Note

Sucrochemistry Part VII¹. Preparation and reactions of penta-O-benzoylsucrose 1',6,6'-tris(chlorosulphate) and hexa-O-benzoylsucrose 6,6'-bis(chlorosulphate)

R. Khan

Tate and Lyle Research Centre, Westerham Road, Keston, Kent BR2 6HJ (Great Britain) (Received May 15th, 1972; accepted for publication, May 22nd, 1972)

The reaction of sulphuryl chloride with sugars was first reported by Helferich and his co-workers⁵⁻⁷ to give products in which the primary hydroxyl groups were substituted by chlorine and the secondary hydroxyl groups were either esterified by intramolecular cyclic sulphate or substituted by chlorine with inversion of configuration. The latter reaction was the first, direct, nucleophilic displacement at a secondary position to be reported. Subsequently, Jones *et al.*^{8,9} observed that the substitution of HO-4 of methyl α -D-glucopyranoside, when treated with sulphuryl chloride and pyridine in chloroform at room temperature, proceeded *via* the 4,6-bis(chlorosulphate) by an S_N2 process, with chloride as the nucleophile, to give methyl 4,6-dichloro-4,6dideoxy- α -D-galactopyranoside 2,3-bis(chlorosulphate). Recently, reaction of 4,6dichloro-4,6-dideoxy- α -D-galactopyranoside 2,3-bis(chlorosulphate) with sodium azide in *N*,*N*-dimethylformamide at room temperature has been reported¹⁰ to give methyl 4,6-dichloro-4,6-dideoxy- α -D-galactopyranoside, its 2- and 3-(chlorosulphate) derivatives, and an azido-sulphate derivative.

The reaction of sucrose with sulphuryl chloride and pyridine in chloroform has been suggested to give a mixture of products, from which 1',4,6-trichloro-1',4,6trideoxysucrose 2(3),3'(6')-bis(chlorosulphate) and 4,6,6'-trichloro-4,6,6'-trideoxysucrose tetrakis(chlorosulphate) were isolated¹¹. The structures of these compounds still need to be confirmed. The value of chlorosulphate (OSO₂Cl) as a leaving group was demonstrated by kinetic studies with alkyl chlorosulphates¹²⁻¹⁵. We now report on nucleophilic substitution reactions of some chlorosulphate derivatives of sucrose.

Treatment of 2,3,3',4,4'-penta-O-benzoylsucrose² with sulphuryl chloride and pyridine in chloroform at -75° gave crystalline penta-O-benzoylsucrose 1',6,6'-tris-(chlorosulphate) (1) in 87% yield. Likewise, 1',2,3,3',4,4'-hexa-O-benzoylsucrose³ afforded hexa-O-benzoylsucrose 6,6'-bis(chlorosulphate) (2) in 91% yield. When sucrose hexabenzoate³ was treated with sulphuryl chloride and pyridine in chloroform at -18° , it gave, after column chromatography, crystalline 6,6'-dichloro-6,6'-dideoxysucrose hexabenzoate⁴ (5, 16%). Although some of the physical properties of 5 were NOTE

different from those reported⁴ previously, the n.m.r. spectra were identical. These discrepancies are probably due to differences in crystalline form.



Treatment of 1 with pyridinium chloride in chloroform at 50° gave penta-Obenzoyl-6,6'-dichloro-6,6'-dideoxysucrose 1'-chlorosulphate (3). The structure of 3 was ascertained by removal of the chlorosulphate group by treatment with sodium iodide in methanol to give an amorphous hydroxy compound 4 which, on benzoylation, afforded the 6,6'-dichloride⁴ 5. The preferential displacement of the chlorosulphate groups at C-6 and C-6' in 1 is comparable to the nucleophilic displacement of the mesyl or tosyl groups in the sulphonate derivatives of sucrose^{4,16}. Reaction of the bis(chlorosulphate) 2 with pyridinium chloride in chloroform at 50° gave the expected 6,6'-dichloride⁴ 5 in 96% yield.

