Nucleophilic Displacement Reactions in Carbohydrates. Part XXII.[1] Formation of 1,4-Anhydropyranoses from 1-*O*-Acetyl-6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-α-L-manno- and -talo-pyranose with Sodium Azide [2]

By **John S. Brimacombe,* Jonathan Minshall,** and **Leslie C. N. Tucker,** Chemistry Department, The University, Dundee DD1 4HN

1-*O*-Acetyl-6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-α-L-mannopyranose (10; R = Ac) and the epimeric L-talopyranose sulphonate (12; R = Ac) yielded 1,4-anhydro-6-deoxy-2,3-*O*-isopropylidene-β-L-talopyranose (11) and 1,4-anhydro-6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranose (13), respectively, on treatment with sodium azide in *NN*-dimethylformamide at 140°. A mechanism involving initial deacetylation is proposed for these and related reactions.

WHEREAS D-gluco- and -galacto-pyranoside 4-alkanesulphonates undergo [3,4] S_N2 displacements with ionic nucleophiles in aprotic solvents, corresponding rhamnopyranoside derivatives [*e.g.* (1)] have been shown [5] to give ring-contracted products that can be considered [6] to arise from nucleophilic attack upon, and internal return to, the bicyclic oxonium ion intermediate (2). The inability of rhamnopyranoside 4-sulphonates to undergo direct displacement has been attributed [4] to steric inhibition to the nucleophile's approach caused by the β-*trans*-axial substituent at C-2. A similar ring-contraction mechanism has recently been proposed [7] to account for the conversion of 1-*O*-acetyl-2,3-di-*O*-benzoyl-4,6-di-*O*-methylsulphonyl-α-D-glucopyranose (3) and related compounds into the corresponding 1,4-anhydro-sugars (5) on treatment with sodium azide. Loss of the acetoxy-group is suggested to occur after ring contraction leading to a carbonium (or oxonium) ion intermediate (4). Richardson *et al.*[7] have pointed out that it is difficult to explain the differences in behaviour towards azide ion of the 1-acetate (3) and the corresponding glycosides [*e.g.*(6)], which undergo normal S_N2 displacements. Certainly, it is difficult to rationalise a complete change of mechanism for these displacements when the C-1 methoxy-group is replaced by an acetoxy-group, at a site fairly far removed from the reaction centre. This dilemma could be resolved if loss of the 1-acetoxy-group to yield the oxyanion (7) † preceded formation of the 1,4-anhydro-ring. Analogies [8-10] are available to indicate that the transformation (7) ⟶ (5) would be extremely easy. Moreover, partial deacetylation to give the

† We have tacitly assumed that the 6-sulphonyloxy-group is displaced with azide ion much more rapidly than the oxyanion is formed, although nothing is known regarding the relative rates of these processes.

[1] Part XXI, J. S. Brimacombe, J. Minshall, and L. C. N. Tucker, *Carbohydrate Res.*, in the press.

[2] Preliminary communication, J. S. Brimacombe, J. Minshall, and L. C. N. Tucker, *J.C.S. Chem. Comm.*, 1973, 142.

[3] See D. H. Ball and F. W. Parrish, *Adv. Carbohydrate Chem.*, 1969, **24**, 139, for a review; C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *J. Org. Chem.*, 1966, **31**, 2822; C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, D. N. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *J. Amer. Chem. Soc.*, 1964, **86**, 2939; C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, *ibid.*, p. 2937; C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, 1966, **31**, 2817.

[4] A. C. Richardson, *Carbohydrate Res.*, 1969, **10**, 395.

[5] C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and F. Sirokman, *J. Amer. Chem. Soc.*, 1966, **88**, 2073; S. Hanessian, *Chem. Comm.*, 1966, 796; C. L. Stevens, R. P. Glinski, G. E. Gutowski, and J. P. Dickerson, *Tetrahedron Letters*, 1967, 649.

[6] B. Capon, *Chem. Rev.*, 1969, **69**, 471; J. S. Brimacombe, *Fortschr. Chem. Forsch.*, 1970, **14**, 367; A. K. Al-Radhi, J. S. Brimacombe, and L. C. N. Tucker, *J.C.S. Perkin I*, 1972, 315.

