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Note

2-Hexuloses: selective sulphonylation of *O*-isopropylidene derivatives of D-fructopyranose and L-sorbofuranose

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Interest in sulphonyl derivatives of D-fructose and L-sorbose stems from their usefulness in the synthesis of deoxyhalo sugars[1]. Several deoxyhalosucroses[2,3] are intensely sweet-tasting and some possess anti-cariogenic[4,5] and male anti-fertility[6,7] properties.

Apart from a brief mention of the reaction[8] between tosyl chloride and 2,3-*O*-isopropylidene-α-L-sorbofuranose[9], there has been no report on selective sulphonylation of 2-hexuloses. The selective sulphonylation of 1,2-*O*- (**1**) and 2,3-*O*-isopropylidene-β-D-fructopyranose[10,11] and 2,3-*O*-isopropylidene-α-L-sorbofuranose[9] is now reported.

Treatment of **1** (ref. 10) with 3.6 mol. equiv. of tosyl chloride in pyridine for 2.5 h at room temperature gave one major and two minor fast-moving (t.l.c.) products. Chromatography on silica gel gave 1,2-*O*-isopropylidene-3,4,5-tri-*O*-tosyl- (**2**, 32%), -4,5-di-*O*-tosyl- (**3**, 62%), and -5-*O*-tosyl-β-D-fructopyranose (**4**; 4%, isolated as the diacetate **5**). The yield of **3** could be increased (41%) by carrying out the reaction with 1.5 mol. equiv. of tosyl chloride for 2.5 h at ~10°. The tritosylate **2** was identical with an authentic sample[12], and the structures of the ditosylate **3** and monotosylate **4** were confirmed by their ^{1}H- and ^{13}C-n.m.r. spectra (Tables I and II). The resonance due to H-3 in **3** was at rather high field (δ 4.1–4.3), indicating the presence of a hydroxyl group at C-3. Addition of trichloroacetyl isocyanate to the n.m.r. solution produced a singlet (due to the imino proton of the resulting carbamate) at δ 8.57 and caused H-3 to be deshielded by ~0.2 p.p.m. (δ 4.40, d, $J_{3,4}$ 9.5 Hz). The coupling constants $J_{3,4}$ 9.5 and $J_{4,5}$ 2.8 Hz are consistent with the expected $^1C_4$ conformation of the pyranose ring. Further confirmation of the location of tosyl groups at C-4 and C-5 in **3** was obtained from the ^{13}C-n.m.r. spectrum (Table II). Only the resonances for C-4,5 were shifted downfield (~8 p.p.m.) in comparison with the signals for **1**. Furthermore, the acetate and the benzoate of **3** were identical to the compounds synthesised by unambiguous routes[12,13].

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TABLE I

^{1}H-N.M.R. DATA: FIRST-ORDER CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz) IN CHLOROFORM AT 90 MHz

