Note

Conversion of 1,4-anhydroerythritol into 1,4-anhydro-DL-threitol: chloride displacement of sulfonate

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Displacement of secondary sulfonic groups by chloride ions has been demonstrated in both 5- and 6-membered rings; however, the reactions are more favored in 5-membered rings¹⁻⁵. Sinclair⁶ used lithium bromide and hexamethylphosphoric triamide in toluene to displace sulfonate groups by bromide ions in methyl 2,3-di-O-benzoyl-4,6-di-O-(methylsulfonyl)- α -D-glucopyranoside. The low (23%) yield of 4,6-dibromo derivative, obtained after 116 h of refluxing, shows the difficulty of displacing secondary sulfonate with a halide on a pyranoside ring, even though an adjacent *trans* acyloxy group was present.

Owen and Smith³ demonstrated chloride displacement of a sulfonic ester group in mono-O-tosyl-1,2-cyclopentanediol. We now describe a facile conversion of

TABLE I

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Ni -	<u></u>
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1	
R ²	R4

Compound number	R ¹	R ²	<i>R</i> ³	R ⁴	
1	н	OH	н	ОН	
2	н	OTs ^a	н	он	
3	н	OMs	н	OMs	
4	н	OTs	н	OTs	
5	Cl	н	н	OMs	
6	Cl	H	н	OTs	
7	OH	н	н	ОН	
8	OMs	H	н	OMs	
9	OTs	H	н	OTs	
10	PNB	н	н	PNB	

 $T_S = p \cdot CH_3C_6H_4SO_2-$, $M_8 = CH_3SO_2-$, $PNB = p \cdot NO_2C_6H_4(C=0)-$.

1,4-anhydroerythritol (1) (Table I) into 1,4-anhydro-DL-threitol (7) in 23% overall yield by chloride displacement of a tosyloxy group, and 34% overall yield for chloride displacement of a mesyloxy group.

The greater reactivity of methanesulfonyl chloride over *p*-toluenesulfonyl chloride in esterifying adjacent hydroxyl groups in a furanoid ring was reported by Yung et al.⁷. Methanesulfonylation of 1 with 2 moles of methanesulfonyl chloride in pyridine for 18 h at 25° produced 1,4-anhydro-2,3-di-O-(methylsulfonyl)erythritol (3) crystalline in 93% yield. No mono-O-mesyl derivative was isolated. The much slower p-toluenesulfonylation of 1 with 2 moles of p-toluenesulfonyl chloride in pyridine for 9 days at 25° gave a mixture of 1,4-anhydro-2-O-p-tolylsulfonylerythritol (2) and 1,4-anhydro-2,3-di-O-p-tolylsulfonylerythritol (4), which was resolved into the crystalline compounds. Compound 3, when refluxed with pyridine hydrochloride in pyridine, produced crystalline 1,4-anhydro-2-chloro-2-deoxy-3-O-(methylsulfonyl)-DL-threitol (5) in 51% yield. Similar treatment of 4 gave 1,4-anhydro-2-chloro-2deoxy-3-O-p-tolylsulfonyl-DL-threitol (6) in 67% yield. Compound 5 was formed directly in 51% yield by refluxing **1** in pyridine with 2 moles of methanesulfonyl chlorice, whereas 6 was formed in 40% yield from 1 with 2 moles of p-toluenesulfonyl chloride. When the mono-O-tosylanhydroerythritol was treated with pyridine hydrochloride under reflux, the tosyl group was eliminated, but no products were isolated from the reaction mixture. However, the i.r. spectrum of the mixture disclosed evidence of a chlorohydrin, tetrahydrofuranone³, and 2,5-dihydrofuran⁵.

Methyl 4,6-*O*-methylene-2,3-di-*O*-*p*-tolyl(or methyl)sulfonyl- α -D-glucopyranoside⁸, when treated with pyridine hydrochloride in the same way as 3 and 4, was unchanged after 24 h. Hence, a relatively fixed, gauche orientation of vicinal sulfonate groups in a 6-membered ring is unfavorable for their displacement by chloride.

By hydrolysis of 5 with base, 7 was isolated in 71% yield, but the yield was lower for 6 (62.4%).

EXPERIMENTAL

General methods. — All reactions were monitored by t.l.c. Purity of the compounds was established by t.l.c. and g.l.c. and by elemental analyses (Table II). T.l.c. was conducted on 0.25-mm layer of EM Reagent Silica Gel G (Brinkmann Instruments Inc.*) with air-dried plates. The spots were detected by spraying with 5% ethanolic sulfuric acid and charring. G.l.c. analyses were recorded by an F&M Model 700 laboratory chromatograph with flame-ionization detector, which was fitted with a 1/8 in. \times 6 ft stainless-steel column containing 3% JXR silicone gum on 100– 120 mesh Gas-Chrom Q support (Anspec, Ann Arbor, Michigan). Trimethylsilyl ethers were prepared for compounds 1, 7, and DL-threitol. I.r. spectra were determined in carbon tetrachloride (5mm solutions) and also in potassium bromide pellets

