305. *Some Nucleophilic Substitution Reactions of Primary and Secondary Sulphonate Esters* *

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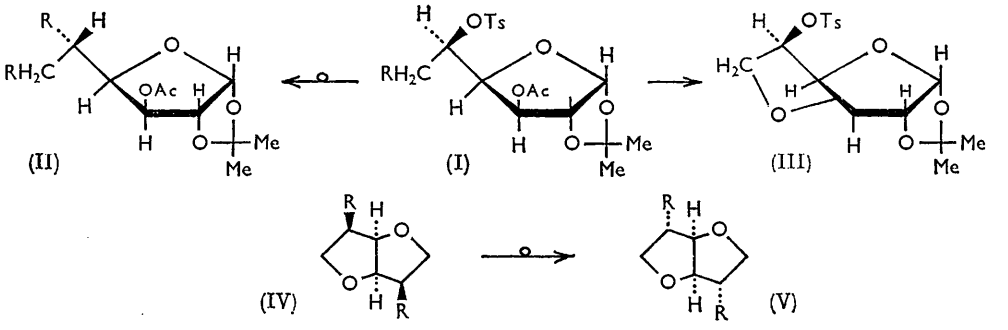
Replacement of the sulphonyloxy-groups in 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-tosyl-α-D-glucofuranose (I; R = O·SO_2·C_7H_7) by treatment with sodium benzoate in *NN*-dimethylformamide afforded 3-*O*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose under mild conditions, and 3-*O*-acetyl-5,6-di-*O*-benzoyl-β-L-idofuranose under more forcing conditions. Reaction of (I; R = O·SO_2·C_7H_7) with either sodium acetate or potassium thiocyanate in 95% 2-methoxyethanol gave 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose. Replacement of the 6-tosyloxy-group with thiolbenzoate was achieved in ethyl methyl ketone.

1,4:3,6-Dianhydro-2,5-di-*O*-benzoyl-L-iditol (V; R = O·CO·Ph) was conveniently prepared from 1,4:3,6-dianhydro-2,5-di-*O*-methanesulphonyl-D-mannitol by use of the sodium benzoate–*NN*-dimethylformamide reagent.

Attempts to prepare derivatives of 5,6-dideoxy-5,6-epimino-1,2-*O*-isopropylidene-β-L-idofuranose by the action of lithium aluminium hydride or sodium ethoxide on 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulphonyl-α-D-glucofuranose or 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methanesulphonyl-α-D-glucofuranose were unsuccessful.

Interest in the replacement of primary and secondary sulphonates by nucleophilic reagents prompted a study of the 5,6-di-*O*-tosyl derivative of 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (I; R = O·SO_2·C_7H_7). Primary replacement by benzoate was readily achieved in *NN*-dimethylformamide at 95—100°, giving the 6-*O*-benzoyl derivative (I; R = O·CO·Ph), and secondary replacement at the boiling point of the solvent, with inversion of configuration at C-5, resulting in the formation of the 5,6-di-*O*-benzoyl-



1,2-*O*-isopropylidene-L-idofuranose (II; R = O·CO·Ph). Similar transformations, using sodium acetate in acetic anhydride, were described by Vargha,[1] and the replacement of secondary sulphonates by sodium benzoate in *NN*-dimethylformamide has been obtained [2] under stereochemical conditions favourable to either a bimolecular S_N2 process or neighbouring-group participation. The 5,6-ditosylate (I; R = O·SO_2·C_7H_7) was recovered unchanged after refluxing with sodium benzoate in ethyl methyl ketone, thus confirming the enhancement of reactivity of nucleophiles by *NN*-dimethylformamide.[2]

When the ditosylate (I; R = O·SO_2·C_7H_7) was treated with potassium thiolbenzoate in *NN*-dimethylformamide under a variety of conditions, no chloroform-soluble material,

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[1] Vargha, *Chem. Ber.*, 1954, **87**, 1351.