[7] C. Bullock, L. Hough, and A. C. Richardson, *Chem. Comm.*, 1971, 1276.

[8] J. Kops and C. Schuerch, *J. Org. Chem.*, 1965, **30**, 3951.

[9] J. S. Brimacombe and L. C. N. Tucker, *Carbohydrate Res.*, 1967, **5**, 36.

[10] J. S. Brimacombe, F. Hunedy, and A. K. Al-Radhi, *Carbohydrate Res.*, 1969, **11**, 331.

alcohol (9; R = H) accompanied the displacement reaction [11] with azide ion in *NN*-dimethylformamide on benzyl 2-acetamido-3-*O*-acetyl-6-*O*-benzoyl-2-deoxy-4-*O*-methylsulphonyl-α-D-glucopyranoside (8), indicating that acetate groups may be labile under conditions normally employed for displacements with azide ion. In anticipation of the intrinsically greater reactivity of the 1-acetoxy-group towards nucleophilic attack,[12] we sought evidence to substantiate the proposal that the conversion of (3) into (5) in aprotic solvents proceeds by way of the oxyanion (7). Buchanan [13] has suggested a similar mechanism for this transformation.

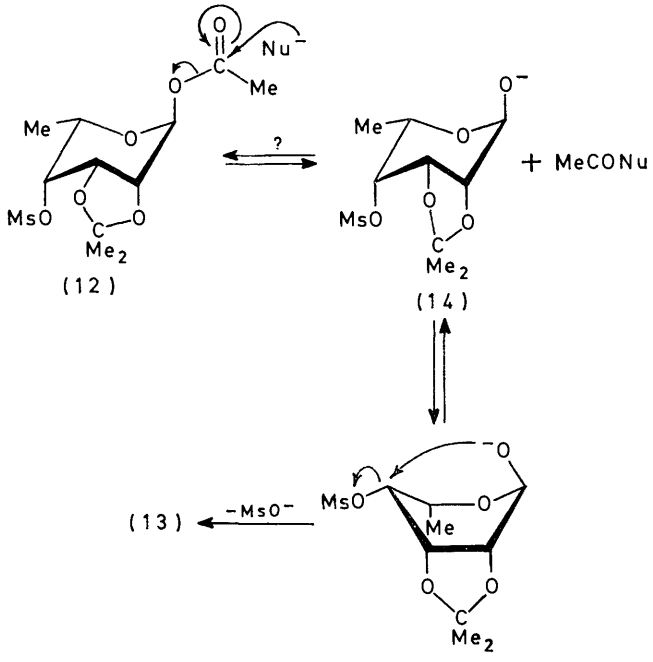
The possibility of converting 1-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-α-L-mannopyranose (10; R = Ac) and the epimeric L-talopyranose sulphonate (12; R = Ac) into the corresponding 1,4-anhydrosugars (11) and (13) by using sodium azide in *NN*-dimethylformamide was examined. The acetates (10; R = Ac) and (12; R = Ac) were prepared by acetylation

[11] W. Meyer zu Reckendorf and N. Wassiliadou-Micheli, *Chem. Ber.*, 1972, **105**, 2998.

[12] R. M. Rowell and M. S. Feather, *Carbohydrate Res.*, 1967, **4**, 486.

[13] J. G. Buchanan, in 'MTP International Review of Science—Carbohydrates,' ed. G. O. Aspinall, Butterworths, London, 1973, p. 40.

of the known α-alcohols (10; R = H) [9] and (12; R = H) [10] under conditions where anomerisation was unlikely. These compounds were chosen for study because the derived anhydro-sugars (11) [9] and (13) [10]

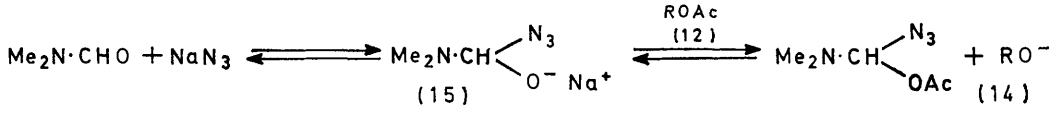


have been thoroughly characterized, and, more importantly, because a synchronous ring-contraction mechanism is obviously precluded on stereochemical grounds for the transformation (12) ⟶ (13). Indeed, it has been demonstrated [14] that unsaturated sugars and minor amounts of the inverted 4-azide are formed when methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-α-L-talopyranoside (12; R = Me) reacts with sodium azide in boiling *NN*-dimethylformamide.

