978. *Cyclitols. Part XVI.*[1] *Toluene-*p*-sulphonyl Derivatives of Myoinositol. Acetyl Migration in Anhydrous Pyridine Solution*

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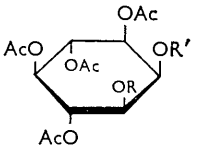
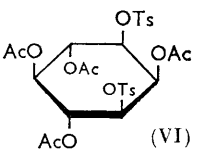
Reaction of 1,4,5,6-tetra- and 1,3,4,5,6-penta-*O*-acetylmyoinositol with toluene-*p*-sulphonyl chloride in anhydrous pyridine at 120° gives the 1,3-di-*O*-tosyl and the 3-*O*-tosyl derivative, respectively, owing to acetyl migration. At room temperature the reaction is not accompanied by migration. Reductive detosylation could not be achieved without concurrent deacetylation.

Acylations and other reactions of partially acetylated carbohydrates are often performed in anhydrous pyridine solutions on the assumption that migration of the acetyl groups does not occur. We are not aware of any described case of acetyl migration under these conditions. The reactions described in this Paper should serve as a warning that acyl migrations might occur in anhydrous pyridine, particularly at temperatures over 100°.

1,2,4,5,6-Penta-*O*-acetylmyoinositol (I) is a potentially important intermediate for the synthesis of biologically active 1-*O*-substituted derivatives of myoinositol. In attempting to synthesise it, one route that was pursued was the reductive desulphonylation of 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol (II); although this attempt was unsuccessful it led to the discovery of an unexpected acetyl migration.

(I) R = H; R′ = Ac
(II) R = Ts; R′ = Ac
(III) R = R′ = H
(IV) R = Ts; R′ = H
(V) R = R′ = Ts
(VII) R = Ac; R′ = H
(VIII) R = Ac; R′ = Ts





(VI)

(Ts = *p*-Me·C_6H_4·SO_2)

The required 3-tosyl compound (II) is readily prepared from 1,4,5,6-tetra-*O*-acetylmyoinositol (III).[2] The reaction with toluene-*p*-sulphonyl chloride is highly selective, the equatorial 3-hydroxyl group reacting almost exclusively. The structure of the monotosyltetra-acetyl compound (IV) thus obtained was proven by treatment [3] with dihydropyran, followed by detosylation with sodium amalgam which caused simultaneous deacetylation; the resulting product was indistinguishable by paper chromatography from 2-*O*-(2-tetrahydropyranyl)myoinositol but was clearly separated from 1-*O*-(2-tetrahydropyranyl)-myoinositol.[3] Acetylation of the 3-*O*-tosyl tetra-acetate (IV) gave the desired 3-*O*-tosyl penta-acetate (II).

Introduction of a second tosyl group on to the axial oxygen atom on C-2 is difficult. When the tetra-acetate (III) was treated with toluene-*p*-sulphonyl chloride (4 mol.) in pyridine at room temperature for 1 week, a mixture of the 3-tosyl and a ditosyl derivative was obtained; fractional crystallisation gave the ditosyl compound, m. p. 173°, in only 14% yield. To increase the yield the reaction was carried out at 120° for 18 hours; surprisingly, a different ditosyl derivative, m. p. 220—222°, was obtained. Thin-layer chromatography indicated that the products were homogeneous, though dissimilar.

Presumably, ditosylation of the tetra-acetate proceeds first through esterification of the equatorial hydroxyl to form the 3-tosyl derivative (IV). Accordingly, the latter was further tosylated in two separate experiments, at 100° and at 120°; at the lower temperature a mixture of the two ditosyl compounds was formed, whereas after reaction at 120° only the higher-melting isomer was detected. Both isomers therefore have one of the tosyl groups in the 3-position. It was assumed that the product formed at room temperature was the expected 2,3-ditosyl derivative (V), and that at the higher temperature acetyl migration had occurred from C-1 to C-2, the rearranged product then being more

[1] Part XV, S. J. Angyal, P. A. J. Gorin, and M. Pitman, *J.*, 1965, 1807.
[2] S. J. Angyal, M. E. Tate, and S. D. Gero, *J.*, 1961, 4116.
[3] S. J. Angyal and S. D. Gero, following Paper.

readily tosylated on the equatorial O-1 than the starting material on the axial O-2, yielding the 1,3-ditosyl compound (VI). In agreement with this assignment, the symmetrical isomer (VI) has the higher melting point.