^{*}Mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

Compound	M.p. (degrees)	С		H		Cl or N		S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
2 $C_{11}H_{14}O_5S$	73–75	51.2	51.1	5.46	5.59			12.41	12.54
$3 C_6 H_{12} O_7 S_2$	117-118	27.6	27.6	4.94	4.70			24.7	24.5
$4 C_{18}H_{20}O_7S_2$	91.5-92.5	52.4	52.4	4.89	4.85			15.55	16.05
5 C ₅ H ₉ ClO ₅ S	59.5-61	29.9	29.7	4.52	4.50	17.67	17.84	15.98	16.0
6 C11H13ClO5	51.5-52.5	47.7	47.7	4.74	4.97	12.81	12.66	11.59	11.51
$7 C_4 H_8 O_3$		46.2	46.1	7.75	7.73				
8 $C_6H_{12}O_7S_2$	117.5119	27.6	27.4	4.94	4.70			24.7	24.6
9 $C_{18}H_{20}O_7S_2$	99.5–101 99–100°	52.4	52.7	4.89	5.00			15.55	15.43
10 $C_{18}H_{14}N_2O_9$	201.5–202.5 201–202ª	53.7	53.5	3.50	3.39	7.00	6.90		

TABLE II

ANALYSES	OF	NEW	COMPOUNDS

^aAuthentic 9 and 10.

(1.22-mm thick containing 0.1M concentrations) with a Perkin-Elmer Model 621 spectrophotometer. N.m.r. spectra were recorded with a Varian Model HA-100 spectrometer; chemical shifts were assigned by spin-decoupling experiments and referred to internal tetramethylsilane. The ABX patterns were confirmed also by spin-decoupling experiments. Melting points, measured in capillary tubes, are not corrected.

The identities of 2, 3, 4, 5, and 6 were supported by their i.r. and n.m.r. spectra. The C-Cl stretching absorption band usually appears in the range of 700–750 cm⁻¹ for monochlorinated derivatives⁹. The i.r. spectra of 5 and 6 showed strong absorption-bands at 748 and 770 cm⁻¹; however, no bands were found in this region for 3 and 4. The spectra for 5 and 6 displayed only one absorption band at 890 cm⁻¹; whereas two bands (810 and 850; 828 and 850 cm⁻¹) were found for 3 and 4; these correspond to axial and equatorial orientation of sulfonyloxy groups, respectively¹⁰.

In the n.m.r. spectra, the methine protons showed the expected, large, chemicalshift differences of 0.50 for 2, 0.83 for 5, and 0.86 for 6; only minimal differences of 0.07 for 4, and 0.02 for 3; and equivalent protons for 1,4-anhydro-2,3-di-O-(methylsulfonyl)-DL-threitol (8) and 1,4-anhydro-2,3-di-O-p-tolylsulfonyl-DL-threitol (9).

Authentic 7, prepared from DL-threitol by the procedure of Otey and Mehltretter¹¹, was identical to 7 prepared as in Table I, as indicated by m.p. and mixed m.p. of the di-O-mesyl (8), di-O-p-tosyl (9), and di-O-p-nitrobenzoyl (10) derivatives.

Both 1 and 7 crystallized when they were redistilled into a flask cooled by solid carbon dioxide; however, both compounds melted below 25° and were hygroscopic when exposed to air.

Sulfonic esters. — Compounds 3 and 8 were prepared by the reaction of methanesulfonyl chloride (2:1 molar ratio) and 1 or 7 in pyridine (200 ml) for 18 h at

25°. Compounds 2, 4, and 9 were prepared by reaction of *p*-toluenesulfonyl chloride and 1 or 7 (2:1 molar ratio) in pyridine (200 ml) for 9 days at 25°. Compounds 3 and 4 were treated with pyridine hydrochloride (2:1 molar ratio) in boiling pyridine (200 ml), which gave 5 and 6 after 18 and 24 h under reflux. Compounds 5 and 6 also were formed directly by refluxing 1 with 2 moles of methanesulfonyl chloride and *p*-toluenesulfonyl chloride in pyridine, which gave 51 and 40% yields, respectively. The products were isolated by pouring the mixtures onto ice, extracting with chloroform, and removing pyridine by repeated evaporation of toluene from the nonvolatile products. The residue was dissolved in chloroform-methanol and treated with activated charcoal and Celite 535 before crystallization from methanol.

1,4-Anhydroerythritol (1) was prepared by cyclization of erythritol¹² with acidic cation-exchange resin¹¹. The second distillation of the product gave crystals that were very hygroscopic and quickly liquefied when exposed to air.

1,4-Anhydro-2-O-p-tolylsulfonylerythritol (2). — After crystallization of 4, the mother liquor contained a mixture of 2 and 4. After evaporation of the solvent, the residual mixture was separated by dry-column chromatography on Silica Gel G (3% water) with 25% acetone-toluene as eluent. A 31.5% yield of 2 (based on 1) was obtained by crystallization from benzene; n.m.r. data (chloroform-d): τ 5.12 and 5.62 (methine protons), 7.51 (tolyl methyl protons), 7.26 (hydroxyl proton), and 2.14–2.63 (aromatic protons). A complex multiplet for the methylene protons was centered at 6.16. The i.r. spectrum showed a very broad hydroxyl band.

