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Note

Partial sulfonylation of methyl α- and β-D-xylopyranoside

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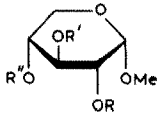
In previous publications, on selective sulfonylation of 1,5-anhydro-D-glucitol[1] and 1,5-anhydroxylitol[2] with *p*-toluenesulfonyl chloride, the influences of steric and electronic factors on the relative reactivity of the hydroxyl groups were reported. In connection with these studies, the partial tosylation of methyl α- and β-D-xylopyranoside (**1** and **12**) is now described.

Selective sulfonylation of **1** with two molar equivalents of *p*-toluenesulfonyl chloride in pyridine at 0° gave a mixture of the 2,3,4-trisulfonate **2** (8.7%), the 2,4-disulfonate **3** (70.3%), the 2,3-disulfonate **4** (10.2%), and the 2-sulfonate **6** (10.8%), as shown by t.l.c. Monomolar tosylation of **1** gave **3** (11.6%), **4** (2.2%), the 3-sulfonate **5** (0.6%), **6** (79.2%), and the 4-sulfonate **7** (6.3%).

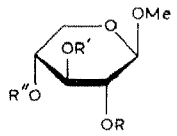


	R	R′	R″
1	H	H	H
2	Ts	Ts	Ts
3	Ts	H	Ts
4	Ts	Ts	H
5	H	Ts	H
6	Ts	H	H
7	H	H	Ts
8	Ts	Bz	Ts
9	Ts	Ts	Bz
10	Bz	Ts	Ts
11	Bz	Ts	Bz

Bz = PhCO

Ts = $SO_2C_6H_4Me$-*p*

The structure of **3** was demonstrated by comparison of the p.m.r. spectra of **3** and its benzoate (**8**). The signal of H-3 in the spectrum of **3** appeared at higher field than those of H-2 and H-4, whereas the H-3 signal of **8** occurred to low field of all other ring-proton resonances. This finding indicates that C-3 of **3** and **8** is substituted with a hydroxyl and a benzoyloxy group, respectively. The structure of **4** was confirmed by benzoylation of **4**, giving the 4-benzoate **9**, the physical and spectral properties of which were readily distinguished from those of the 3-benzoate **8** and 2-benzoate[3] **10**. The monosulfonates **6** and **7** were reported by Buchanan and Fletcher[4] as the products of monomolar tosylation of **1** in yields of 47 and 4%, respectively. The structure of **5** was established by conversion into the known 2,4-dibenzoate[3] **11**.



	R	R'	R"
12	H	H	H
13	Ts	Ts	Ts
14	Ts	H	Ts
15	H	Ts	Ts
16	H	H	Ts
17	Ts	Bz	Ts
18	Bz	Ts	Ts
19	Bz	Bz	Ts

Dimolar tosylation of **12** gave the 2,3,4-trisulfonate **13** (15.5%), the 2,4-disulfonate **14** (33.8%), the 3,4-disulfonate **15** (19.5%), and the 4-sulfonate **16** (31.2%), as shown by t.l.c. The structures of **14**, **15**, and **16** were established by preparing the corresponding *O*-benzoyl derivatives **17**, **18**, and **19**, the structures of which were characterized as has already been described[3].

The respective isolation of the 2,4-disulfonate and the 2-sulfonate as the major product from di- and mono-molar tosylation of **1** indicates that the relative reactivity of the secondary hydroxyl groups of **1** is in the order OH-2 > OH-4 > OH-3, which is consistent with the results[5] of selective methanesulfonylation of **1**, and tosylation of benzyl α-D-xylopyranoside.

On the other hand, the order of the reactivity of the hydroxyl groups of **12** is OH-4 > OH-2 > OH-3, indicated by the isolation of a preponderance of the 2,4-disulfonate in the disulfonates, and of the 4-sulfonate in the monosulfonates from dimolar tosylation of **12**. This result contrasts with that[5] obtained by Chalk and Ball for selective mesylation of **12**, which was in the order OH-4 > OH-3 > OH-2. The high reactivity of the OH-2 group in **1** may be due to intramolecular hydrogen-bonding between the OH-2 group and the axial methoxyl group at C-1. The OH-3 group in both anomers (**1** and **12**) is the least reactive in tosylation. This result is predictable

from the observation[2] that the tosyl group has a substantial decelerating effect on the reactivity of the neighboring hydroxyl groups.

