788. *Aspects of Stereochemistry. Part XIV.*[1] *Some Further Benzoate Exchange Reactions.*

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Reaction of 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-D-mannitol with sodium benzoate in dimethylformamide yielded 1,2:5,6-di-*O*-isopropylidene-D-talitol, the 3,4-di-*O*-benzoate, and a mono-*O*-benzoate. Displacement of the methanesulphonyloxy-residue occurred directly by attack of benzoate ions and also by participation of the neighbouring benzoyl group.

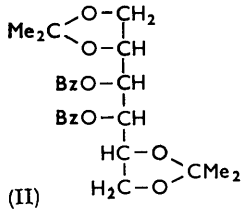
3-*O*-Methyl-D-glucitol afforded a 1,2:5,6-di-*O*-isopropylidene derivative, the methanesulphonate group of which underwent a simple benzoate exchange to yield 4-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-galactitol. The structures of these compounds have been established.

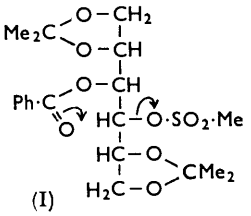
The conversion of certain carbohydrate secondary sulphonates into benzoates with inverted configuration can be effected [2] by reaction with sodium benzoate in dimethylformamide. The reaction has been exploited in the structural determination of the isopropylidene derivatives of L-rhamnitol [3] and of the pentitols [4] for locating the position of free hydroxyl groups, and in the preparation of *trans*-2-alkyl-5-hydroxy-1,3-dioxan derivatives from the corresponding *cis*-methanesulphonates.[5] In evaluating further the scope of the reaction we examined the effect of a neighbouring benzoate and methoxyl group by subjecting 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-D-mannitol (I) and 1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-3-*O*-methyl-D-glucitol to benzoate exchange reactions.

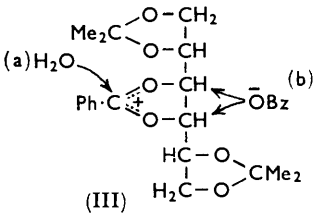
The mannitol derivative (I) was more readily obtained by methanesulphonylation of the known [6] 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol than by selective methanesulphonylation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol followed by benzoylation. When compound (I) was treated with sodium benzoate in boiling, moist dimethylformamide, a mixture was obtained from which were separated 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol (II) (8%), an *O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol

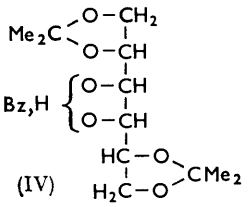
[1] Part XIII, Barker, Foster, Haines, Lehmann, Webber, and Zweifel, preceding paper.
[2] Reist, Spencer, and Baker, *J. Org. Chem.*, 1959, **24**, 1618.
[3] Bukhari, Foster, Lehmann, and Webber, *J.*, 1963, 2287.
[4] Bukhari, Foster, Lehmann, Webber, and Westwood, *J.*, 1963, 2291.
[5] Baggett, Bukhari, Foster, Lehmann, and Webber, *J.*, 1963, 4157.
[6] Sugihara and Yuen, *J. Amer. Chem. Soc.*, 1957, **79**, 5780.

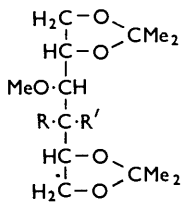
(IV) (5·5%), and a small amount of 1,2:5,6-di-*O*-isopropylidene-D-talitol. Since the first two products were isolated from mixtures by repeated crystallisation, in all probability they represent only a minor proportion of the compounds actually formed. This view is supported by the observation that, in a second experiment, after benzoylation of the


(II)


(I)


(III)


(IV)



(V: R = H, R′ = OH)
(VI: R = BzO, R′ = H)

crude product from the benzoate exchange, a 43% yield of 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol was isolated. In parallel with previous observations [5] considerable decomposition occurred in the benzoate exchange of compound (I). Identification of 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol (II) was effected by saponification which gave the known [6] 1,2:5,6-di-*O*-isopropylidene-D-talitol and by formation of D-talitol by acidic hydrolysis of the latter compound. The talitol configuration was assigned to the mono-*O*-benzoate (IV) since it gave compound (II) on benzoylation.