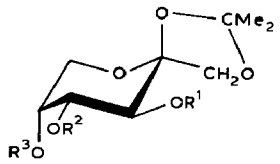
Atom	**3**[a]	**4**	**5**	**8**	**9**	**9**[a]	**11**	**11**[a]	**12**	**13**	**13**[a]	**14**
H-1	3.99(s)	4.19(s)	4.08(s)	4.12(s)	3.63(d)	4.1–4.5(m)	3.9–4.3(m)	4.12(s)	3.9–4.1(m)	4.38(s)	4.2–4.5(m)	4.3–4.5(m)
H-1′	4.12(s)	4.30(s)	4.23(s)	4.16(s)	3.87(d)			4.29(s)		4.48(s)		
H-3	4.40(d)	4.8–5.1(m)	5.35(d)	4.73(s)	4.41(s)	4.69(s)	4.44(s)	4.72(s)	4.44(s)	4.55(s)	4.71(s)	4.48(s)
H-4	4.84(dd)		5.03(dd)	5.38(d)	4.17(d)	5.39(d)	3.9–4.3(m)	5.38(d)	4.78(d)	4.47(d)	5.38(d)	5.13(d)
H-5	4.2–4.3(m)		5.1–5.4(m)	4.5–4.6(m)		4.6–4.7(m)		4.58(dd)	4.36(dd)		4.6–4.7(m)	4.68(dd)
H-6	4.01(d)	3.8–4.2(m)	3.6–4.2(m)	4.21(dd)	4.0–4.4(m)	4.1–4.5(m)		4.1–4.4(m)	3.9–4.1(m)	4.2–4.4(m)	4.2–4.5(m)	4.3–4.5(m)
H-6′	3.86(dd)			4.15(d)								
$J_{1,1'}$					11.4							
$J_{3,4}$	9.5		10.3	0	0	0		0	0	0	0	0
$J_{4,5}$	2.8		3.4	3.1	3.1	3.1		3.1	2.9	2.2	2.9	2.9
$J_{5,6}$	1.7			5.5				5.5	5.7			5.3
$J_{6,6'}$	5.1			5.5								
$C(CH_3)_2$	1.25(s)	1.18(s)	1.41(s)	1.32(s)	1.32(s)	1.35(s)	1.29(s)	1.32(s)	1.25(s)	1.40(s)	1.39(s)	1.40(s)
	1.43(s)	1.39(s)	1.45(s)	1.48(s)	1.47(s)	1.50(s)	1.43(s)	1.48(s)	1.38(s)	1.55(s)	1.53(s)	1.55(s)
Ts–CH_3	2.44(s)	2.43(2 s)		2.43(s)	2.44(s)	2.44(s)	2.45(2 s)	2.44(s)	2.44(2 s)			
		2.46(s)		2.45(s)			2.45(s)	2.48(s)				
CH_3SO_2										3.08(2 s)	3.08(s)	3.09 (2 s)
										3.09(s)	3.16(s)	
NH	8.57(s)			9.13(s)	8.79(s)		9.21(s)			9.26(s)		
					9.10(s)							

[a]In $CDCl_3$ after addition of trichloroacetyl isocyanate.

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFTS (P.P.M.) FOR SOLUTIONS IN $CHCl_3$

Atom	**1**	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
C-1	71.94	71.62	71.78	71.89	71.95	61.27	68.04	67.82	60.66	66.53	65.93	67.99	65.23
C-2	105.80	104.28	104.50	104.18	104.57	112.82	111.54	112.27	112.19	111.54	111.71	111.76	111.98
C-3	68.80	73.08	68.80	69.72	69.19	86.73	85.10	86.08	81.31	79.04	80.88	79.74	79.96
C-4	69.40	77.36	78.12	69.56	67.06	81.04	79.03	79.41	75.63	74.33	77.42	79.74	79.96
C-5	64.20	72.27	72.97	73.89	67.02	76.06	74.32	74.10	86.41	85.11	82.88	85.11	83.54
C-6	64.19	62.14	63.44	62.19	62.53	63.87	66.47	63.43	63.60	68.04	67.18	68.26	67.23
$C(CH_3)_2$	26.27	25.52	25.69	26.00	26.12	26.27	26.11	26.16	26.27	26.11	26.22	26.32	26.27
	26.44	26.22	26.33	26.22	26.28	27.19	27.19	27.08	27.14	27.19	27.14	27.41	27.14
CMe_2	111.98	112.68	112.47	112.47	112.31	113.60	113.32	113.87	113.71	113.22	113.93	112.95	114.15
Ph–CH_3		21.72	21.72	21.62	21.66		21.66	21.61		21.67	21.67		
											21.78		
CH_3SO_2												37.38	37.65
												39.11	37.76
													38.63
CH_3CO_2				20.53	20.62								
				20.83	20.76								
					20.96								

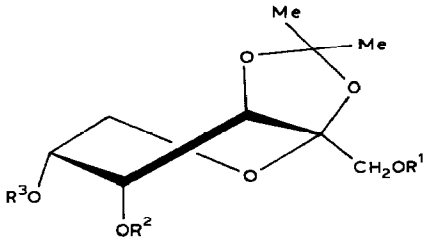


1 $R^1 = R^2 = R^3 = H$
2 $R^1 = R^2 = R^3 = Ts$
3 $R^1 = H, R^2 = R^3 = Ts$
4 $R^1 = R^2 = H, R^3 = Ts$
5 $R^1 = R^2 = Ac, R^3 = Ts$
6 $R^1 = R^2 = R^3 = Ac$

The monotosylate fraction **4** was contaminated with traces of a compound having very similar polarity. Purification was conveniently achieved by chromatography of the acetylated mixture, and the major product was shown to be 3,4-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-tosyl-β-D-fructopyranose (**5**) from its ^{13}C-n.m.r. data (Table II). The resonance due to C-5 (δ 73.89) was shifted downfield by ~7 p.p.m. with respect to that of 3,4,5-tri-*O*-acetyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**6**). The C-3,4 signals were not shifted significantly.

