

482. *Aspects of Stereochemistry. Part XVII.*¹ *Behaviour of 1,2:5,6-Di-O-isopropylidene-3,4-di-O-toluene-p-sulphonyl-D-mannitol on Benzoate Exchange.*

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Reaction of 1,2:5,6-di-O-isopropylidene-3,4-di-O-toluene-*p*-sulphonyl-D-mannitol with sodium benzoate in dimethylformamide yields two groups of products. Firstly, (–)-*trans*-1,2-bis-(2,2-dimethyl-1,3-dioxolan-4-yl)-vinyl toluene-*p*-sulphonate (II) and (–)-*trans*-1,2-bis-(1,2-dihydroxyethyl)-vinyl toluene-*p*-sulphonate (III) arising by elimination of toluene-*p*-sulphonic acid and hydrolysis of the ketal groups. Secondly, 3,4-di-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-talitol (VI) and 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-itol (VII) arising by way of displacement of one toluene-*p*-sulphonate group by benzoate ion and participation of the resultant benzoyl group in the displacement of the second toluene-*p*-sulphonate group.

PROVIDING that certain steric requirements are fulfilled,¹ carbohydrate secondary sulphonates can be converted into benzoates with inversion of configuration at the appropriate carbon atom by treatment with sodium benzoate in boiling dimethylformamide.² The scope of the "benzoate exchange reaction" has been investigated in previous Papers³ and the influence of various neighbouring groups on the course of the reaction has been examined.⁴ We now report on the behaviour of a vicinal di-O-sulphonate under benzoate exchange conditions. The compound selected was 1,2:5,6-di-O-isopropylidene-3,4-di-O-toluene-*p*-sulphonyl-D-mannitol (I) since its symmetry properties were expected to simplify fractionation of the reaction products.

In preliminary experiments it was found that reaction did not occur as readily as in the previously studied examples³ and, moreover, the first product isolated in addition to unchanged starting material was not a usual benzoate exchange product but had an elemental analysis in agreement with the formula C₁₉H₂₆O₇S. This corresponds to the elimination of one mol. of toluene-*p*-sulphonic acid from the di-O-toluene-*p*-sulphonate (I). The structure, (–)-*trans*-1,2-bis-(2,2-dimethyl-1,3-dioxolan-4-yl)vinyl toluene-*p*-sulphonate (II) was assigned mainly on the basis of the nuclear magnetic resonance (n.m.r.) spectrum which showed the following absorptions: * a quartet at 7.65 (relative area 4) which is typical for an A₂B₂ pattern of aromatic protons; a quartet at 5.76 (1) for the olefinic proton with *J. ca.* 9 and 1 c./sec. due to coupling with the 1,3-dioxolan rings; a multiplet at 5.0–4.5 (2) which can be assigned to the CH groups of the 1,3-dioxolan rings and which is composed of the X parts of two ABX systems superimposed with further coupling with the olefinic proton; a multiplet at 4.2–3.4 (4) which can be assigned to the methylene groups of the 1,3-dioxolan rings and corresponds to the AB parts of the two ABX systems (all 16 lines were distinguished); a singlet at 2.5 (3) for the aromatic methyl group; a quartet at 1.4 (12) which indicates four different methyl groups in two pairs and which clearly originates from the methyl groups in the isopropylidene residues. Whilst the configuration about the double bond in the vinyl derivative (II) could not be ascertained from this data, and cannot yet be unequivocally established, it seems likely that a *trans*-elimination of toluene-*p*-sulphonic acid would be involved in its formation (I, route *a*); the symmetry of the di-O-toluene-*p*-sulphonyl derivative (I) is such that *trans*-elimination of H-3 and TsO₄ or of H-4 and TsO₃ would give rise to the same product (II).

* Determined in deuteriochloroform with tetramethylsilane as internal reference using a Varian A60 spectrometer. Absorptions given on the δ scale.