With the intention of preparing azido derivatives of sucrose, the reactions of 1 and 2 with sodium azide in butanone were studied. However, when the tris(chlorosulphate) 1 was treated with sodium azide in refluxing butanone, the only isolable product was the 1'-chlorosulphate 3 (83%). Likewise, similar treatment of the bis(chlorosulphate) 2 afforded the 6,6'-dichloride 5 (69%). The fact that 3 and 5 were obtained instead of the corresponding azido derivatives suggested effective competition by the chloride anion which could only have arisen from the chlorosulphate groups of the precursors 1 and 2. It is of interest to note that, under similar reaction conditions, sucrose octamethanesulphonate on treatment with sodium azide gave 6,6'-diazido-6,6'-dideoxysucrose hexamethanesulphonate⁴ and monoazido-monodeoxysucrose heptamethanesulphonate¹⁷.

When the tris(chlorosulphate) 1 was refluxed in butanone without any added nucleophile, 40% of the 1'-chlorosulphate 3 was obtained. Similarly, the bis(chlorosulphate) 2 gave the 6,6'-dichloride 5 (35%). Furthermore, when 1 was heated in hexamethylphosphoric triamide at 95° it gave, after column chromatography, 1',6,6'-trichloro-1',6,6'-trideoxysucrose pentabenzoate (6, 63%) together with the slow-moving, minor product 4 which on benzoylation afforded the 6,6'-dichloride⁴ 5. In the light of these facts, the displacement of the chlorosulphate groups in 1 and 2 by chloride ion may involve an intramolecular process, akin to the S_Ni reaction of alkyl chlorosulphites or alkyl chloroformates.

The reaction of the tris(chlorosulphate) 1 with sodium chloride in hexamethylphosphoric triamide afforded the trichloride 6 in a better yield (88%). It should be emphasised that the displacement of the C-1' sulphonate by chloride ion under similar reaction conditions has so far been unsuccessful¹⁹. The facile displacement of the chlorosulphate group in 1 not only provided a convenient route to the trichloride 6 but also demonstrated an advantage over some of the standard methods^{1,4,18,19}. Catalytic de-esterification of 6, using sodium methoxide in methanol, afforded 1',6,6'-trichloro-1',6,6'-trideoxysucrose (7).

The reaction of the bis(chlorosulphate) 2 with sodium azide in hexamethylphosphoric triamide gave 6,6'-diazido-6,6'-dideoxysucrose hexabenzoate⁴ (8), possibly by initial formation of the 6,6'-dichloride 5 by an S_N process followed by a bimolecular displacement reaction with azide ion to afford the 6,6'-diazide⁴ 8.

EXPERIMENTAL

The general experimental data are as described in Part VI¹.

2,3,3',4,4'-Penta-O-benzoylsucrose 1',6,6'-tris(chlorosulphate) (1). — A solution of 2,3,3',4,4'-penta-O-benzoylsucrose² (5 g) in pyridine (25 ml) and chloroform (75 ml) was treated with sulphuryl chloride (7 ml) at -75° for 25 min. The reaction mixture was poured into ice-cold sulphuric acid (10%, 500 ml) with vigorous shaking and then extracted with dichloromethane. The organic layer was washed successively with water, aqueous sodium hydrogen carbonate, water, and dried (Na₂SO₄). The solution was concentrated to a syrup which was crystallised from ether to give 1 (5.2 g, 78%), m.p. 133–134°, $[\alpha]_D$ +19.8° (c 1.31, chloroform); n.m.r. data: τ 3.95 (d, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.59 (q, 1 proton, $J_{2,3}$ 10 Hz, H-2), 4.02 (q, 1 proton, $J_{3,4}$ 9 Hz, H-3), 4.45 (q, 1 proton, $J_{4,5}$ 10 Hz, H-4), 4.14 (d, 1 proton, $J_{3',4'}$ 6 Hz, H-3'), 4.13 (q, 1 proton, $J_{4',5'}$, 4 Hz, H-4'), 1.75–2.8 (m, 25 protons, 5 Bz).

Anal. Calc. for $C_{47}H_{39}Cl_{3}O_{22}S_{3}$: C, 48.7; H, 3.4; Cl, 9.3; S, 8.3. Found: C, 49.4; H, 3.8; Cl, 10.8; S, 7.8.