Reaction of the acetylated sulphonate (10; R = Ac) with sodium azide in *NN*-dimethylformamide at 140° gave exclusively 1,4-anhydro-6-deoxy-2,3-*O*-isopropylidene-β-L-talopyranose (11), whereas analogous treatment of the epimeric sulphonate (12; R = Ac) afforded a number of products that included 1,4-anhydro-6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranose (13) (*ca.* 60%). The anhydro-sugars (11) and (13) were characterised by comparison (m.p. and/or n.m.r. and i.r. spectra) with authentic materials.[9,10] The transformation (10; R = Ac) ⟶ (11) was completed within 2 h and is thus significantly faster than authenticated ring contractions [5] involving the corresponding glycoside (1).

Preclusion of a ring-contraction mechanism logically requires * the sulphonate (12; R = Ac) to be converted into the 1,4-anhydro-sugar (13) by way of the oxyanion (14) formed by deacetylation at C-1 (see diagram). The ready conversion of the alcohol (12; R = H) into the anhydro-sugar (13) under mild basic conditions [10] can be cited in support of this mechanism; the latter reaction also yields a number of other products, just as observed in the present case. In view of their readiness, a mechanism involving initial deacetylation at C-1 also seems likely for the conversions (10; R = Ac) ⟶ (11) and (3) ⟶ (5); in these cases, anomerisation of the oxyanion to the β-form must precede intramolecular displacement of the sulphonyloxy-group at C-4 [*e.g.* (7) ⟶ (5)]. There are, however, literature analogies for these processes.[8,9]

Finally, we comment on the mechanism of the deacetylation reaction effected by sodium azide in *NN*-dimethylformamide. Preliminary experiments showed that azide ion has an essential role in these deacetylations: no chemical change was discerned when the acetate (10; R = Ac) was heated at 140° in *NN*-dimethylformamide in the absence of sodium azide. Deacetylation can be envisaged as involving attack on the 1-acetoxy-group either by azide ion [13] or, more probably, by an intermediate anion (15) formed in a reaction between *NN*-dimethylformamide and sodium azide.†



Our work and that of Richardson *et al.*[7] demonstrate the generality of this type of reaction and underline the ineffectiveness of the acetate group for protection of the anomeric centre of sugars in displacements with azide ion and, presumably, related nucleophiles.

EXPERIMENTAL

T.l.c. was performed on Kieselgel G, and spots were detected with vanillin–sulphuric acid.[16] I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer Infracord spectrophotometer, and n.m.r. spectra were determined for solutions in deuteriochloroform (1% tetramethylsilane as internal standard) with a Perkin-Elmer R10 spectrometer.

* It seems reasonable in this case to discount a mechanism involving participation by O-1 of the acetoxy-group since neighbouring-group participation is not evinced by the C-1 methoxy-group in azide displacements on the corresponding glycoside sulphonate [14] (12; R = Me), although such participation should be more favoured on electronic grounds. Moreover, participation of this type by a group at the anomeric centre invariably results [15] in migration of the group, due to the mesomeric effect of the ring-oxygen atom in opening of the cyclic intermediate. Cleavage of the acetoxy-group in the manner indicated in an *aprotic* solvent, however, would furnish a highly nucleophilic species.

† This suggestion was advanced by a referee of our preliminary communication,[2] whom we thank.

[14] J. S. Brimacombe, O. A. Ching, and M. Stacey, *J. Chem. Soc.* (*C*), 1969, 1270.
[15] J. S. Brimacombe and O. A. Ching, *J. Chem. Soc.* (*C*), 1969, 964, and references cited therein.
[16] E. Merck A. G., 'Chromatography,' Darmstadt, 2nd edn., p. 30.