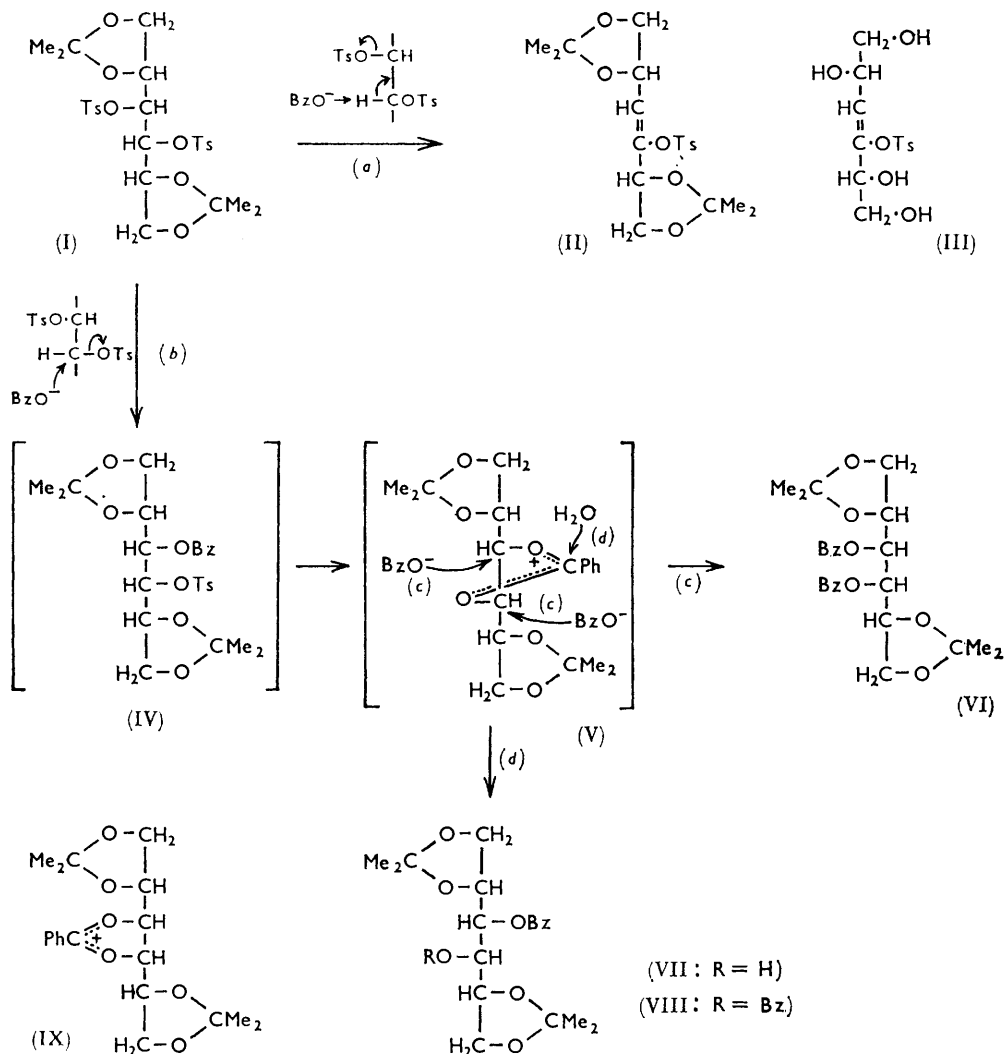
¹ Part XVI, Foster, Harrison, Lehmann, and Webber, *J.*, 1963, 4471.

² Reist, Spencer, and Baker, *J. Org. Chem.*, 1959, 24, 1618.

³ Publications cited in ref. 1.

⁴ Bukhari, Foster, Lehmann, Randall, and Webber, *J.*, 1963, 4167.

From a large-scale benzoate exchange reaction on the di-*O*-toluene-*p*-sulphonate (I) two fractions were obtained on dilution of the reaction mixture with water: a crystalline precipitate *A* and a syrupy product *B* by chloroform extraction of the residual solution. Fractional crystallisation of *A* gave, in addition to starting material (I) and the vinyl toluene-*p*-sulphonate (II), a second enol sulphonate to which the structure (–)-*trans*-1,2-bis-(1,2-dihydroxyethyl)vinyl toluene-*p*-sulphonate (III) was assigned since the



compound could be converted into the enol sulphonate (II) by reaction with acetone, sulphuric acid, and copper sulphate. The conversion of enol sulphonates (II) \rightarrow (III) could be effected by brief treatment with boiling 0.1*N*-hydrochloric acid. The chemistry of compounds (II) and (III) is being further examined.