1,4-Anhydro-2,3-di-O-(*methylsulfonyl*)*erythritol* (3). — A 2.7-g (93.4%) yield of 3 was obtained after crystallization from methanol; v_{max} 810 and 850 cm⁻¹ (sulfonyloxy groups¹⁰); n.m.r. data (chloroform-*d*): τ 5.92 and 5.94 (complex multiplets, methine protons), 6.91 (mesyl methyl protons), and 5.94 (complex multiplet, methylene protons).

1,4-Anhydro-2,3-di-O-p-tolylsulfonylerythritol (4). — A 17.1-g (41.5%) yield of 4 was obtained after crystallization from methanol; v_{max} 828 and 850 (sulfonyloxy groups¹⁰), 1600 cm⁻¹ (aromatic-ring vibrations); n.m.r. data (chloroform-d): τ 5.08 and 5.15 (complex multiplets, methine protons), 7.54 (tolyl methyl protons), and 2.25-2.68 (aromatic protons). The methine and methylene protons of the spectrum showed a clear ABX pattern.

1,4-Anhydro-2-chloro-2-deoxy-3-O-(methylsulfonyl)-DL-threitol (5). — A 1.1-g (51%) yield of 5 was obtained after crystallization from methanol; v_{max} 890 (sulfonyl-oxy group¹⁰) 748 cm⁻¹ (strong, C–Cl); n.m.r. data (chloroform–d): τ 5.97 (chloromethine), 5.14 (mesyl methine), (both complex multiplets), 7.88 (mesyl methyl), and 6.30 (complex multiplet, methylene).

1,4-Anhydro-2-chloro-2-deoxy-3-O-p-tolylsulfonyl-DL-threitol (6). — A 2.4-g (67%) yield of 6 was obtained after crystallization from methanol; v_{max} 890 (sulfonyl-oxy group¹⁰), 1600 (aromatic ring vibrations), 770 cm⁻¹ (strong, C-Cl); n.m.r. data (benzene- d_6): τ 5.93 (chloro-methine), 5.07 (tolyl methine) (both complex multiplets), 8.07 (tolyl methyl protons), and 2.35–3.19 (aromatic protons). The methine and methylene protons of the spectrum showed two clear ABX patterns.

1,4-Anhydro-DL-threitol (7). — Compounds 5 and 6 were treated with aqueous sodium hydroxide (5%) for 16 h at 75° to give 1.1-g (71%) and 0.97-g (62.4%) yields of 7, respectively. The mixtures were neutralized with M sulfuric acid, and the product was recovered by extracting with ethyl acetate. The solvent was removed by evaporation under diminished pressure. The residue was redissolved in methanol and treated with activated charcoal and Celite 535.

1,4-Anhydro-2,3-di-O-(methylsulfonyl)-DL-threitol (8). — A yield of 0.74 g (71.2%) was obtained after crystallization from methanol; n.m.r. data (chloroformd): τ 4.76 (complex multiplet, methine protons), 6.93 (mesyl methyl protons), and 6.93 (complex multiplet, methylene protons).

1,4-Anhydro-2,3-di-O-p-tolylsulfonyl-DL-threitol (9). — A yield of 0.41 g (55.2%) of product was obtained after crystallization from methanol; n.m.r. data (chloroform-d): τ 5.05 (complex multiplet, methine protons), 7.47 (tolyl methyl protons), and 2.23–2.64 (aromatic protons). The methine and methylene protons of the spectrum showed a clear ABX pattern.

1,4-Anhydro-2,3-di-O-p-nitrobenzoyl-DL-threitol (10). — Compound 10 was prepared by the reaction of *p*-nitrobenzoyl chloride and 7 in pyridine. A 0.53-g (63%) yield of product was obtained by crystallization from methanol; reported¹³ for 1,4-anhydro-2,3-di-O-*p*-nitrobenzoyl-L-threitol, m.p. 191–192°.

DL-Threitol. — Prepared by a modification of the procedure of Bose *et al.*¹⁴, *cis*-2-butene-1,4-diol (91% *cis*) was oxidized with aqueous peroxyformic acid¹⁵. DL-Threitol was isolated by extraction of the neutralized hydrolyzate with hot acetone and was recrystallized from 4:1 acetone-ethanol; yield 24 g (30%); m.p. 66.5–67.5°; reported¹⁴ m.p. 59–64°; m.p.¹⁶ 72°; m.p.¹⁷ 72°. The dibenzylidene acetal was prepared by the procedure of Klosterman and Smith¹³, yield 2.1 g (83.7%); m.p. 218–220°; reported¹⁴ m.p. 221–223°. Debenzylidenation¹³ gave back DL-threitol, m.p. 66.5–67.5°. The tetraacetate was prepared in 71.4% yield; m.p. 47–48.5°; reported¹⁸ m.p. 53°.

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