[2] Reist, Goodman, and Baker, *J. Amer. Chem. Soc.*, 1958, **80**, 5775; Reist, Spencer, and Baker, *J. Org. Chem.*, 1959, **24**, 1618; Reist, Spencer, Baker, and Goodman, *Chem. and Ind.*, 1962, 1794; Baker and Haines, *J. Org. Chem.*, 1963, **28**, 438.

and hence no thiolbenzoyl derivatives of 1,2-*O*-isopropylidene-α-D-gluco- and -β-L-ido-furanose could be obtained, presumably because of episulphide formation and subsequent polymerisation.[3] However, under milder conditions, using ethyl methyl ketone as solvent, the primary tosyloxy-group underwent selective displacement, affording the 6-*S*-thiol-benzoyl-5-*O*-tosyl derivative (I; R = S·CO·Ph), in an analogous manner to the preparation of the 6-*S*-thiolacetyl derivative.[3] The greater nucleophilic power of thiolacetate and thiolbenzoate was thereby demonstrated, since acetate and benzoate failed to react in this solvent under similar conditions.

An attempt to effect primary acetate replacement in the 5,6-ditosyl derivative (I; R = $O{\cdot}SO_2{\cdot}C_7H_7$), followed by secondary replacement by participation of the introduced neighbouring ester group,[4] rather than by direct replacement, was unsuccessful, since reaction with sodium acetate in boiling 95% 2-methoxyethanol gave 3,6-anhydro-1,2-iso-propylidene-5-*O*-tosyl-α-D-glucofuranose (III); potassium thiocyanate gave the same product (III). The 3,6-anhydro-compound resulted from the base-catalysed hydrolysis of the 3-*O*-acetyl group and elimination of the 6-tosyloxy-substituent by participation of the 3-hydroxyl group. No evidence of direct replacement by acetate was found, as in the case of *trans*-diaxial ring substituents.[4]

The secondary *endo*-methanesulphonyloxy-groups in 1,4:3,6-dianhydro-2,5-di-*O*-methanesulphonyl-D-mannitol (IV; R = $O{\cdot}SO_2{\cdot}Me$), were smoothly replaced, with inversion of configuration, by benzoate in *NN*-dimethylformamide, thus providing an improved method for the preparation of 1,4:3,6-dianhydro-L-iditol (V; R = OH), erroneously termed D-iditol by Cope and Shen.[5a] *endo*-Sulphonyloxy-groups are more readily displaced by nucleophilic reagents than are *exo*-substituents when situated on a bicyclic fused five-membered-ring system,[5] because nucleophilic attack comes from the *exo*-positions, which are relatively unhindered with respect to the V-shape formed by the fused rings. The above observations support the suggestion, made by Horton and Hutson,[5b] that the 2,5-di-*S*-thiolacetyl derivative, formed from the D-mannitol derivative (IV; R = $O{\cdot}SO_2{\cdot}Me$) by replacement of the methanesulphonyloxy-groups by thiol-acetate,[5c] has the L-*ido*-configuration (V; R = S·CO·Me).

Attempts were made to prepare derivatives of 5,6-dideoxy-5,6-epimino-1,2-*O*-isopropyl-idene-β-L-idofuranose by an intramolecular displacement of a sulphonyloxy-group by a neighbouring nitrogen atom, in a manner analogous to that already described [6] for the preparation of 2,3-epimino-derivatives of pyranosides. Accordingly, 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulphonyl-α-D-glucofuranose, the structure of which was assigned by consideration of the known [3] greater reactivity of the 5- than the 3-position of 1,2-*O*-isopropylidene-α-D-glucofuranose derivatives, was prepared. Treatment of this with lithium aluminium hydride or sodium ethoxide gave only 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. When 6-benzamido-6-deoxy-1,2-*O*-iso-propylidene-3,5-di-*O*-methanesulphonyl-α-D-glucofuranose was treated with lithium aluminium hydride or with ethanolic sodium ethoxide, either hot or at room temperature, there was obtained, in each case, an uncrystallisable syrup. The infrared spectra of these syrups showed no NH absorption peak in the region 3300—3200 cm.$^{-1}$, indicating that no ethylenimine derivative had been formed. No purification could be effected by *N*- or *O*-acetylation of the syrup. Similar difficulties have been encountered by Meyer zu Reckendorf on treatment of methyl 2,6-benzamido-2,6-dideoxy-5-*O*-methanesulphonyl-3-*O*-methyl-β-D-glucofuranoside with sodium ethoxide.[7] It may be that elimination of the 5-*O*-methanesulphonyl group with a hydrogen atom on C-6 is occurring, since this is a facile reaction.[8]