2,3-*O*-Isopropylidene-β-D-fructopyranose[11] (**7**) showed higher selectivity towards tosyl chloride than 1,2-*O*-isopropylidene-β-D-fructopyranose (**1**). The reaction of **7** with 3.6 mol. equiv. of tosyl chloride at room temperature for 10 h gave only minor amounts of 2,3-*O*-isopropylidene-1,5-di-*O*-tosyl-β-D-fructopyranose (**8**, 15%). The major product (55%) was 2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-fructopyranose (**9**). Traces of another slow compound (t.l.c.) were also detected, with an R_F value identical to that of 2,3-*O*-isopropylidene-1-*O*-tosyl-β-D-fructopyranose.

The structure of **8** was indicated by the ^1H-n.m.r. data (Table I). The presence of two tosyl substituents was observed (δ 2.43 and 2.45). The resonances due to the ring protons were poorly resolved; on addition of trichloroacetyl isocyanate to the n.m.r. solution of **8**, an imino-proton singlet signal appeared at δ 9.13 and H-4 was deshielded by ~1 p.p.m., indicating that the hydroxyl group in **8**



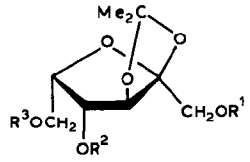
7 $R^1 = R^2 = R^3 = H$
8 $R^1 = R^3 = Ts, R^2 = H$
9 $R^1 = R^2 = H, R^3 = Ts$

was located at C-4. The H-3 resonance was a singlet (δ 4.73) and that of H-4 a doublet (δ 4.73, $J_{4,5}$ 3.1 Hz). This feature was also observed in the ^{1}H-n.m.r. spectrum of 1,2-*O*-isopropylidene-5-*O*-tosyl-β-D-fructopyranose (**9**). Molecular models showed this to be consistent with the twist-boat ($^1S_3$) conformation, probably as a result of the torsional strain due to the 1,3-acetal ring. Such a conformation would also be favoured because the bulky 5-substituent can assume a quasi-equatorial position.

The ^{1}H-n.m.r. spectrum of compound **9** showed the presence of only one tosyl group (δ 2.44). The singlet at δ 4.41 was assigned to H-3 and the two doublets at δ 3.63 and 3.87 ($J_{1,1'}$ 11.4 Hz) to H-1,1′. The resonances due to H-4,5,6 (δ 3.9–4.4) overlapped but, after reaction of **9** with trichloroacetyl isocyanate, H-1,1′,4 were deshielded by >0.8 p.p.m. The resonances due to H-1,1′ now overlapped those due to H-5,6,6′, whereas that due to H-4 appeared as a doublet at δ 5.39 ($J_{4,5}$ 3.1 Hz), consistent with the presence of hydroxyl groups at these positions. The two imino protons of the resulting carbamate groups gave singlets at δ 8.79 and 9.10.

The isolation of a 2,3-*O*-isopropylidene-di-*O*-tosyl-α-L-sorbofuranose from the reaction of 2,3-*O*-isopropylidene-α-L-sorbofuranose[9] (**10**) with tosyl chloride (3 mol. at 20°) was briefly described by Ohle[8]. Re-examination of the reaction showed that, even with an excess (4 mol.) of tosyl chloride, only one product was present after 2 h at room temperature and there was no change up to 24 h. The product isolated (75%) was shown to be 2,3-*O*-isopropylidene-1,6-di-*O*-tosyl-α-L-sorbofuranose (**11**) from its ^{1}H- and ^{13}C-n.m.r. data. The 1,4,6-tritosylate **12** could be obtained only by using a large excess (15 mol.) of tosyl chloride but, even after reaction for 2 months at room temperature, some **11** was still detected.

