

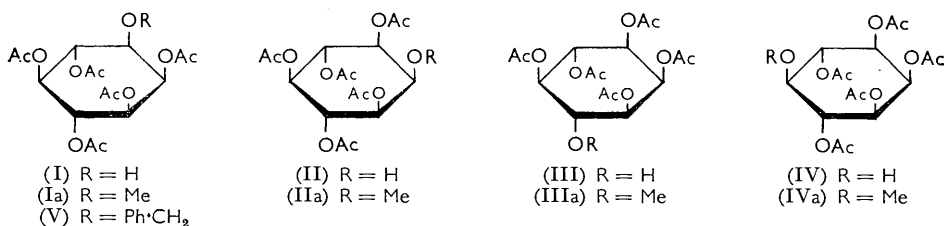
1198. Cyclitols. Part XIX.¹ Control of Acetyl Migration during Methylation of Partially Acetylated Cyclitols

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A systematic study was made of the methylation of penta-*O*-acetylmyoinositols in order to find conditions which allow methylation without concurrent acetyl migration. It was found possible to suppress *trans* migration nearly completely, but not the *cis* migration of acetyl groups.

THERE appears to be no satisfactory method for the methylation of the free hydroxyl groups in partially acetylated contiguous polyols; acetyl migration usually occurs and mixtures are obtained, or derivatives in which the methoxyl groups are not located in the positions of the originally free hydroxyl groups. Many such instances have been reported in carbohydrate chemistry²⁻⁹ and two in the literature of cyclitols.^{10,11} The aim of the present investigation was to find conditions under which acetyl migration during methylation could be suppressed; this aim was not fully achieved.

The readily available 1,3,4,5,6-penta-*O*-acetylmyoinositol (II) was used in most experiments; methylation of this compound with silver oxide and methyl iodide in dioxan was reported¹⁰ to give penta-*O*-acetyl-1-*O*-methylmyoinositol (Ia), owing to acetyl migration. 1,2,3,4,5-Penta-*O*-acetylmyoinositol (III) and 1,2,3,4,6-penta-*O*-acetylmyoinositol (IV) were used in some experiments.



Methylation in *NN*-dimethylformamide¹² with methyl iodide and silver oxide, which is regarded as the best method, resulted in over 90% methylation of penta-acetylmyoinositols but also in extensive acetyl migration. Indeed, migration was more rapid than methylation and, as a result, treatment of either penta-acetate (II) or (III), or of the equilibrium mixture¹ of all isomers (I)—(IV), gave approximately the same mixture of

TABLE I
Methylations of penta-*O*-acetylmyoinositols in dimethylformamide

Starting material	Products (%)			
	(Ia)	(IIa)	(IIIa)	(IVa)
(II)	52	8	26	15
(III)	49	7	29	15
(I)—(IV) (equilibrium mixture)	45	6	31	18

¹ Part XVIII, S. J. Angyal and G. J. H. Melrose, preceding Paper.

² W. A. Bonner, *J. Org. Chem.*, 1959, **24**, 1388.

³ B. Helferich and W. Klein, *Annalen*, 1927, **455**, 173.

⁴ W. N. Haworth, E. L. Hirst, and E. G. Teece, *J.*, 1930, 1405; 1931, 2858.

⁵ J. S. D. Bacon, D. J. Bell, and H. W. Kosterlitz, *J.*, 1939, 1248.

⁶ L. von Vargha, *Ber.*, 1934, **67**, 1223.

⁷ G. J. Robertson, *J.*, 1933, 737.

⁸ A. S. Perlin, *Canad. J. Chem.*, 1963, **41**, 555.

⁹ P. J. Garegg, *Acta Chem. Scand.*, 1962, **16**, 1849.

¹⁰ L. Anderson and A. M. Landel, *J. Amer. Chem. Soc.*, 1954, **76**, 6130.

¹¹ S. J. Angyal, P. T. Gilham, and L. G. Macdonald, *J.*, 1957, 1417.

¹² R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, 1955, **67**, 32.

penta-*O*-acetyl-*O*-methylmyoinositols, (Ia)—(IVa) (Table 1). A similar observation was made by Garegg⁹ who obtained the same mixture of dimethyl ethers by the methylation of either the 2- or the 3-acetate of benzyl 4-*O*-methyl- β -D-xylopyranoside.