G.l.c. was performed with a Pye 104 gas chromatograph (nitrogen carrier gas at 7 lb in^{-2}, flame ionization detector, column of 25% silicone gum on Celite, operating temperature 140°). Evaporations were performed under vacuum at ambient temperature or just above in experiments yielding anhydro-sugars as products. Light petroleum refers to the fraction having b.p. 60—80°.

1-O-*Acetyl*-6-*deoxy*-2,3-O-*isopropylidene*-4-O-*methylsulphonyl*-α-L-*mannopyranose* (10; R = Ac).—A solution of the alcohol (10; R = H) [9] (0·6 g) in dry pyridine (15 ml) containing acetic anhydride (12 ml) was set aside for 2 h at room temperature; the reaction was then complete. Work-up gave the α-*acetate* (10; R = Ac) (0·3 g), m.p. 120—121° (from ether–light petroleum), $[\alpha]_D$ −10° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 1750 cm^{-1} (OAc) (Found: C, 44·7; H, 6·25; S, 9·75. $C_{12}H_{20}O_8S$ requires C, 44·4; H, 6·2; S, 9·9%).

1-O-*Acetyl*-6-*deoxy*-2,3-O-*isopropylidene*-4-O-*methylsulphonyl*-α-L-*talopyranose* (12; R = Ac).—This *compound* (87%), m.p. 111—112° (decomp.) (from ethyl acetate–light petroleum), $[\alpha]_D$ −16° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 1740 cm^{-1} (OAc) (Found: C, 44·4; H, 6·2; S, 9·8%), was obtained from the alcohol (12; R = H) [10] as described in the previous experiment.

Reaction of the α-*Acetate* (10; R = Ac) *with Sodium Azide*.—The acetate (0·19 g) in dry *NN*-dimethylformamide (3 ml) containing sodium azide (0·19 g) was heated at 140° for 2 h; t.l.c. (toluene–ether, 4 : 1) revealed the formation of a single product. Water (20 ml) and ether (20 ml) were then added to the cooled solution and the aqueous layer was further extracted with ether (3 × 20 ml). The combined extracts were washed with water (10 ml) and dried ($MgSO_4$). Careful removal of the solvent left an oil that g.l.c. showed to contain substantially one component (>90%), which gave a single peak on co-injection with an authentic sample of the anhydro-sugar [9] (11). Chromatography on silica gel (elution with light petroleum–ether, 5 : 1) gave a sample of (11), m.p. 70—71° (after sublimation), $[\alpha]_D$ −48 ± 1° (*c* 0·75 in MeOH) {lit.[9] m.p. 71—73°, $[\alpha]_D$ −51° (*c* 1 in MeOH)}, identical (mixed m.p., n.m.r. and i.r. spectra) with authentic material.

Without the addition of sodium azide no reaction took place during 2 h. However, the anhydro-sugar (11) was formed (and identified by g.l.c.) following addition of sodium azide and continued heating.

Reaction of the α-*Acetate* (12; R = Ac) *with Sodium Azide*.—The acetate (0·33 g) in dry *NN*-dimethylformamide (5 ml) containing sodium azide (0·33 g) was heated at 140° for 5 h; the mixture was then processed as in the preceding experiment. G.l.c. and t.l.c. showed that a number of products were formed, but the main component (*ca.* 60%) had mobilities identical with those of the anhydro-sugar (13) [10] and could not be distinguished on co-chromatography. Preparative chromatography on silica gel afforded material (61 mg), $[\alpha]_D$ +89 ± 1° (*c* 0·4 in $CHCl_3$), which could not be obtained crystalline (lit.,[10] m.p. 39—41°) on sublimation. However, its highly characteristic n.m.r. spectrum was identical with that of an authentic sample of (13).

We thank Professor J. G. Buchanan, Heriot-Watt University, for discussion and for communicating his results to us prior to publication. We also thank the University of Dundee for a studentship (to J. M.).

[3/1355 *Received*, 27*th June*, 1973]