The ^{1}H-n.m.r. spectrum of **11** showed the presence of two tosyl groups (δ 2.45) (Table I). The resonance due to H-4 (δ 3.9–4.3) appeared at relatively high field, indicating that C-4 probably carried a hydroxyl group. Addition of trichloroacetyl isocyanate to the n.m.r. solution of **11** in $CDCl_3$ produced a low-field imino-proton singlet (δ 9.21) and deshielded H-4 by ~1 p.p.m. (δ 5.38, $J_{4,5}$ 3.1 Hz), confirming the presence of the hydroxyl group at C-4. The resonance due to H-3 was a singlet at δ 4.72, which showed the dihedral angle between H-3 and H-4 to



10 $R^1 = R^2 = R^3 =$ H
11 $R^1 = R^3 =$ Ts, $R^2 =$ H
12 $R^1 = R^2 = R^3 =$ Ts
13 $R^1 = R^3 =$ Ms, $R^2 =$ H
14 $R^1 = R^2 = R^3 =$ Ms

be ~90°. The ^{13}C-n.m.r. data of **11** (Table II) also confirmed the proposed structure. The signals for C-1 (δ 66.53) and C-6 (δ 68.04) were shifted by 4–6 p.p.m. to lower field with respect to those of 2,3-*O*-isopropylidene-α-L-sorbofuranose (**10**), whereas that due to C-4 (δ 78.78) was not significantly different, thus indicating positions 1 and 6 to be tosylated.

The reaction of **10** with mesyl chloride (3.6 mol.) also showed this selectivity, and 2,3-*O*-isopropylidene-1,6-di-*O*-mesyl-α-L-sorbofuranose (**13**) was obtained (69%) after reaction for 15 min at room temperature. The 1,4,6-trimesylate **14** was detected after ~30 min, and an ~1:1 mixture of **13** and **14** was present after ~1 h at room temperature; 72% of **14** was isolated after reaction for 3 h. The structures of **13** and **14** were indicated by their ^{1}H- and ^{13}C-n.m.r. data (Tables I and II).

EXPERIMENTAL

Solvents were evaporated under reduced pressure at 45–55°. Unless otherwise stated, optical rotations were measured on solutions in dichloromethane. Dry-column chromatography was performed on Kieselgel 7734 (Merck). ^{1}H- and ^{13}C-n.m.r. spectra were recorded at 90 MHz with a Jeol JMN-FX90 instrument, using Me_4Si and sodium 3-(trimethylsilyl)-1-propanesulphonate (DSS), respectively, as internal standards.

Reaction of 1,2-O-isopropylidene-β-D-fructopyranose (**1**) *with tosyl chloride.* — (*a*) A solution of **1** (1.0 g) in pyridine (10 mL), cooled in ice, was treated with tosyl chloride (3.2 g, 3.6 mol. equiv.) during 0.5 h. The solution was then stored at room temperature and monitored by t.l.c. (toluene–ethyl acetate, 1:3). After 2.5 h, two major and one minor fast-moving compounds were formed. The solution was poured into ice–water and extracted with dichloromethane, and the extract was washed successively with cold aqueous 10% H_2SO_4, aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), and concentrated. Column chromatography (toluene–ethyl acetate, 8:1) of the residue gave, first, 1,2-*O*-isopropylidene-3,4,5-tri-*O*-toluene-*p*-sulphonyl-β-D-fructopyranose (**2**; 1.0 g, 32.2%), m.p. 126–127° (from ethanol), $[\alpha]_D$ −111° (*c* 0.35); lit.[8] m.p. 125.5°, $[\alpha]_D$ −121.4° (chloroform).

Eluted second was 1,2-*O*-isopropylidene-4,5-di-*O*-toluene-*p*-sulphonyl-β-D-fructopyranose (**3**; 1.5 g, 62.5%), m.p. 133–134° (from ether–light petroleum), $[\alpha]_D$ −76.5° (*c* 0.4) (Found: C, 52.35; H, 5.6; S, 12.05. $C_{23}H_{28}O_{10}S_2$ calc.: C, 52.3; H, 5.3; S, 12.1%).