This finding indicates that the influence of gauche interactions on the reactivity of hydroxyl groups should be taken into account as an inactivating factor in sulfonylation. The facts of the higher reactivity of the OH-4 group compared with the OH-3 group in **1**, and the highest reactivity of the OH-4 group in **12**, apparently support the prediction[1] that intramolecular hydrogen-bonding is the most important activating factor, and that stereochemical factors (depression of the steric hindrance derived from the methylene group at C-5 in the six-membered ring) follow next, rather than electronic effects, in sulfonylation.

EXPERIMENTAL

General methods. — Quantitative analysis of the products from partial tosylation was performed by thin-layer chromatography on a quartz rod sintered with silica gel 60 H (Merck) and glass powder (1:2), with chloroform (solvent *A*) or 10:1 toluene–acetone (solvent *B*), and spots were detected by using an Iatoron chromatoscanner TH-10 equipped with a hydrogen flame-ionization detector. Percentages are expressed on a relative molar basis. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck). P.m.r. spectra were recorded with a Hitachi R-24 60-MHz instrument for solutions in chloroform-*d*, with tetramethylsilane as the internal standard, unless otherwise stated.

p-*Toluenesulfonylation of methyl* α-D-*xylopyranoside* (**1**). — (*a*) *With two molar equivalents.* To a solution of **1** (1 g) in absolute pyridine (20 mL) at 0° was added *p*-toluenesulfonyl chloride (2.55 g, 2.2 mol. equiv.) portionwise, with stirring. The mixture was kept for 24 h at 0°, stirred for 24 h at 5° and for 24 h at room temperature, and then extracted with chloroform. The extract was successively washed with dilute sulfuric acid, saturated sodium hydrogencarbonate, and water, and dried (sodium sulfate). The chloroform solution was used for t.l.c. analysis in solvent *A*.

The foamy product obtained by evaporation of the solution was fractionated on silica gel (250 g). Stepwise elution with the solvent systems benzene–ethyl acetate, 9:1, 4:1, 2:1, and 1:1, and pure ethyl acetate gave four fractions, the 2,3,4-trisulfonate **2** (206 mg, 5%), the 2,4-disulfonate **3** (1.695 g, 59%), the 2,3-disulfonate **4** (248 mg, 9%), and the 2-sulfonate **6** (332 mg, 17%).

(*b*) *With one molar equivalent.* Treatment of **1** (1 g) with *p*-toluenesulfonyl chloride (1.39 g, 1.2 mol. equiv.) in pyridine (20 mL), followed by chromatographic fractionation of the product on silica gel as described in (*a*), afforded five fractions: **3** (244 mg, 9%), **4** (39 mg, 1%), the 3-sulfonate **5** (29 mg, 2%), **6** (944 mg, 49%), and the 4-sulfonate **7** (105 mg, 5%).

Methyl 2,3,4-tri-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**2**) could not be crystallized; R_F 0.69; $[\alpha]_D^{26}$ +35.5° (*c* 6.6, chloroform); p.m.r.: δ 5.08 (t, 1 H, $J_{2,3} = J_{3,4} =$ 8 Hz, H-3), 4.72 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.38 (q, 1 H, H-2), 4.25 (sextet, 1 H,

$J_{4,5a}$ 10, $J_{4,5e}$ 5 Hz, H-4), 3.73 (q, 1 H, $J_{5a,5e}$ 12 Hz, H-5*a*), 3.70 (q, 1 H, H-5*e*), 3.22 (s, 3 H, OCH_3), and 2.38 (s, 9 H, 3 $C_6H_4CH_3$).

Methyl 2,4-di-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**3**) crystallized from chloroform–petroleum ether; R_F 0.54; m.p. 191–192°, $[\alpha]_D^{28}$ +61.8° (*c* 1.3, chloroform); p.m.r.: δ 4.63 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.20 (sextet, 1 H, $J_{3,4}$ 9, $J_{4,5a}$ 10, $J_{4,5e}$ 5 Hz, H-4), 4.03 (q, 1 H, $J_{2,3}$ 9 Hz, H-2), 3.65 (t, 1 H, H-3), 3.60 (t, 1 H, $J_{5a,5e}$ 10 Hz, H-5*e*), 3.55 (t, 1 H, H-5*a*), 3.23 (s, 3 H, OCH_3), and 2.42 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{20}H_{24}O_9S_2$: C, 50.83; H, 5.13; S, 13.57. Found: C, 50.54; H, 5.21; S, 13.52.