Chromatography of *B* on alumina gave, in addition to further amounts of compounds (I)–(III), 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-talitol (VI) which was identified by comparison with authentic material,⁴ and 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (VII) which was identified as follows. Hydrolysis of the monobenzoate (VII)

and subsequent acidic hydrolysis of the crystalline product, 1,2:5,6-di-*O*-isopropylidene-*D*-iditol, gave *D*-iditol, characterised as the hexa-benzoate. The formation of compounds (VI) and (VII) from the di-*O*-toluene-*p*-sulphonate (I) can be explained as follows. Displacement of either toluene-*p*-sulphonate group by benzoate ions (I, route *b*) would give 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-toluene-*p*-sulphonyl-*D*-talitol (IV) which, on the basis of previous results,⁴ would be expected to react readily by either or both of two routes: (1) by direct displacement of the toluene-*p*-sulphonate group by benzoate ions to yield 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (VIII), and (2) by participation of the benzoate group in the release of the toluene-*p*-sulphonate group to yield the intermediate cation (V). Further reaction of the cation (V) with water (route *d*) would yield 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (VII) and/or with benzoate ions (route *c*) to yield 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-talitol (VI); the symmetry of the intermediate cation is such that it can give only one mono- and one di-benzoate by routes *c* and *d*.

3,4-Di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (VIII) which could arise as indicated in route (1) could not be isolated from the reaction products nor could its absence or presence be ascertained by chromatography. In previous work,⁴ 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-talitol, arising by a route analogous to (1) has been isolated when 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-*D*-mannitol was subjected to a benzoate exchange reaction. On the other hand, in the latter reaction, the products 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-mannitol and the *D*-iditol analogue arising by attack of benzoate ions on the intermediate cation in a manner analogous to that described in route (2) could not be isolated. The postulated intermediate *O*-benzoate *O*-toluene-*p*-sulphonate (IV) also could not be isolated, possibly because, once formed, it would react readily and hence not accumulate in the reaction mixture. The recovery of substantial amounts of starting material (I) after reaction under standard conditions for benzoate exchange indicates that initial reaction is not easy. Under similar reaction conditions 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-*D*-mannitol did not survive.⁴ Participation of the benzoate group in the ionisation of the vicinal sulphonate group should occur more readily in 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-toluene-*p*-sulphonyl-*D*-talitol (IV) than in 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-*D*-mannitol since the respective resultant cyclic cations would have *threo*- (V) and *erythro*-configurations (IX). Steric interaction of the 2,2-dimethyl-1,3-dioxolanyl groups would be involved in the formation of the *erythro*-cation. It is possible that, because of the absence of this steric effect, the *O*-benzoate *O*-toluene-*p*-sulphonate (IV) might react principally by way of a participation reaction to yield the products (VI) and (VII) and not to any great extent by direct benzoate exchange to give the dibenzoate (VIII). On the other hand, 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-*D*-mannitol might be expected to react principally by direct benzoate exchange to yield 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-talitol. Full experimental support for these views could not be provided since, in each benzoate exchange reaction, there were considerable amounts of unidentified non-crystalline material but it is perhaps significant that the products isolated accord with these predictions.

EXPERIMENTAL

Reaction of 1,2:5,6-Di-O-isopropylidene-3,4-di-O-toluene-p-sulphonyl-D-mannitol with Sodium Benzoate in Dimethylformamide.—(a) A solution of the di-*O*-toluene-*p*-sulphonate⁵ (2.3 g.; m. p. 119–120°; $[\alpha]_D^{20} +9^\circ$ in CHCl₃) in dimethylformamide (100 ml.) was boiled under reflux with continuous stirring in the presence of sodium benzoate (6 g.) for 6 hr. Ice-cold saturated aqueous sodium hydrogen carbonate (ca. 100 ml.) was added to the cooled mixture which was then stored at 0° overnight. The precipitate was collected, washed with water, and its solution

⁵ Brigl and Grüner, *Ber.*, 1934, **67**, 1969.

in chloroform (100 ml.) was washed with water, dried (MgSO_4), and concentrated. Crystallisation of the residue (1.24 g.) from methanol gave, as the first crop, starting material (0.61 g., 26%) and subsequently (—)-trans-1,2-bis-(2,2-dimethyl-1,3-dioxolan-4-yl)vinyl toluene-*p*-sulphonate (II) (0.23 g.), m. p. 89–90°, $[\alpha]_D -55^\circ$ (*c* 0.13 in CHCl_3) (Found: C, 57.4; H, 6.3; S, 8.15. $\text{C}_{19}\text{H}_{26}\text{O}_7\text{S}$ requires C, 57.3; H, 6.5; S, 8.0%).