[3] Hall, Hough, and Pritchard, *J.*, 1961, 1537; Creighton and Owen, *J.*, 1960, 1024.
[4] Jeanloz and Jeanloz, *J. Amer. Chem. Soc.*, 1958, **80**, 5692; Winstein and Heck, *ibid.*, 1952, **74**, 5584.
[5] (*a*) Cope and Shen, *J. Amer. Chem. Soc.*, 1956, **78**, 3177, 5912, 5916; (*b*) Horton and Hutson, *Adv. Carbohydrate Chem.*, 1963, **18**, 170; (*c*) Bladon and Owen, *J.*, 1950, 585.
[6] Buss, Hough, and Richardson, *J.*, 1963, 5295.
[7] Meyer zu Reckendorf, *Tetrahedron*, 1963, **19**, 2033.
[8] Gramera, Ingle, and Whistler, *J. Org. Chem.*, 1964, **29**, 878.

Experimental

All solutions were concentrated under reduced pressure. Optical rotations were measured at 24° ± 1° and are for chloroform solutions unless otherwise stated. Melting points were determined on a Kofler micro-hot-stage apparatus. Thin-layer chromatography was carried out as described previously.[6]

Replacement Reactions of 3-O-*Acetyl*-1,2-O-*isopropylidene*-5,6-*di*-O-*tosyl*-α-D-*glucofuranose*.[9]—(a) *With sodium benzoate in* NN-*dimethylformamide*. The ditosyl compound (I; R = O·SO_2·C_7H_7) (3·31 g.) and sodium benzoate (3·0 g.), in *NN*-dimethylformamide (45 ml.), were heated at 95—100° for 7 hr. The solution was concentrated to dryness, and the residue fractionated between water (30 ml.) and chloroform (3 × 30 ml.). The combined chloroform extracts were dried ($CaSO_4$) and concentrated to a syrup, which was triturated with ethanol to give colourless needles (1·75 g., 64%), m. p. 151—152°, of 3-*O*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose. A sample recrystallised from ethanol had m. p. 152—153°, $[\alpha]_D$ −3·75° (*c* 2·3) (lit.,[10] $[\alpha]_D$ +0·98°, m. p. 151°) (Found: C, 57·8; H, 5·65; S, 6·35. Calc. for $C_{25}H_{28}O_{10}S$: C, 57·65; H, 5·45; S, 6·15%).

When the reaction was repeated with heating under reflux for 6 hr., a colourless crystalline solid, m. p. 128—131°, was obtained in 50% yield. After further recrystallisation from ethanol, the 3-O-*acetyl*-5,6-*di*-O-*benzoyl*-1,2-O-*isopropylidene*-β-L-*idofuranose* had m. p. 132—133°, $[\alpha]_D$ −21·5° (*c* 1·6) (Found: C, 63·85; H, 5·45. $C_{25}H_{26}O_9$ requires C, 63·8; H, 5·6%). The D-*gluco*-isomer has m. p. 90°, $[\alpha]_D$ −26·4.[11] Saponification of the 5,6-dibenzoate gave 1,2-*O*-isopropylidene-β-L-idofuranose, m. p. 112—113°, $[\alpha]_D$ −30° (*c* 0·14 in H_2O), which, on acetylation, gave the 3,5,6-tri-*O*-acetate, m. p. 82—84°, $[\alpha]_D$ −2° (*c* 1·7) (lit.,[1] m. p. 95—96°, $[\alpha]_D$ 0°). A sample prepared by the method of Vargha [1] had m. p. and mixed m. p. 83—84°, $[\alpha]_D$ −1°.