Methyl 2,3-di-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**4**) crystallized from ethanol; R_F 0.44; m.p. 168–169°, $[\alpha]_D^{22}$ +60.3° (*c* 1.7, chloroform); p.m.r.: δ 4.72 (t, 1 H, $J_{2,3} = J_{3,4}$ = 8 Hz, H-3), 4.67 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.25 (q, 1 H, H-2), 4.0–3.3 (m, 3 H, H-4,5*a*,*e*), 3.22 (s, 3 H, OCH_3), and 2.42 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{20}H_{24}O_9S_2$: C, 50.83; H, 5.13; S, 13.57. Found: C, 50.69; H, 5.04; S, 13.44.

Methyl 3-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**5**) was obtained as a syrup; R_F 0.27; $[\alpha]_D^{22}$ +110.6° (*c* 1.5, chloroform). The 3-sulfonate **5** (29 mg) was treated with benzoyl chloride (0.05 mL) in pyridine (1 mL) at 0°. The mixture was stirred overnight at room temperature, and extracted with chloroform. Evaporation of the extract gave a syrup (48 mg, 100%) which crystallized, and was recrystallized, from ethanol, to give methyl 2,4-di-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**11**), m.p. 116–118°. The p.m.r. spectra of **11** and an authentic sample[3] were identical.

Methyl 2-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**6**) crystallized from ethanol; R_F 0.20; m.p. 135–136°, $[\alpha]_D^{32}$ +84.1° (*c* 1.0, chloroform); lit.[4] m.p. 135–136°, $[\alpha]_D$ +85.9° (*c* 0.55, chloroform); p.m.r. (dimethyl sulfoxide-d_6): δ 4.50 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.02 (q, 1 H, $J_{3,4}$ 9 Hz, H-2), 3.15 (s, 3 H, OCH_3), and 2.40 (s, 3 H, ($C_6H_4CH_3$).

Methyl 4-*O*-*p*-tolylsulfonyl-α-D-xylopyranoside (**7**) crystallized from benzene; R_F 0.14; m.p. 59–60°, $[\alpha]_D^{16}$ +101.6° (*c* 2.0, chloroform); lit.[4] m.p. 57–58°, $[\alpha]_D$ +97.1° (*c* 0.48, chloroform).

*Methyl 3-*O*-benzoyl-2,4-di-*O*-p-tolylsulfonyl-α-D-xylopyranoside* (**8**). — Benzoylation of the 2,4-disulfonate **3** (100 mg) with benzoyl chloride (0.04 mL) in pyridine (2 mL) at 0° gave a solid which, on recrystallization from chloroform–ethanol, yielded the title compound **8** (72 mg, 60%); m.p. 200–201° (dec.), $[\alpha]_D^{23}$ +61.7° (*c* 0.4, chloroform); p.m.r.: δ 5.65 (t, 1 H, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3), 4.88 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.57 (sextet, 1 H, $J_{4,5a}$ 10, $J_{4,5e}$ 6 Hz, H-4), 4.47 (q, 1 H, H-2), 3.90 (q, 1 H, $J_{5a,5e}$ 10 Hz, H-5*e*), 3.77 (t, 1 H, H-5*a*), 3.42 (s, 3 H, OCH_3), and 2.18 and 2.13 (2 s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{27}H_{28}O_{10}S_2$: C, 56.23; H, 4.90; S, 11.12. Found: C, 55.95; H, 4.76; S, 11.18.

*Methyl 4-*O*-benzoyl-2,3-di-*O*-p-tolylsulfonyl-α-D-xylopyranoside* (**9**). — The 2,3-disulfonate **4** (70 mg), treated with benzoyl chloride (0.04 mL) in pyridine (2 mL),

afforded the title compound **9** (80 mg, 94%). Attempts to crystallize it failed; $[\alpha]_D^{26}$ −24.1° (*c* 4.6, chloroform); p.m.r.: δ 5.17 (sextet, 1 H, $J_{3,4}$ 9, $J_{4,5a}$ 10, $J_{4,5e}$ 6 Hz, H-4), 5.25 (t, 1 H, $J_{2,3}$ 9 Hz, H-3), 4.93 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.40 (q, 1 H, H-2), 3.90 (q, 1 H, $J_{5a,5e}$ 11 Hz, H-5*e*), 3.63 (q, 1 H, H-5*a*), 3.35 (s 3 H, OCH_3), and 2.37 and 2.20 (2 s, 6 H, 2 $C_6H_4CH_3$).