The di-*O*-benzoate (II) was undoubtedly formed by direct displacement of the methanesulphonyloxy-group from compound (I) by benzoate ions; numerous examples of this type of reaction have been reported.[2-5] Two origins of the mono-*O*-benzoate (IV) must be considered: (1) by hydrolysis of the di-*O*-benzoate (II), and (2) as a result of a participation reaction [7] to give the intermediate (III) which is then decomposed by water (III, a) to give the mono-*O*-benzoate (IV). The latter alternative seems the most likely since the small amount of 1,2:5,6-di-*O*-isopropylidene-D-talitol isolated after the benzoate exchange of compound (I) indicated that hydrolysis was occurring but only to a small extent. The participation of acyloxy-groups in the ionisation of neighbouring sulphonyloxy-groups is well established.[7]

No conclusive chromatographic evidence was obtained for the presence or absence of a second mono-*O*-benzoate or of the di-*O*-benzoates of 1,2:5,6-di-*O*-isopropylidene-D-mannitol and the D-iditol analogue in the mixture of compounds formed from the methanesulphonate (I) on benzoate exchange. The last two compounds could arise by attack of benzoate ions as shown in formula (III, b).

Results which are parallel to those described above have been obtained by Baker and Haines [8] who found that treating the methanesulphonate (I) with sodium acetate in boiling, wet dimethylformamide gave a mixture of the mono-*O*-benzoates of 1,2:5,6-di-*O*-isopropylidene-D-talitol together with a small amount of a syrupy *O*-acetate *O*-benzoate. The last compound clearly had arisen by direct displacement. These authors pointed out that the extent of occurrence of the direct displacement depends on the nucleophilicity of the attacking anion. Thus, only direct displacement occurs when azide ion is the attacking species.

[7] Lemieux, *Adv. Carbohydrate Chem.*, 1955, **9**, 1.
[8] Baker and Haines, *J. Org. Chem.*, 1963, **28**, 438.

Reduction of 3-*O*-methyl-D-glucose with sodium borohydride and acid-catalysed condensation of the product with acetone gave 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-glucitol (V). A 1,2:5,6-distribution of the isopropylidene groups in this compound would be expected on analogy with the known [9] pattern of condensation of D-glucitol with acetone. The location of the free hydroxyl group in compound (V) was established by subjecting its methanesulphonate to a benzoate exchange reaction; crystalline 4-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-galactitol (VI) was produced. The D-*galacto*-configuration was established for compound (VI) when saponification of the benzoyl group followed by cleavage of the acetal residues and the methyl ether group with boron trichloride [10] gave galactitol. The formation of galactitol in this reaction sequence requires that the free hydroxyl group in compound (V) be located at position 4.

A 1,2:5,6-distribution of the isopropylidene groups follows since the two alternative arrangements (1,6:2,5 and 1,5:2,6) involve a 9- and a 7-membered ring and two 8-membered ketal rings.

Although formed in moderate yield, the product of benzoate exchange of 1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-3-*O*-methyl-D-glucitol appeared to be solely 4-*O*-benzoyl-1,2:5 6-di-*O*-isopropylidene-3-*O*-methyl-D-galactitol, indicating that the methoxyl group did not participate in the displacement of the neighbouring methanesulphonyloxy-residue. This result accords with expectations since the methoxyl group has been assigned [7,11] a low driving force for participation reactions. The determination of the location of the free hydroxyl group in compound (V) provides another example of the use of the benzoate exchange in structural determination.

Experimental

Thin-layer chromatography was performed on kieselgel with benzene–methanol (9 : 1), detection being by iodine vapour and sulphuric acid–vanillin.[12]

3-O-*Benzoyl*-1,2:5,6-*di*-O-*isopropylidene*-4-O-*methanesulphonyl*-D-*mannitol*.—A mixture of 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol [6] (7·32 g.) in dry pyridine (10 ml.) and methanesulphonyl chloride (4 ml.) was kept at room temperature for 3 hr. and then poured into ice–water (400 ml.) containing sodium hydrogen carbonate. The aqueous mixture was extracted with chloroform (3 × 100 ml.), and the combined extracts were washed with water, dried ($MgSO_4$), and decolorised with charcoal. Concentration of the extract and crystallisation of the residue from methanol gave the *product* (6·94 g., 78%), m. p. 71—72°, $[\alpha]_D^{31}$ +21° (*c* 0·6 in $CHCl_3$) (Found: C, 53·8; H, 6·5; S, 7·2. $C_{20}H_{28}O_9S$ requires C, 54·05; H, 6·3; S, 7·2%).