Eluted third was impure 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-β-D-fructopyranose (**4**). The fraction (0.95 g) was acetylated (pyridine–acetic anhydride) and the product was eluted from a small column of silica gel (toluene–ethyl acetate, 4:1) to give 3,4-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-β-D-fructopyranose (**5**; 0.08 g, 4.0%), m.p. 108–110° (from ether–light petroleum), $[\alpha]_D$ −126° (*c* 0.3) (Found: C, 52.3; H, 5.75; S, 7.1. $C_{20}H_{26}O_{10}S$ calc.: C, 52.4; H, 5.7; S, 7.0%).

(*b*) A solution of **1** (1.0 g) in pyridine (10 mL), cooled in ice, was treated with

tosyl chloride (1.3 g, 1.5 mol. equiv.) and stored for 2.5 h at ~10°. T.l.c. (toluene–ethyl acetate, 1:1) then revealed one major product and several minor faster-moving compounds. The solution was cooled and treated with acetic anhydride (1.5 mL), and kept at room temperature for 12 h. Work-up as in (*a*) and chromatography of the product gave 41% of **5** identical to that obtained above.

2,3-O-Isopropylidene-1,5-di-O-toluene-p-sulphonyl-β-D-fructopyranose (**8**) *and 2,3-O-isopropylidene-5-O-toluene-p-sulphonyl-β-D-fructopyranose* (**9**). — A solution of **7** (0.4 g) in pyridine (5 mL) was treated with tosyl chloride (1.9 g, 5.6 mol. equiv.) at 0° for 1 h and then at room temperature for 5 days. T.l.c. (toluene–ethyl acetate, 1:1) then revealed one major and one minor compound. Work-up as described above and column chromatography (toluene–ethyl acetate, 6:1) gave **8** (0.15 g, 15.2%), m.p. 126–127.5° (from ether–light petroleum), $[\alpha]_D$ +4° (*c* 0.25) (Found: C, 51.8; H, 4.9; S, 12.6. $C_{23}H_{28}O_{10}S_2$ calc.: C, 52.3; H, 5.3; S, 12.1%).

Eluted second was **9** (0.38 g, 55.4%), $[\alpha]_D$ +5° (*c* 0.2) (Found: C, 51.8; H, 5.85; S, 9.0. $C_{16}H_{22}O_8S$ calc.: C, 51.3; H, 5.9; S, 8.55%).

2,3-O-Isopropylidene-1,6-di-O-toluene-p-sulphonyl-α-L-sorbofuranose (**11**). — A solution of 2,3-*O*-isopropylidene-α-L-sorbofuranose (**10**, 5.0 g) in pyridine (30 mL) was treated with tosyl chloride (15.6 g, 3.6 mol. equiv.) at 0° for 0.5 h and then at room temperature for 2 h. Work-up as described above and crystallisation of the product from ethanol–light petroleum gave **11** (8.7 g, 73.7%), m.p. 128–129°, $[\alpha]_D$ +12° (*c* 0.5); lit.[11] m.p. 128.5–129.5°, $[\alpha]_D$ +14.1° (chloroform).

2,3-O-Isopropylidene-1,6-di-O-methanesulphonyl-α-L-sorbofuranose (**13**). — A solution of **10** (4.0 g) was treated with mesyl chloride (5.1 mL, 3.0 mol. equiv.) as described for **11**. T.l.c. (toluene–ethyl acetate, 1:1) revealed only one faster-moving product after 15 min. Work-up of the mixture as described above and recrystallisation of the product from methanol–water gave **13** (4.7 g, 68.8%), m.p. 141–142°, $[\alpha]_D$ −18.5° (*c* 0.15, methanol) (Found: C, 35.6; H, 5.5; S, 16.6. $C_{11}H_{20}O_{10}S_2$ calc.: C, 35.1; H, 5.3; S, 17.0%).

When storage of the above mixture was prolonged, **13** and 2,3-*O*-isopropylidene-1,4,6-tri-*O*-methanesulphonyl-α-L-sorbofuranose (**14**) were formed in the ratio ~1:1 after 1 h. After 2.5 h, **14** (72.3%) was isolated; m.p. 122–123° (from ethanol–light petroleum), $[\alpha]_D$ +18° (*c* 0.4) (Found: C, 31.6; H, 4.9; S, 21.6. $C_{12}H_{22}O_{12}S_3$ calc.: C, 31.7; H, 4.85; S, 21.15%).

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