These structures were proven by the proton magnetic resonance spectra of the compounds. Thus, the spectrum of the higher-melting isomer (VI) clearly indicates that it is symmetrical. Only three types of acetate groups appear (at δ 1·90, 1·99, and 2·04) of relative intensities 1 : 1 : 2, the latter arising from the equivalent groups on C-4 and C-6. Similarly, the equivalence of the two tosyl groups is shown by the single methyl signal at δ 2·46, and the aromatic protons form an AB pattern (at 7·35 and 7·75, J = 8·5 c./sec.). On the extremities of the complex pattern of ring protons can be seen H-2 as a triplet at δ 5·60 (J = 2·75 c./sec., coupling to two *cis* neighbouring protons), and the equivalent H-1 and H-3 protons as a pair of doublets at 4·77 (J = 2·75 and 9·0 c./sec., coupling to a *cis*- and to a *trans*-proton). In contrast, the spectrum of the lower-melting ditosyl derivative indicates a lack of symmetry; two different methyl groups (at δ 2·42 and 2·46) and four different acetyl groups appear (at 1·82, 1·96, 2·00, and 2·05); the aromatic and the ring protons form unresolved patterns.

Because of the unusual nature of the acetyl migration, another similar case was studied. 1,3,4,5,6-Penta-*O*-acetylmyoinositol (VII) [4] did not react readily with toluene-*p*-sulphonyl chloride; most of it was recovered from a reaction carried out under the customary conditions. Under forcing conditions at 100° two compounds were formed; these were the 3-tosyl derivative (II) and a new compound to which the 2-tosyl structure (VIII) was assigned since it differed from the known penta-acetates of the 4- and 5-*O*-tosylmyoinositols.[5] Under the same conditions, but at 120°, only the rearranged isomer (II) was obtained.

Such acetyl migration is only noticeable when the main reaction is slow, as in the tosylation of the axial 2-hydroxyl group of myoinositol. It was found that the reaction of 1,3,4,5,6-penta-*O*-acetylmyoinositol with propionic anhydride in pyridine at 120° occurred without migration, giving only the 2-propionate. Prolonged heating with pyridine alone at 100° caused no migration,[6] but at 120° considerable migration was detectable after 3 hr. by vapour-phase chromatography.

In attempting to remove the tosyl group by reduction with sodium amalgam,[7] alkaline conditions had to be avoided to forestall side-reactions such as deacetylation, acetyl migration, and epoxide formation. The last-named reaction is apparently slow compared to the detosylation, for penta-acetyl-3-*O*-tosylmyoinositol yielded mainly myoinositol, and, as stated above, 1,4,5,6-tetra-*O*-acetyl-2-*O*-(2-tetrahydropyranyl)-3-*O*-tosylmyoinositol gave 2-*O*-(2-tetrahydropyranyl)myoinositol in alkaline solution. It was hoped that detosylation could be carried out at a pH of *ca.* 5 without acetyl migration. Encouragingly, it was found that 1-*O*-tosylmyoinositol gave myoinositol in good yield when stirred with sodium amalgam in aqueous methanol buffered to pH 5, and under these conditions, in another experiment, 1,3,4,5,6-penta-*O*-acetylmyoinositol was recovered unchanged. However, detosylation of 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol (II) under these conditions proceeded very slowly; useful yields could not be obtained, and this synthetic approach was discontinued when another one proved successful.[8]

Experimental

Melting points are corrected. All the asymmetrical compounds described are racemic. Pyridine was dried over, and then distilled from, potassium hydroxide pellets, followed by distillation from phosphorus pentoxide. Thin-layer chromatography was carried out on silica gel G (Merck) with benzene–methanol (95 : 5 or 90 : 10 v/v).

[4] T. Posternak, *Helv. Chim. Acta*, 1941, **24**, 1045.
[5] S. J. Angyal and J. S. Murdoch, unpublished results.
[6] S. J. Angyal and G. J. H. Melrose, Part XVIII, *J.*, 1965, in the press.
[7] K. Freudenberg and F. Brauns, *Ber.*, 1922, **55**, 3233; R. S. Tipson in "Methods in Carbohydrate Chemistry," ed. R. L. Whistler and M. L. Wolfrom, Academic Press, New York. 1963, vol. II, p. 250.
[8] S. J. Angyal and M. E. Tate, unpublished results.