Action of Sodium Benzoate in Dimethylformamide on the Foregoing Methanesulphonate.—(*a*) A solution of the methanesulphonate (11·44 g.) in dimethylformamide (275 ml.) was boiled under reflux in the presence of sodium benzoate (21·9 g.) for 6 hr. The cooled mixture was poured into ice and water (600 ml.) containing sodium hydrogen carbonate, and stored overnight at 0°. Insoluble material was collected and shown by thin-layer chromatography to contain three major components (R_F 0·93, 0·80, and 0·37) together with traces of other products; two recrystallisations from methanol gave 3,4-*di*-O-*benzoyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*talitol* (0·75 g., 8%), R_F 0·93, m. p. 144—145°, $[\alpha]_D^{29}$ +57° (*c* 1·8 in $CHCl_3$) (Found: C, 66·6; H, 6·5. $C_{26}H_{30}O_8$ requires C, 66·4; H, 6·4%).

The combined mother-liquors from recrystallisation of the di-*O*-benzoate were evaporated and the residue was extracted with hot methanol. Concentration of the extract and distillation of the residue (1·2 g.) gave a product (0·58 g.), b. p. 130—140°/0·3 mm., $[\alpha]_D^{32}$ −5° (*c* 0·4 in $CHCl_3$), which on examination by thin-layer chromatography was found to contain a major component (R_F 0·39), a second component in moderate amount (R_F 0·83), and traces of other substances (R_F 0·30, 0·28, 0·24, and 0·11). The infrared spectrum (Nujol mull) showed absorptions for OH and benzoyl C=O). Partial crystallisation occurred on storage and recrystallisation of a portion (134 mg.) from light petroleum (b. p. 60—80°) gave a product (32 mg.) with m. p. 61—62° alone or in admixture with 1,2:5,6-di-*O*-isopropylidene-D-talitol described below and

[9] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 138.
[10] Bonner, Bourne, and McNally, *J.*, 1960, 2929.
[11] Winstein, Grunwald, and Ingraham, *J. Amer. Chem. Soc.*, 1948, **70**, 821.
[12] "Chromatography," E. Merck AG, Darmstadt, 2nd edn., p. 30.

with R_F 0·39. Benzoylation of a portion (0·31 g.) of the mixture before crystallisation of the 1,2:5,6-di-*O*-isopropylidene-D-talitol gave a moderate yield (30%) of 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol.

The residual aqueous solution described in the first stage of the experiment was extracted with chloroform (400 ml.), and the extract was washed with water, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue thrice from methanol gave an O-*benzoyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*talitol* (0·52 g., 5·5%), R_F 0·80, m. p. 124—125°, $[\alpha]_D$ +15° (*c* 0·45 in $CHCl_3$) (Found: C, 62·1; H, 7·1. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·1%). With benzoyl chloride and pyridine under the usual conditions this mono-*O*-benzoate gave 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol (71%). A further amount of the same di-*O*-benzoate (0·53 g.) was obtained by benzoylation of the material remaining in the combined mother-liquors after recrystallisation of the mono-*O*-benzoate.

(*b*) The methanesulphonate (0·68 g.) was treated with sodium benzoate and dimethylformamide as in (*a*). The cooled mixture was poured into water and extracted with chloroform. The residue obtained on concentration of the extract (0·485 g.) was benzoylated in the usual way, yielding 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol (43%). Examination of the mother-liquors by thin-layer chromatography was not conclusive in demonstrating the absence or presence of 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol or of the D-iditol analogue.

Identification of 3,4-*Di*-O-*benzoyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*talitol*.—The di-*O*-benzoate (0·47 g.) was saponified by heating its solution in 13% aqueous-methanolic sodium hydroxide (30 ml.; 40% MeOH) on a boiling-water bath for 3 hr. The cooled solution was extracted with ether overnight and the dried extract ($MgSO_4$) was concentrated. Recrystallisation of the residue (0·172 g.) from light petroleum (b. p. 60—80°) gave 1,2:5,6-di-*O*-isopropylidene-D-talitol (0·15 g., 57%), m. p. 61—62°, $[\alpha]_D^{29}$ +6° (*c* 0·6 in $CHCl_3$). Sugihara and Yuen [6] record m. p. 64·5—65·5°, $[\alpha]_D$ +5·2°.

The above di-*O*-isopropylidene compound (81 mg.) was treated with boiling 0·1N-hydrochloric acid for 2·5 hr. The hydrolysate was evaporated at room temperature *in vacuo* in the presence of sodium hydroxide, to yield crude D-talitol (0·55 g.), m. p. 70—72°. Recrystallisation from methanol gave a product with m. p. 88—89° alone or in admixture with authentic D-talitol; the infrared spectra (Nujol mulls) were indistinguishable.