(b) *With potassium thiolbenzoate in ethyl methyl ketone*. The ditosyl compound (I; R = O·SO_2·C_7H_7) (1·16 g.) and potassium thiolbenzoate (0·90 g., 2·5 mol.) in dry ethyl methyl ketone (30 ml.) were heated under reflux for 35 min. The resultant brown suspension was poured into chloroform (50 ml.) and extracted with water (3 × 20 ml.). The chloroform solution was dried ($CaSO_4$) and concentrated to a thick syrup (1·2 g.) which was decolourised with charcoal in ethanol and crystallised as needles (0·52 g., 50%), m. p. 116—117°. Recrystallisation from ethanol–light petroleum (b. p. 60—80°) afforded 3-O-*acetyl*-1,2-O-*isopropylidene*-6-S-*thiobenzoyl*-5-O-*tosyl*-α-D-*glucofuranose* (0·46 g., 45%), m. p. 116·5—117·5°, $[\alpha]_D$ +5·4° (*c* 1·65), $\nu_{max.}$ (Nujol) 1180, 1380 (–SO_2R); 1500, 1588, 1600 (–Ph); 1673 (–SBz); 1752 (–OAc) cm.$^{-1}$ (Found: C, 55·8; H, 5·1. $C_{25}H_{28}O_9S_2$ requires C, 55·95; H, 5·25%).

(c) *With sodium acetate in* 2-*methoxyethanol*. The ditosyl compound (1·41 g.) and sodium acetate (1·33 g.), in aqueous 2-methoxyethanol (95%; 50 ml.), were heated under reflux for 12 hr. The resultant solution was concentrated to a brown semi-crystalline residue, which was extracted with hot acetone. Concentration of the acetone solution afforded a brown syrup which partially crystallised from ethanol. The ethanol solution was concentrated, the residue extracted with chloroform, and the solution again concentrated to dryness. The residue crystallised from ethanol–light petroleum (b. p. 60—80°) as fine needles of 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose,[11] m. p. and mixed m. p. 135—136° (Found: C, 53·85; H, 5·5. Calc. for $C_{16}H_{20}O_7S$: C, 53·95; H, 5·6%).

(d) *With potassium thiocyanate in* 2-*methoxyethanol*. To a solution of the sulphonate (290 mg.) in 2-methoxyethanol (10 ml.) was added potassium thiocyanate (370 mg.); the mixture was heated under reflux for 24 hr., then concentrated to dryness, and the residue fractionated between chloroform and water. The organic layer was concentrated to a syrup, an ethanol solution of which was decolourised (charcoal) and concentrated to a syrup (224 mg.). Crystallisation from ethanol–water gave needles (138 mg.), which were shown by thin-layer chromatography to contain two components; no separation was effected by a further recrystallisation from the same solvent pair. The products were separated on one plate, using light petroleum–dioxan (3 : 2 v/v) as the solvent. The faster component was recrystallised from ethanol–light petroleum as flat needles (15 mg.), m. p. 131—133°, shown by infrared spectra and mixed m. p. to be 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose. The slower, unknown component was recrystallised from ethanol–water as needles (63 mg.), m. p. 111—114° (Found: C, 49·9; H, 5·7; N, 3·2; S, 8·8%).

[9] Ohle and Dickhauser, *Ber.*, 1925, **58**, 2593.
[10] Ohle, Euler, and Lichtenstein, *Ber.*, 1929, **62**, 2885.
[11] Ohle, Vargha, and Erlbach, *Ber.*, 1928, **61**, 1211.

Treatment of a chloroform solution of the latter product with sodium ethoxide gave neither 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose nor 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-β-L-idofuranose, as shown by thin-layer chromatography. The unknown compound cannot, therefore, be the expected 6-thiocyanate.

1,4:3,6-Dianhydro-2,5-di-O-benzoyl-L-iditol.[5]—1,4:3,6-Dianhydro-2,5-di-*O*-methanesulphonyl-D-mannitol [12] (1·00 g.) and sodium benzoate (2·0 g.), in *NN*-dimethylformamide (75 ml.), were heated under reflux for 24 hr. The solution was cooled, filtered, concentrated, and the residue extracted with chloroform. The extracts were concentrated to a syrup which crystallised spontaneously, and was recrystallised from ethanol–light petroleum (b. p. 60—80°). After a further recrystallisation from the same solvents, the 1,4:3,6-dianhydro-2,5-di-*O*-benzoyl-L-iditol (1·00 g., 85%) had m. p. 109—110°, $[\alpha]_D$ +144° (*c* 6·5) (Found: C, 67·4; H, 5·1. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1%).