1'2,3,3',4,4'-Hexa-O-benzoylsucrose 6,6'-bis(chlorosulphate) (2). — A solution of 1',2,3,3',4,4'-hexa-O-benzoylsucrose³ (10 g) in pyridine (50 ml) and chloroform (150 ml) was treated with sulphuryl chloride (5 ml) at -75° for 25 min. The reaction was worked up as described previously. The ether extract on concentration afforded 2 (11 g, 91%) as an amorphous powder, $[\alpha]_{D}$ +13.1° (c 1.43, chloroform); n.m.r. data: τ 3.86 (d, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.58 (q, 1 proton, $J_{2,3}$ 10 Hz, H-2), 3.81 (q, 1 proton, $J_{3,4}$ 9.5 Hz, H-3), 4.43 (q, 1 proton, $J_{4,5}$ 10 Hz, H-4), 3.95 (d, 1 proton, $J_{3'4'}$, 5.5 Hz, H-3'), 4.28 (t, 1 proton, $J_{4',5'}$ 5.5 Hz, H-4'), 1.75–2.95 (m, 30 protons, 6 Bz).

Anal. Calc. for C₅₄H₄₄Cl₂O₂₁S₂: C, 55.8; H, 3.8; Cl, 6.0; S, 5.5. Found: C, 56.4; H, 4.0; Cl, 6.0; S, 4.7.

2,3,3',4,4'-Penta-O-benzoyl-6,6'-dichloro-6,6'-dideoxysucrose 1'-chlorosulphate (3). — (a) A solution of the tris(chlorosulphate) 1 (3 g) in chloroform (100 ml) containing pyridinium chloride (1.5 g) was heated at 50° for 4 h. T.I.c. (ether-light petroleum, 4:1) showed a fast-moving, major product. The reaction mixture was diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate and water, and dried (Na₂SO₄). The solution, on concentration, afforded a syrup which was crystallised from methanol to give 3 (2 g, 76%), m.p. 136-138°, $[\alpha]_D$ +11.5° (c 1.12, chloroform); n.m.r. data: τ 3.98 (d, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.59 (q, 1 proton, $J_{2,3}$ 9.5 Hz, H-2), 4.07 (t, 1 proton, $J_{3,4}$ 9.5 Hz, H-3), 4.47 (t, 1 proton,

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 $J_{4,5}$ 9.5 Hz, H-4), 4.2 (d, 1 proton, $J_{3',4'}$ 6 Hz, H-3'), 4 (q, 1 proton, $J_{4',5'}$ 6.5 Hz, H-4'), 1.7–2.83 (m, 25 protons, 5 Bz).

Anal. Calc. for $C_{47}H_{39}Cl_{3}O_{16}S$: C, 56.5; H, 3.9; Cl, 10.7; S, 3.2. Found: C, 56.7; H, 3.9; Cl, 10.6; S, 3.4.

(b) A solution of the tris(chlorosulphate) 1 (2.5 g) in butanone (100 ml) containing sodium azide (2.2 g) was refluxed for 3 h. The reaction mixture was filtered off and the filtrate concentrated to dryness. The residue was partitioned between dichloromethane and water. The organic layer was dried (Na₂SO₄) and concentrated, and the residue was crystallised from methanol to give 3 (1.8 g, 83%) as fine needles, m.p. and mixed m.p. 136–138°, $[\alpha]_D + 11.7^\circ$ (c 1.41, chloroform). The i.r. and n.m.r. spectra were identical with that of the 1'-chlorosulphate 3 prepared in (a).

(c) A solution of the tris(chlorosulphate) 1 (200 mg) in butanone was refluxed for 5 h. T.l.c. (ether-light petroleum, 6:1) showed a major product which was coincident with 3 prepared in (a) and (b). The solution was decanted, concentrated, and diluted with dichloromethane. The dichloromethane extract was washed with water, dried (Na₂SO₄), and concentrated, and the residue was crystallised from methanol to give 3 (70 mg, 40%), m.p. and mixed m.p. 135–138°, $[\alpha]_D + 12^\circ$ (c 0.91, chloroform). The i.r. and n.m.r. spectra were identical with that of 3 prepared in (a) and (b).

2,3,3',4,4'-Penta-O-benzoyl-6,6'-dichloro-6,6'-dideoxysucrose (4). — To a solution of 3 (500 mg) in methanol (15 ml), a solution of sodium iodide (400 mg) in methanol (0.5 ml) and water (0.5 ml) was added. The solution was then neutralised with barium hydroxide. The filtered mixture was concentrated to a syrup which was partitioned between dichloromethane and water. The organic layer was washed with aqueous sodium thiosulphate and water, and dried (Na₂SO₄). T.1.c. (ether-light petroleum, 6:1) showed a slow-moving product. The solution was concentrated to give 4 (400 mg, 89%) as an amorphous powder, $[\alpha]_D - 11^{\circ}$ (c 0.76, chloroform).