*Dimolar sulfonylation of methyl β-*D*-xylopyranoside* (**12**). — Compound **12** (1 g) was treated with *p*-toluenesulfonyl chloride (2.55 g, 2.2 mol. equiv.) as described for the β anomer. The resulting chloroform solution was used for t.l.c. analysis (solvent *B*).

Evaporation of the solution, followed by chromatographic fractionation as described for the α anomer, afforded four fractions: the 2,3,4-trisulfonate **13** (309 mg, 8%), the 2,4-disulfonate **14** (660 mg, 23%), the 3,4-disulfonate **15** (488 mg, 17%), and the 4-sulfonate **16** (763 mg, 39%).

Methyl 2,3,4-tri-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**13**) crystallized from dichloromethane–ethanol; R_F 0.68; m.p. 145–146°, $[\alpha]_D^{25}$ −33.7° (*c* 1.0, chloroform); p.m.r.: δ 4.70 (t ,1 H, $J_{2,3} = J_{3,4} = 4$ Hz, H-3), 4.5–4.2 (m, 3 H, H-1,2,4), 4.07 (q, 1 H, $J_{4,5e}$ 4, $J_{5a,5e}$ 12 Hz, H-5*e*), 3.42 (q, 1 H, H-5*a*), 3.10 (s, 3 H, OCH_3), and 2.43 (s, 9 H, 3 $C_6H_4CH_3$).

Anal. Calc. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 51.83; H, 4.57; S, 15.32.

Methyl 2,4-di-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**14**) crystallized from dichloromethane–ethanol; R_F 0.55; m.p. 178–179°, $[\alpha]_D^{25}$ −47.1° (*c* 1.1, chloroform); p.m.r. (dimethyl sulfoxide-d_6): δ 5.75 (d, 1 H, $J_{3,OH}$ 6 Hz, OH-3, exchanges on addition of D_2O), 4.5–3.9 (m, 3 H, H-1,2,4), 3.9–3.1 (m, 3 H, H-3,5*a*,5*e*), 3.03 (s, 3 H, OCH_3), and 2.40 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{20}H_{24}O_9S_2$: C, 50.83; H, 5.13; S, 13.57. Found: C, 50.64; H, 4.98; S, 13.44.

The 2,4-disulfonate **14** (100 mg) was benzoylated as described for **11**, to yield methyl 3-*O*-benzoyl-2,4-di-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**17**; 110 mg, 90%), m.p. 148–149°. The p.m.r. spectrum was identical with that of an authentic sample[3] reported previously.

Methyl 3,4-di-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**15**) crystallized from ethanol; R_F 0.37; m.p. 141–142°, $[\alpha]_D^{25}$ −12.8° (*c* 1.1, chloroform); p.m.r.: δ 4.62 (t, 1 H, $J_{2,3} = J_{3,4} = 8$ Hz, H-3), 4.6–4.2 (m, 2 H, H-2,4), 4.17 (d, 1 H, $J_{1,2}$ 7 Hz, H-1), 4.07 (q, 1 H, $J_{4,5e}$ 4, $J_{5a,5e}$ 11 Hz, H-5*e*), 3.45 (s, 3 H, OCH_3), 2.90 (d, 1 H, $J_{2,OH}$ 4 Hz, OH-2, exchanges on addition of D_2O), and 2.43 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{20}H_{24}O_9S_2$: C, 50.83; H, 5.13; S, 13.57. Found: C, 50.55; H, 5.04; S, 13.46.

The 3,4-disulfonate **15** (100 mg) was converted by benzoylation into methyl 2-*O*-benzoyl-3,4-di-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**18**; 86 mg, 70%); m.p. 101–103°. The p.m.r. spectrum was identical with that of an authentic sample[3] reported previously.

Methyl 4-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**16**) crystallized from 2-

propanol–petroleum ether; R_F 0.13; m.p. 128–129°, $[\alpha]_D^{25}$ −56.4° (*c* 1.2, chloroform).

Anal. Calc. for $C_{13}H_{18}O_7S$: C, 49.04; H, 5.71; S, 10.07. Found: C, 49.32; H, 5.67; S, 10.18.

Treatment of the 4-sulfonate **16** (100 mg) with benzoyl chloride gave methyl 2,3-di-*O*-benzoyl-4-*O*-*p*-tolylsulfonyl-β-D-xylopyranoside (**19**; 149 mg, 90%); m.p. 141–142°. The p.m.r. spectrum was identical with that of an authentic sample[3] reported previously.

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