Tosylations of 1,4,5,6-*Tetra*-O-*acetylmyoinositol* (III).—(a) *At* 100°. A solution of 1,4,5,6-tetra-*O*-acetylmyoinositol [4] (1·0 g.) and toluene-*p*-sulphonyl chloride (0·8 g.) in pyridine (10 ml.) was heated at 100° for 3 hr. The mixture was poured into water and extracted with chloroform; the extract was washed with dilute hydrochloric acid and water, and evaporated. Recrystallisation of the residue from aqueous ethanol yielded 1,4,5,6-*tetra*-O-*acetyl*-3-O-*tosylmyoinositol* (IV) as prisms (0·8 g., 55%), m. p. 195—197° (Found: C, 50·35; H, 5·4. $C_{21}H_{26}O_{12}S$ requires C, 50·2; H, 5·2%).

(b) *At room temperature.* 1,4,5,6-Tetra-*O*-acetylmyoinositol (0·50 g.) and toluene-*p*-sulphonyl chloride (1·10 g.) were allowed to stand in pyridine (3 ml.) for 1 week. Water was added, and the resulting gum (0·87 g.) gradually solidified. After several fractional crystallisations from ethanol, the less soluble component, 1,4,5,6-*tetra*-O-*acetyl*-2,3-*di*-O-*tosylmyoinositol* (V) was obtained as needles (0·13 g., 14%), m. p. 173° (Found: C, 51·5; H, 5·1. $C_{28}H_{32}O_{14}S_2$ requires C, 51·2; H, 4·9%). Concentration of the mother-liquors gave crude monotosyl derivative, which, on recrystallisation from ethanol, yielded 1,4,5,6-tetra-*O*-acetyl-3-*O*-tosylmyoinositol (0·10 g., 14%), m. p. 195—197°, identical with the compound described above.

(c) *At* 120°. Tetra-acetate, toluene-*p*-sulphonyl chloride, and pyridine, in the above proportions, were heated at 120° for 18 hr. Thin-layer chromatography, using chloroform on silica gel, gave only one spot in the same position as 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-tosylmyoinositol (see below) which was clearly resolved from the slightly slower moving 2,3-di-*O*-tosyl isomer. The product was worked up as usual; two crystallisations from ethanol gave the 1,3-ditosyl compound (0·28 g., 30%), m. p. 215—221° (see below).

1,4,5,6-*Tetra*-O-*acetyl*-2-O-(2-*tetrahydropyranyl*)-3-O-*tosylmyoinositol.*—A solution of 1,4,5,6-tetra-*O*-acetyl-3-*O*-tosylmyoinositol (1·23 g.) in 1,2-dichloroethane (35 ml.) and dihydropyran (5 ml.) was cooled while toluene-*p*-sulphonic acid (100 mg.) in chloroform (10 ml.) was added. After 40 min. thin-layer chromatography indicated that the reaction was complete; the solution was poured into excess of sodium hydrogen carbonate solution. The product was extracted with additional chloroform and the organic layer was washed several times with sodium hydrogen carbonate solution. After drying (K_2CO_3) and evaporation, an oil was obtained which crystallised in rectangular plates (1·115 g., 86%), m. p. 169—170°. Recrystallisation from methanol did not alter the m. p. of the *compound* (Found: C, 53·3; H, 5·7. $C_{26}H_{34}O_{13}S$ requires C, 53·2; H, 5·8%).

1,2,4,5,6-*Penta*-O-*acetyl*-3-O-*tosylmyoinositol* (II).—1,4,5,6-Tetra-*O*-acetyl-3-*O*-tosylmyoinositol (60 mg.) was heated with acetic anhydride (1 ml.) and pyridine (1 ml.) for 2 hr. at 100°. The solution was then evaporated *in vacuo* and the solid residue crystallised from ethanol. The *penta-acetate* was obtained as prisms (57 mg., 88%), m. p. 151° (Found: C, 50·65; H, 5·2. $C_{23}H_{28}O_{13}S$ requires C, 50·75; H, 5·2%).

Tosylation of 1,4,5,6-*tetra*-O-*acetyl*-3-O-*tosylmyoinositol.*—(a) *At* 100°. The compound (950 mg.) and toluene-*p*-sulphonyl chloride (800 mg.), dissolved in pyridine (10 ml.), were heated at 100° for 3 hr. The mixture was then poured into water, extracted with chloroform, and the product isolated in the usual way. Thin-layer chromatography, using chloroform as irrigant, resolved the crude product into two spots with R_F values identical with those of (V) and (VI), respectively, together with a small spot corresponding to starting material.