Anal. Calc. for $C_{47}H_{40}Cl_2O_{14}$: C, 62.7; H, 4.5; Cl, 7.9. Found: C, 63.0; H, 4.5; Cl, 7.6.

1'2,3,3',4,4'-Hexa-O-benzoyl-6,6'-dichloro-6,6'-dideoxysucrose⁴ (5). — (a) A solution of **4** (400 mg) in pyridine (10 ml) was treated with benzoyl chloride (0.2 ml) at 0° and stored at room temperature for 24 h. The reaction was worked up in the usual way to give a syrup which was crystallised from methanol to give 5 (350 mg, 78%) as fine needles, m.p. 165–167°, $[\alpha]_D + 9°$ (c 0.87, chloroform); lit.⁴, m.p. 85–87°, $[\alpha]_D + 5.8°$ (c 1.0, chloroform); n.m.r. data: τ 3.9 (d, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 4.57 (q, 1 proton, $J_{2,3}$ 10.5 Hz, H-2), 3.84 (q, 1 proton, $J_{3,4}$ 9.5 Hz, H-3), 4.39 (q, 1 proton, $J_{4,5}$ 10.5 Hz, H-4), 4 (d, 1 proton, $J_{3',4'}$ 5.5 Hz, H-3'), 4.1 (t, 1 proton, $J_{4',5'}$ 5.5 Hz, H-4'), 1.8–2.95 (m, 30 protons, 6 Bz).

Anal. Calc. for $C_{54}H_{44}Cl_2O_{15}$: C, 64.6; H, 4.4; Cl, 7.1. Found: C, 64.7; H, 4.5; Cl, 6.9. The i.r. and n.m.r. spectra were identical with the authentic sample⁴.

(b) The bis(chlorosulphate) 2 (300 mg) in chloroform (20 ml) containing pyridinium chloride (100 mg) was heated at 55° for 4 h. The solution was decanted off, washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4),

and concentrated. The resulting syrup was crystallised from methanol to give 5 (250 mg, 96%), m.p. and mixed m.p. 165–167°. The i.r. and n.m.r. spectra were identical with those of the sample prepared in (a).

(c) To a cooled (-18°) solution of sucrose hexabenzoate³ (1.2 g) in pyridine (5 ml) and chloroform (15 ml), sulphuryl chloride (1.2 ml) was added over a period of 0.5 h. The reaction mixture was stored at -5° for 24 h. The solution was diluted with dichloromethane and washed successively with cold, dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, and dried (Na₂SO₄). T.I.c. (ether-light petroleum, 6:1) showed a fast-moving, minor product and a major product which stayed on the base line. The solution on concentration and then elution from silica gel (30 g), using dichloromethane–light petroleum (2:1), gave 5 (200 mg, 16%), m.p. and mixed m.p. 165–167°. The i.r. and n.m.r. spectra were identical with those of 5 prepared in (a) and (b).

(d) A solution of 2 (500 mg) in butanone (50 ml) containing sodium azide (500 mg) was refluxed for 5 h. The filtered mixture was concentrated and the residue partitioned between dichloromethane and water. The organic layer was dried (Na_2SO_4) and concentrated. Elution of the residue from a column of silica gel (25 g), using ether-light petroleum (1:1), gave a syrup which was crystallised from methanol to afford 5 (300 mg, 69%), m.p. and mixed m.p. 165–167°. The i.r. and n.m.r. spectra were identical with those of 5 prepared in (a), (b), and (c).

(e) A solution of the bis(chlorosulphate) 2 (500 mg) in butanone (50 ml) was refluxed for 8 h. T.l.c. (ether-light petroleum, 6:1) showed three products; the fast-moving component was coincident with 5. The reaction was worked up as described previously. The residual syrup was eluted from a column of silica gel (25 g), using ether-light petroleum (1:1), to give a syrup which on crystallisation from methanol gave 5 (150 mg, 35%), m.p. and mixed m.p. 165-167°. The i.r. and n.m.r. spectra were identical with those of the samples prepared in (a), (b), (c), and (d).

