6-*tetra*-O-*acetyl*-2,3-*di*-O-(2-*tetrahydropyranyl*)*myoinositol* (II), m. p. 204—206° (Found: C, 55·9; H, 7·0. $C_{24}H_{36}O_{12}$ requires C, 55·8; H, 7·05%). The same compound was obtained (76%) on acetylation of 1,2-di-*O*-(2-tetrahydropyranyl)myoinositol.

The filtrate was evaporated under reduced pressure and the residue was heated with pyridine (80 ml.) and acetic anhydride (50 ml.) for 3 hr. on a steam-bath. The mixture was evaporated to dryness, and the residue hydrolysed with boiling acetic acid (70 ml.; 80%) for 25 min. After evaporation, the residue was warmed with water (20 ml.); next day hexa-*O*-acetylmyoinositol (3·1 g.), m. p. 215°, was filtered off.

The filtrate was evaporated to dryness and the residue was crystallised from ethanol, to give a mixture of penta-*O*-acetylmyoinositols (0·8 g.), m. p. 158—162° (Found: C, 46·85; H, 6·05. Calc. for $C_{16}H_{22}O_{11},H_2O$: C, 47·05; H, 5·9%). Tosylation and crystallisation from ethanol gave 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol (6%), m. p. 149—151°, undepressed by an authentic sample.[1]

(*c*) The crude mixture resulting from another similar run was acetylated and hydrolysed with 50% acetic acid and then propionylated, as above. The resulting product gave four distinct peaks on g.l.c., corresponding to the acetates of myoinositol, its 2- and 3-propionate, and its 2,3-dipropionate.

Hydrolysis of 1,4,5,6-*Tetra*-O-*acetyl*-2,3-*di*-O-(2-*tetrahydropyranyl*)*myoinositol*.—The compound (169 mg.) was heated for 15 min. on a steam-bath with 50% acetic acid (6 ml.). The mixture was evaporated, redissolved in water, and again evaporated; the residue was crystallised from ethanol–water, and then from anhydrous ethanol, to give 1,4,5,6-tetra-*O*-acetylmyoinositol (85 mg., 74%), m. p. 126—128°, undepressed on admixture with an authentic sample.

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