1,2:5,6-*Di*-O-*isopropylidene*-3-O-*methyl*-D-*glucitol*.—A solution of 3-*O*-methyl-D-glucose [13] (0·5 g.) in water (25 ml.) was added dropwise to a solution of sodium borohydride (75 mg.) in water (25 ml.) during 0·5 hr. After storage overnight the solution was neutralised with 50% acetic acid and then deionised by using Amberlite resins IR-120 (H^+) and IRA-400 (HO^-). Concentration of the solution gave 3-*O*-methyl-D-glucitol (0·43 g., 86%), $[\alpha]_D$ +7·7° (*c* 5·7 in H_2O), which failed to crystallise. Examination by paper chromatography with the organic phase of butanol–ethanol–water (4 : 1 : 5) and detection with silver nitrate [14] and periodate permanganate [15] revealed a single component.

A mixture of 3-*O*-methyl-D-glucitol (3·1 g.), acetone (100 ml.), and concentrated sulphuric acid (1·2 ml.) was shaken at room temperature for 7 hr. The mixture was then neutralised with potassium carbonate, filtered, and concentrated. The residue was extracted with chloroform, and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Distillation of the residue gave 1,2:5,6-*di*-O-*isopropylidene*-3-O-*methyl*-D-*glucitol* (3·03 g., 71%), b. p. 120°/0·02 mm. The product crystallised on storage and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 56°, $[\alpha]_D$ −18° (*c* 1·1 in $CHCl_3$) (Found: C, 56·4; C, 8·7. $C_{13}H_{24}O_6$ requires C, 56·5; H, 8·7%).

The *methanesulphonate*, prepared in the usual way, had m. p. 118° (from methanol), $[\alpha]_D$ +13° (*c* 1·6 in $CHCl_3$) (Found: C, 47·3; H, 7·1; S, 9·05. $C_{14}H_{26}O_8S$ requires C, 47·5; H, 7·3; S, 9·0%).

4-O-*Benzoyl*-1,2:5,6-*di*-O-*isopropylidene*-3-O-*methyl*-D-*galactitol*.—A solution of 1,2:5,6-di-*O*-isopropylidene-4-*O*-methanesulphonyl-3-*O*-methyl-D-glucitol (1 g.) in dimethylformamide (30 ml.) was boiled under reflux in the presence of sodium benzoate (2·47 g.) for 6 hr. The cooled solution was poured into aqueous sodium hydrogen carbonate (200 ml.). The precipitate was collected, washed with water, and recrystallised from methanol, to yield the *product* (0·33 g.),

[13] Glen, Myers, and Grant, *J.*, 1951, 2568.
[14] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[15] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.

m. p. 143°, $[\alpha]_D$ +11° (*c* 2·0 in $CHCl_3$) (Found: C, 62·95; H, 7·4. $C_{20}H_{28}O_7$ requires C, 63·15; H, 7·4%). Thin-layer chromatography indicated that the crude product was homogeneous.

Characterisation of the Foregoing Product.—A solution of the foregoing benzoate (90 mg.) in 50% aqueous methanol (30 ml.) containing sodium hydroxide (0·176 g.) was boiled under reflux for 4 hr. The cooled solution was extracted with chloroform, and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated to yield crude 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-galactitol (69 mg.) which showed a mobility in thin-layer chromatography similar to that of 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-glucitol and appeared to be homogeneous.

Boron trichloride (*ca.* 2·5 ml.) was added to a solution of the foregoing alcohol (69 mg.) in dichloromethane (2—3 ml.) at −80°. The mixture was allowed to attain room temperature and then stored thereat overnight. Methanol was distilled from the dark red product five times, thereby yielding a solid of m. p. 179—184°. Decolorisation of an aqueous solution of the product gave galactitol (36 mg., 78%) which was shown to be uncontaminated with D-glucitol by ionophoresis in borate (pH 10). Acetylation of the galactitol with acetic anhydride and pyridine in the usual manner gave galactitol hexa-acetate, m. p. 170—171° alone or in admixture with the authentic compound.

De-O-methylation of 3-O-*Methyl-D-glucitol and Its* 1,2:5,6-*Di-O-isopropylidene Derivative.*—3-*O*-Methyl-D-glucitol (68 mg.) was treated with boron trichloride as described above. The crude product (60 mg.) was found on examination by paper chromatography to contain mainly D-glucitol, together with traces of unidentified components. With pyridine (1 ml.) and acetic anhydride the product gave D-glucitol hexa-acetate (50 mg.) with m. p. 99—100° (from ethanol) alone or in admixture with the authentic compound.

Likewise, when 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-glucitol (81 mg.) was put through the above process, D-glucitol (64 mg.) was obtained which yielded crude hexa-acetate (91 mg.) with m. p. 99·5° after recrystallisation from ethanol.

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