The above aqueous dimethylformamide filtrate and washings were combined and extracted with chloroform (100 ml.), and the extract was washed with water, dried (MgSO_4), and concentrated. Crystallisation of the residue from methanol gave more (0.13 g., total yield 22%) of the vinyl derivative (II).

(b) In a large-scale experiment, the di-*O*-toluene-*p*-sulphonate (107 g.) in dimethylformamide (2 l.), was treated with sodium benzoate (278 g.) as in experiment (a) and the mixture was processed in a similar manner to yield, after dilution with water, a crude crystalline product (A, 24 g.), m. p. 80–90°, and a syrupy product (B, ca. 24 g.) from the chloroform extract. Fractional crystallisation of A, by using the sequence methanol, ethyl acetate, aqueous ethanol, benzene–light petroleum (b. p. 60–80°), and methanol–ethyl acetate gave starting material (I) (5 g.), vinyl derivative (II) (8.2 g.), and (—)-trans-1,2-bis-(1,2-dihydroxyethyl)vinyl toluene-*p*-sulphonate (III) (ca. 3 g.), m. p. 130° (decomp.), $[\alpha]_D -66^\circ$ (*c* 0.2 in MeOH) (Found: C, 48.7; H, 5.6; S, 10.0. $\text{C}_{13}\text{H}_{18}\text{O}_7\text{S}$ requires C, 49.1; H, 5.7; S, 10.1%).

Examination of product (B) by thin-layer chromatography on Kieselgel by irrigation with benzene–ether (9 : 1) and detection with iodine or vanillin–sulphuric acid⁶ revealed components with R_F 0.0, 0.13, 0.27, and 0.44, together with traces of other components. A solution of product B (28 g.) in benzene (ca. 50 ml.) was fractionated on a column (52 × 3.5 cm.) of neutral alumina⁷ (Brockmann III) and the following fractions obtained: 1 (2.9 g.), eluted with benzene (300 ml.), for which thin-layer chromatography showed components with R_F 0.44 with traces at 0.48 and 0.53, $[\alpha]_D +4^\circ$ in CHCl_3 ; 2 (6.1 g.), benzene (850 ml.), R_F 0.44 and traces at 0.48, 0.26, 0.19, and 0.11, +9°; 3 (2.7 g.), benzene (1150 ml.), R_F 0.19 and 0.26, +8°; 4 (0.8 g.), benzene–ether (1 : 1) (200 ml.), R_F as for 3; 5 (8.2 g.), ether (1.2 l.), m. p. 64°, R_F 0.19, +12°; 6 (0.7 g.), ether (850 ml.), R_F 0.19 with traces of slower running components; 7 (1.1 g.), ether–chloroform (1 : 1) (200 ml.), chloroform (200 ml.), chloroform–methanol (1 : 1) (100 ml.), and methanol (300 ml.), R_F as for 6; 8 (3.3 g.), methanol (800 ml.), R_F 0.11, 0.13, 0.19, and 0.26, +14°.

Crystallisation of fractions 1 and 2 from methanol gave vinyl toluene-*p*-sulphonate (II) (1.3 g.; R_F 0.44) and 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-talitol (0.4 g.), m. p. 144–145° [from chloroform–light petroleum (b. p. 60–80°)] alone or in admixture with authentic material,⁴ $[\alpha]_D +50^\circ$ (*c* 0.14 in CHCl_3); the infrared spectrum (Nujol) was indistinguishable from that for the authentic compound. Recrystallisation of fraction 5 from light petroleum (b. p. 60–80°) gave 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (5.1 g.), m. p. 72–74°, $[\alpha]_D^{30} +13^\circ$ (*c* 1.5 in CHCl_3) (Found: C, 62.5; H, 7.3. $\text{C}_{19}\text{H}_{26}\text{O}_7$ requires C, 62.3; H, 7.1%). Seeding of fractions 3 and 4 gave a further amount of the monobenzoate (1.3 g.). Further column chromatography of the remaining fractions and of the residues from fractions 1–5 gave no crystalline product other than small amounts of those already found.