6-Benzamido-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose.—Raney nickel (*ca.* 2 g.) was added to a solution of 6-azido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose [13] (5·0 g.) in methanol (150 ml.), and the mixture was shaken in an atmosphere of hydrogen at room temperature and pressure for 1½ hr. The catalyst was filtered off and washed with ethanol. The combined filtrates were concentrated to *ca.* 100 ml., and then benzoic anhydride (5·0 g.) was added. The solution crystallised spontaneously; filtration gave the *benzamido-compound* (3·4 g., 51%), m. p. 222—224° (decomp.) (Found: C, 59·3; H, 6·5; N, 4·4. $C_{16}H_{21}NO_6$ requires C, 59·4; H, 6·5; N, 4·3%).

6-Benzamido-6-deoxy-1,2-O-isopropylidene-5-O-methanesulphonyl-α-D-glucofuranose.—Methanesulphonyl chloride (0·24 ml.) was added to a cooled solution (ice–salt–water) of 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (0·97 g.) in pyridine (20 ml.), and the mixture was kept at 4° for 23 hr. The excess of methanesulphonyl chloride was decomposed with a little water. Concentration afforded a syrup, which crystallised on the addition of ethanol and water. Recrystallisation from ethanol–water gave the *sulphonate* (0·38 g., 32%), m. p. 178—180° (Found: C, 51·2; H, 5·9. $C_{17}H_{23}NO_8S$ requires C, 51·0; H, 5·8%).

6-Benzamido-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methanesulphonyl-α-D-glucofuranose.—Methanesulphonyl chloride (3·6 ml.) was added to a solution of 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (1·67 g.) in pyridine (16 ml.), and the mixture was kept at room temperature for 18 hr. The excess of methanesulphonyl chloride was decomposed with a little water; the addition of more water afforded crystals. Filtration, and recrystallisation from ethanol, gave the *sulphonate* as flat prisms (1·35 g., 55%), m. p. 162—164°, $[\alpha]_D$ −22° (*c* 1·8) (Found: C, 45·0; H, 5·4. $C_{18}H_{25}NO_{10}S_2$ requires C, 45·1; H, 5·25%).

Action of Lithium Aluminium Hydride on 6-Benzamido-6-deoxy-5-O-methanesulphonyl-1,2-O-isopropylidene-α-D-glucofuranose.—Lithium aluminium hydride (0·2 g.) was slowly added to a solution of the sulphonate (0·24 g.) in tetrahydrofuran (9 ml.), and the mixture was heated under reflux for 4 hr. The excess of the hydride was decomposed with an aqueous solution of Rochelle salt (33% w/v), and the residue was thoroughly extracted with tetrahydrofuran and chloroform. The combined extracts were dried ($CaSO_4$), filtered, and concentrated to a syrup. The addition of ethanol afforded crystals (0·03 g.), m. p. 222—224°, which were shown by their infrared spectrum to be 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. Chromatography indicated that the liquors consisted mainly of one component, but it could not be isolated. An infrared spectrum showed no NH peak in the region 3300—3200 cm.$^{-1}$.

Action of Sodium Ethoxide on 6-Benzamido-6-deoxy-1,2-O-isopropylidene-5-O-methanesulphonyl-α-D-glucofuranose.—To a solution of the sulphonate (7 mg.) in ethanol (0·3 ml.) was added 0·27 N-ethanolic sodium ethoxide (0·13 ml.), and the mixture was heated under reflux for 40 min. Concentration afforded a residue to which ethanol and water were added, and the resulting crystals (4 mg., 70%) were filtered off. They had m. p. 220—222°, and were shown by mixed m. p. and infrared spectra to be 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. Chromatography indicated that this was the only product.

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[12] Montgomery and Wiggins, *J.*, 1948, 2204.
[13] Cramer, in "Methods of Carbohydrate Chemistry," ed. Whistler and Wolfrom, Academic Press, New York and London, 1962, vol. I, p. 242.