The results in Table 1 show that most of the starting material was converted into the equilibrium mixture of the four penta-acetates before methylation proceeded to any considerable extent. This equilibrium mixture contains¹ the four penta-acetates (I)—(IV) in the approximate ratio 20 : 20 : 30 : 30; the composition of the reaction products indicates that the rate of methylation is fastest at O-1 and slowest at O-2. This is in contrast to the methylation¹³ with diazomethane and boron trifluoride in which the reaction at O-1 is slower than at O-4 and O-5, and the axial O-2 is not methylated at all.

The effect of various factors on the rate of acetyl migration was investigated. It was found that water has a strong accelerating effect. When 1,3,4,5,6-penta-*O*-acetylmyoinositol was stirred with dry silver oxide in chloroform for 1.5 hr., there was no noticeable migration; but if the oxide was first moistened with water, over 90% of the acetate suffered migration in the same period. The extent of migration could be reduced to 25% by adding anhydrous calcium sulphate before the moist silver oxide; but migration could not be suppressed by calcium sulphate during methylation because water is formed in the methylation reaction, on the catalyst surface, and is adsorbed there despite the presence of the drying agent.

The silver oxide generally used for methylations is prepared from silver nitrate by precipitation with excess sodium hydroxide;¹⁴ such an oxide may contain traces of sodium hydroxide which would strongly catalyse acetyl migration. It was found that a catalyst prepared by the use of excess silver nitrate¹⁵ caused less migration (see Table 2, Nos. 3

TABLE 2
Variables affecting acetyl migration and yield during methylation of
penta-*O*-acetylmyoinositols

No.	Starting material	Solvent	Vol. (ml.)	MeI (ml.)	Temp.	Time (hr.)	Methyl- ation (%)	Products (%)					
								(Ia)	(IIa)	(IIIa)	(IVa)	(II)	(I) + (III) + (IV)
1	(II)	HCONMe ₂	19	1	20°	2	94	48	11	19	17	0	5
2	(II)	CHCl ₃	19	1	20	24	7	7	0	0	0	75	18
3	(II)	(CH ₂ Cl) ₂	19	1	20	24	7	7	0	0	0	71	21
4	(IV)	(CH ₂ Cl) ₂	19	1	20	24	30	1	0	5	24	0	70
5	(II)	(CH ₂ Cl) ₂	19	1	20	120	45	45	0	0	0	45	10
6	(II)	(CH ₂ Cl) ₂	19	1	60	24	80	69	2	6	2	3	18
7	(II)	(CH ₂ Cl) ₂	15	5	20	24	30	23	5	2	0	22	48
8*	(II)	(CH ₂ Cl) ₂	19	1	20	24	26	24	0	2	0	12	61

* The silver oxide used in this run was precipitated with excess sodium hydroxide, and that in all the other runs with insufficient base.

and 8), and was used in subsequent experiments; with this catalyst, however, methylation is slower. Methylation was negligible when silver carbonate was substituted for silver oxide.

The solvent has an important effect on the reaction too. A change from dimethylformamide to chloroform or 1,2-dichloroethane very markedly decreased migration, with accompanying low yields of methylation, in spite of an increase in the time of the reaction to 24 hr. (Table 2, Nos. 1 and 3). The nature (and probably the mechanism) of the reaction also undergoes a change; the axial O-2 is now methylated very slowly. To obtain acceptable yields the reaction must be prolonged (No. 5); even then *trans* migration

¹³ M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1959, **6**, 36.

¹⁴ F. J. Bates and Associates, "Polarimetry, Saccharimetry, and the Sugars," Nat. Bur. Stand., Circular C440, Washington, 1942, p. 507.

¹⁵ B. Helferich and W. Klein, *Annalen*, 1926, **450**, 219.

of acetyl groups, that is, from O-6 to O-1, is negligible. Only one methyl ether, 1-*O*-methylmyoinositol, is obtained, owing to slow *cis* migration and absence of methylation on the axial O-2 atom. Increase of temperature (No. 6) accelerates the reaction but results in some *trans* migration and some axial methylation; nevertheless, the 1-methyl ether is formed in good yield. In all these experiments the concentration of methyl iodide was kept low; its increase (No. 7), and the consequent increase in the polarity of the solvent mixture, results in more *trans* migration and axial methylation.

To summarise, *trans* migration of acetyl groups can be avoided, and *cis* migration minimised, by use of the following conditions: dry, neutral silver oxide, a solvent of low polarity containing a low concentration of methyl iodide, and low temperature. Methylation under these conditions is not complete, and axial hydroxyl groups may not react at all. Any change in conditions which increases the yield of methylation appears also to increase the extent of migration.