2,3,3',4,4'-Penta-O-benzoyl-1',6,6'-trichloro-1',6,6'-trideoxysucrose (6). — (a) A solution of the tris(chlorosulphate) 1 (500 mg) in hexamethylphosphoric triamide (10 ml) was treated with sodium chloride (750 mg) at 95° for 48 h. T.l.c. (ether-light petroleum, 6:1) showed a fast-moving, major product. The reaction mixture was poured into ice-water, and the precipitate was collected, washed well with water, and taken up in dichloromethane. The dried (Na₂SO₄) solution was concentrated to a syrup which on crystallisation from methañol afforded 6 (350 mg, 88%), m.p. 90–92°, [α]_D +3.9° (c 0.49, chloroform); n.m.r. data: τ 4.02 (d, 1 proton, $J_{1,2}$ 3.6 Hz, H-1), 4.65 (q, 1 proton, $J_{2,3}$ 10.2 Hz, H-2), 4.0 (q, 1 proton, $J_{3,4}$ 9.6 Hz, H-3), 4.48 (q, 1 proton, $J_{4,5}$ 10 Hz, H-4), 3.94 (d, 1 proton, $J_{3',4'}$ 6.4 Hz, H-3'), 4.11 (t, 1 proton, $J_{4',5'}$ 6.4 Hz, H-4'), 1.75–2.9 (m, 25 protons, 5 Bz).

Anal. Calc. for $C_{47}H_{39}Cl_3O_{13}$: C, 61.4; H, 4.2; Cl, 11.7. Found: C, 61.7; H, 4.8; Cl, 11.1.

(b) A solution of 3 (500 mg) in hexamethylphosphoric triamide (10 ml) was heated with sodium chloride (500 mg) at 95° for 24 h. The reaction mixture was worked up as described in (a) to give a syrup which on crystallisation from methanol

afforded 6 (360 mg, 78%), m.p. and mixed m.p. 90–92°, $[\alpha]_D + 3.9^\circ$ (c 1.01, chloroform). The i.r. and n.m.r. spectra were identical with those of 6 prepared in (a).

(c) A solution of 1 (500 mg) in hexamethylphosphoric triamide (10 ml) was heated at 95° for 48 h. T.l.c. (ether-light petroleum, 6:1) showed a fast-moving, major product and a slow-moving, minor product. The reaction mixture was worked up as described previously to give a syrupy residue. Separation of the products by elution from silica gel (50 g) with ether-light petroleum (1:1) gave initially the trichloride 6 (250 mg, 63%). The i.r. and n.m.r. spectra were identical with the samples prepared in (a) and (b).

Compound 4 was then eluted and isolated as an amorphous powder (120 mg, 31%) which on benzoylation, in the usual way, gave the dichloride 5.

1',6,6'-Trichloro-1',6,6'-trideoxysucrose (7). — To a solution of 6 (600 mg) in dry methanol (150 ml), a catalytic amount of sodium methoxide was added and the solution was stored at room temperature for 24 h. T.l.c. (chloroform-methanol, 6:1) showed one product. The solution was deionised by shaking with Amberlyst-15 resin, concentrated, and purified by elution from a column of silica gel (20 g), using chloroform-acetone (2:1), to give 7 (150 mg, 87%), [α]_D +52.5° (c 0.66, acetone).

Anal. Calc. for $C_{12}H_{19}Cl_{3}O_{8}$: C, 36.2; H, 4.8; Cl, 26.8. Found: C, 36.4; H, 5.2; Cl, 23.2.

Reaction of the bis(chlorosulphate) 2 with sodium azide in hexamethylphosphoric triamide. — A solution of 2 (500 mg) in hexamethylphosphoric triamide (10 ml) containing sodium azide (500 mg) was heated at 90° for 24 h. The reaction was worked up, as described previously, to give an amorphous powder which on crystallisation from ethanol afforded the 6,6'-diazide 8 (250 mg, 57%), m.p. 76–78°, $[\alpha]_D$ +40° (c 0.55, chloroform); lit.⁴ m.p. 75–78°, $[\alpha]_D$ +42.5° (c 1.6, dichloromethane). The i.r. and n.m.r. spectra were identical with those for the authentic sample⁴.

Anal. Calc. for C₅₄H₄₄N₆O₁₅: C, 63.8; H, 4.3; N, 8.3. Found: C, 64.1; H, 4.5; N, 8.0.

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