(b) *At* 120°. A tosylation, similar to the above but at 120° for 18 hr., gave a product, shown by thin-layer chromatography to be almost entirely (VI). The mixture was poured into ice–water. The resulting black viscous oil was taken up in ethanol (30 ml.) and boiled with decolourising carbon for 5 min. After filtration and concentration, rectangular plates of 2,4,5,6-*tetra*-O-*acetyl*-1,3-*di*-O-*tosylmyoinositol* (300 mg., 28%), m. p. 216—221°, were obtained. Two recrystallisations from chloroform–ethanol raised the m. p. to 220—222° (Found: C, 50·9; H, 4·9. $C_{28}H_{32}O_{14}S_2$ requires C, 51·2; H, 4·9%).

Tosylation of 1,3,4,5,6-*Penta*-O-*acetylmyoinositol* (VIII).—(a) *At* 100°. Penta-acetate (200 mg.) and toluene-*p*-sulphonyl chloride (280 mg.) in pyridine (1·0 ml.) were heated at 100° for 9 hr. After cooling, water was added and an oil was obtained which changed into a solid (195 mg.), m. p. 157—190°. The material was extracted with ethanol (5 ml.), from which fine crystals (111 mg., 40%), m. p. 218—219°, separated. Recrystallisation from ethanol (8 ml.) yielded 1,3,4,5,6-*penta*-O-*acetyl*-2-O-*tosylmyoinositol* (VIII) (40 mg.), m. p. 219—220° (Found: C, 50·9; H, 5·3. $C_{23}H_{28}O_{13}S$ requires C, 50·75; H, 5·2%). The ethanolic mother-liquor, on evaporation, gave a residue, m. p. *ca.* 145—150°, which was mainly 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol (p.m.r. results).

(b) *At* 120°. The reactants in the above ratio, heated at 120° for 18 hr., gave a brown oil, which was extracted with ethanol. Crystals, m. p. 148—150°, separated in 39% yield and were shown by p.m.r. and thin-layer chromatography to be essentially 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol.

Propionylation of 1,3,4,5,6-*Penta*-O-*acetylmyoinositol.*—The penta-acetate (20 mg.) in pyridine (1·0 ml.) was heated with propionic anhydride (0·3 ml.) at 120° for 18 hr. After evaporation *in vacuo*, the crude product was taken up in chloroform (2 ml.) and analysed by vapour-phase chromatography;[3] it consisted of 1,3,4,5,6-penta-*O*-acetyl-2-*O*-propionylmyoinositol only.

Detosylation Experiments.—(*a*) 1,4,5,6-Tetra-*O*-acetyl-2-*O*-(2-tetrahydropyranyl)-3-*O*-tosylmyoinositol (240 mg.) was dissolved in methanol (200 ml.) and water (50 ml.). Sodium amalgam (50 g., 2·5%) was added with stirring over 1·5 hr. Paper chromatography of a sample of the solution, using butan-1-ol–ethanol–water (60 : 10 : 15 v/v) as irrigant, gave a spot which was identified as 2-*O*-(2-tetrahydropyranyl)myoinositol[3] and which was resolved from the 1-isomer.[3]

(*b*) Treatment of 1,2,4,5,6-penta-*O*-acetyl-3-*O*-tosylmyoinositol (21 mg.) in 80% aqueous methanol with 2·5% sodium amalgam, as above, yielded a product which was shown by paper chromatography to be mainly myoinositol together with other minor material having higher R_F values.

(*c*) To a solution of 1-*O*-tosylmyoinositol (21 mg.) in 80% aqueous methanol (25 ml.) and acetic acid (0·7 ml.), sodium amalgam (5 g., 2·5%) was added with stirring. The final pH was *ca.* 5. After 2 hr. paper chromatography showed that the product was almost entirely myoinositol.

(*d*) In a control experiment, 1,3,4,5,6-penta-*O*-acetylmyoinositol (21 mg.) was treated as above. Paper chromatography of the resulting solution did not detect any deacetylated products. The solution was evaporated *in vacuo* and the product isolated in the usual way. Propionylation of the product was shown by vapour-phase chromatography[3] to yield only the 2-propionate of the starting material.

(*e*) 1,2,4,5,6-Penta-*O*-acetyl-3-*O*-tosylmyoinositol (21 mg.) was treated as above. Thin-layer chromatography of a sample of the final solution, pH *ca.* 5, indicated starting material together with a minor portion (*ca.* 20%) of a myoinositol penta-acetate. The yield of penta-acetate was not increased by adding the sodium amalgam in increments over 5 hr.

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