*Identification of 3-*O*-Benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol.*—With benzoyl chloride and pyridine in the usual manner the monobenzoate (1 g.) gave a syrupy dibenzoate which crystallised after passage of a solution in chloroform through a column (30 × 2 cm.) of neutral alumina. Recrystallisation from methanol gave 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (0.6 g., 48%), m. p. 98.5–99°, $[\alpha]_D^{29} +68^\circ$ (*c* 0.4 in CHCl_3) (Found: C, 66.4; H, 6.6. $\text{C}_{28}\text{H}_{30}\text{O}_8$ requires C, 66.4; H, 6.4%).

The monobenzoate (1 g.) was treated with 40% aqueous methanol (20 ml.) containing 13% sodium hydroxide on a boiling-water bath for 3 hr. The product was isolated in the manner described previously⁴ to yield a crude product (0.6 g., 85%), m. p. 83–84°. Recrystallisation from light petroleum (b. p. 60–80°) gave 1,2:5,6-di-*O*-isopropylidene-*D*-iditol (0.44 g., 62%), m. p. 85–86°, $[\alpha]_D -1^\circ$ (*c* 1.9 in CHCl_3) (Found: C, 54.8; H, 8.2. $\text{C}_{12}\text{H}_{22}\text{O}_6$ requires C, 55.0; H, 8.4%).

The foregoing compound (0.37 g.) was treated with boiling 0.1N-hydrochloric acid (10 ml.) for 3 hr. The mixture was then evaporated in the presence of sodium hydroxide to yield

⁶ "Chromatography," E. Merck AG, Darmstadt, 2nd edn., p. 30.

⁷ Baggett, Brimacombe, Foster, Stacey, and Whiffen, *J.*, 1960, 2574.

syropy D-*iditol* (0.22 g.), $[\alpha]_D + 4^\circ$ (*c* 0.75 in H₂O); Fischer and Fay⁸ record $[\alpha]_D + 3.5^\circ$ for this compound. With benzoyl chloride (0.5 ml.) and pyridine (0.5 ml.) at room temperature for 4 days, D-*iditol* (0.22 g.) gave a hexabenzoate (0.44 g.) which, after several recrystallisations from ethanol, had m. p. 139—140.5°, $[\alpha]_D - 16^\circ$ (*c* 0.3 in CHCl₃) and an i.r. spectrum (Nujol) indistinguishable from that of L-*iditol* hexabenzoate, m. p. 142—143°, $[\alpha]_D + 17^\circ$ (*c* 0.9 in CHCl₃), which was prepared by a similar benzylation; Bourne *et al.*,⁹ record m. p. 142—143° for D-*iditol* hexabenzoate but a rotation (+48.5° in CHCl₃) substantially different from that noted above.

Interconversion of (–)-trans-1,2-Bis-(1,2-dihydroxyethyl)vinyl Toluene-p-sulphonate (III) and its Isopropylidene Derivative.—A mixture of the vinyl-tetrol (III) (0.29 g.), anhydrous copper sulphate (1 g.), concentrated sulphuric acid (3 drops), and acetone (50 ml.) was shaken at room temperature for 2 days and then worked up by essentially the method of Bukhari *et al.*,¹⁰ to yield (–)-*trans*-1,2-bis-(2,2-dimethyl-1,3-dioxolan-4-yl)vinyl toluene-*p*-sulphonate (II) (0.14 g.), m. p. 89—90° (from methanol) alone or in admixture with the compound described above, $[\alpha]_D - 57^\circ$ (*c* 0.3 in CHCl₃).

The isopropylidene derivative (II) (0.435 g.) was treated with boiling 0.1N-hydrochloric acid (10 ml.) for 10 min. The hydrolysate was then evaporated at room temperature over sodium hydroxide, and the residue was recrystallised from methanol to yield (–)-*trans*-1,2-bis-(1,2-dihydroxyethyl)vinyl toluene-*p*-sulphonate (III), m. p. 130° (decomp.) alone or in admixture with the authentic material described above, $[\alpha]_D - 68^\circ$ (*c* 0.4 in MeOH).

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⁸ Fischer and Fay, *Ber.*, 1895, **28**, 1975.

⁹ Bourne, MacSweeney, and Wiggins, *J.*, 1952, 2542.

¹⁰ Bukhari, Foster, Lehmann, and Webber, *J.*, 1963, 2287.