In contrast to these methods, methylation with diazomethane and boron trifluoride¹³ proceeds without migration but the yields are very low.¹

It was hoped that 1,3,4,5,6-penta-*O*-acetylmyoinositol would yield the 3-benzyl ether (V) when benzyl bromide was substituted for methyl iodide. However, the lower reactivity of benzyl bromide, compared with that of methyl iodide, allowed *trans* migration to proceed appreciably before ether formation; thus, a mixture of the 3- and 4-benzyl ethers was obtained. With a view to obtaining a higher yield of ethers, the use of substituted benzyl bromides was tried but without success; anisyl bromide mainly polymerised under the reaction conditions while 4-nitrobenzyl bromide failed to react.

EXPERIMENTAL

The methods used for analysing the mixture of reaction products was described in the preceding Paper.¹ Solvents were dried over anhydrous calcium sulphate. The silver oxide catalyst was prepared according to Bates *et al.*¹⁴ "Alkali-free" silver oxide was prepared by adding a hot aqueous solution (500 ml.) of sodium hydroxide (4.0 g.) to a well-stirred solution of silver nitrate (51 g., 3 mol.) in water (50 ml.), on a steam-bath during 30 min. The precipitate was repeatedly washed with boiling water and dried at 100° for 1.5 hr.

General Method of Methylation (cf. Tables 1 and 2).—The runs described in Table 1 were carried out with penta-*O*-acetylmyoinositol (50 mg.) and silver oxide (250 mg.) in a mixture of dimethylformamide (1.0 ml.) and methyl iodide (3.5 ml.) for 26 hr. at room temperature. For those in Table 2, penta-*O*-acetylmyoinositol (25 mg.) and silver oxide (250 mg.) were added to a well-stirred mixture of solvent and methyl iodide. After a time interval the mixture was centrifuged, the precipitate washed with chloroform (2 × 5 ml.), and the supernatant liquid dried (Na₂SO₄). In the runs described in Table 1, the solution was then concentrated to ca. 1 ml. and analysed by gas chromatography. In the runs in Table 2, the solution was evaporated *in vacuo* to dryness, the residue was propionylated and analysed.¹

Acetyl Migration in the Presence of Silver Oxide.—1,3,4,5,6-Penta-*O*-acetylmyoinositol (50 mg.) was stirred with chloroform (4.6 ml.) and dry silver oxide (250 mg.) for 1.5 hr.; gas chromatography, after propionylation, showed only the peak corresponding to starting material. In another experiment, the oxide was moistened with water (4 drops), and then caused migration to an extent of 95%. When anhydrous calcium sulphate (250 mg.) was added before the moist silver oxide, 75% of the starting material was found unchanged.

Attempted Benzylations.—(a) A mixture of 1,3,4,5,6-penta-*O*-acetylmyoinositol (250 mg.), 1,2-dichloroethane (130 ml.), benzyl bromide (6.7 ml.), and silver oxide (1.7 g.) was stirred under reflux for 3 days, more silver oxide (1.25 g.) being added after both the first and the second days. Excess benzyl bromide was removed by stirring and heating with ethanol (2 ml.). The solution was decanted, washed with potassium cyanide solution (5%) and water, dried (Na₂SO₄), and evaporated. The oily residue (5 g.) was distributed between light petroleum and methanol; the content (500 mg.) of the methanol layer was deacetylated with sodium methoxide. Paper chromatography (acetone–water, 4:1) revealed myoinositol and faster running compounds (*R_F* 0.8) which were subsequently isolated by chromatography on a cellulose powder column. The fraction (112 mg.) containing the benzyl ethers was acetylated, debenzylated over a palladium–charcoal catalyst, and analysed by methylation and propionylation, as

previously described.¹ Gas-liquid chromatography showed that the mixture of benzylated products contained *ca.* 45% of the 3- and 35% of the 4-benzyl ether, besides other products.

(b) To a solution of 1,3,4,5,6-penta-*O*-acetylmyoinositol (108 mg.) in 1,2-dichloroethane (52 ml.), 4-nitrobenzyl bromide (3.78 g.) and silver oxide (675 mg.) were added. After being stirred under reflux for 18 hr., the mixture was examined by thin-layer chromatography which revealed no inositol derivative other than the starting material.

(c) An experiment in which anisyl bromide was substituted for 4-nitrobenzyl bromide, as above, failed owing to the polymerisation of the reagent.¹⁶

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¹⁶ Cf. A. Lapworth and J. B. Shoemith, *J.*, 1922, **121**, 1391.
