Carbohydrate Research, 81 (1980) 330–334

Note

Selective *p*-toluenesulfonylation of methyl α-D-galactopyranoside

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(Received November 14th, 1979; accepted for publication, December 3rd, 1979)

The relative reactivity of hydroxyl groups in carbohydrates is a complex matter[1,2]. However, in the selective acylation of glycopyranosides with acyl chlorides in pyridine, the esterification of the hydroxyl groups follows a certain, structural order. It is usually found that hydroxyl groups located on primary carbon atoms are esterified before those on secondary carbon atoms, and that, in most cases, equatorial hydroxyl groups are esterified before those attached axially.

The dimolar mesylation[3] of methyl α-D-galactopyranoside affords methyl 2,6-di-*O*-(methylsulfonyl)-α-D-galactopyranoside (20%) as the main product; the 2,3,6-tri-*O*-mesyl (10%) and the 3,6-di-*O*-mesyl (4%) derivatives are also produced.

In the *p*-toluenesulfonylation of methyl α-D-galactopyranoside, Haworth *et al.*[4] isolated a di-*O*-*p*-tolylsulfonyl derivative, which was later identified as methyl 2,6-di-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside[5]. Haworth *et al.*[4] did not, however, study the syrup remaining.

In this work, the product of the dimolar tosylation of methyl α-D-galactopyranoside was studied by chromatography, and the following products were isolated: methyl 2,6-di-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (**1**, 26.6%), methyl 2,3,6-tri-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (**2**, 17.2%), and methyl 3,6-di-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (**3**, 2.2%).

Both the structures and the relative yields of the isolated products are similar to those for the dimolar mesylation of the same glycoside. The lack of reaction of the hydroxyl group on C-4 is also in good agreement with the results reported for the benzoylation of methyl α-D-galactopyranoside[6] and of methyl (methyl α-D-galactopyranosid)uronate[7] with benzoyl chloride in pyridine.

The structures of compounds **2** and **3** were determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy. The chemical shifts of the ^{1}H-n.m.r. spectra (see Table I) show, for each derivative, the characteristic, deshielding effect of the sulfonyl group[8,9], the signals of H-2 or H-3, or both, being shifted to lower field; the positions of the signals of H-6 and H-6′ remain almost the same for all of these compounds. Also,

TABLE I

^{1}H-N.M.R. SPECTRA[a] OF COMPOUNDS 1–3. CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz, IN PARENTHESES)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*OCH$_3$*
1	4.61 ($J_{1,2}$ 3.5)	4.56 ($J_{2,3}$ 9.0)	← 3.92–4.06 →			4.22 ($J_{6,6'}$ 10.5)	4.15 ($J_{5,6'}$ 7.0)	3.24
3	4.73 ($J_{1,2}$ 4.0)	3.94 ($J_{2,3}$ 10.0)	4.56 ($J_{3,4}$ 3.0)	4.12 ($J_{4,5}$ 1.0)	3.98 ($J_{5,6}$ 5.7)	4.19 ($J_{6,6'}$ 11.0)	4.15 ($J_{5,6'}$ 6.5)	3.35
2	4.73 ($J_{1,2}$ 3.3)	4.62 ($J_{2,3}$ 10.0)	4.75 ($J_{3,4}$ 3.0)	4.24 ($J_{4,5}$ 1.0)	4.02 [b]	4.15 [b]	4.15 [b]	3.24

[a]In $CDCl_3$ solution. [b]Deceptively simple, ABX subsystem.

TABLE II

CHEMICAL SHIFTS (δ) OF ^{13}C-N.M.R. SPECTRA

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*O-CH$_3$*	*-C$_6$H$_4$-CH$_3$*
Methyl α-D-galactopyranoside[a]	100.7	70.8	71.1	69.8	72.1	62.7		
1[b]	97.35	77.75 68.31	69.19,	68.57,	67.65,	67.15	55.60	21.65
3[b]	99.44	67.73 66.45	80.83	68.31,	67.73,	66.45	55.65	21.69
2[b]	97.54	73.42	76.43	68.59,	68.01,	67.22	55.78	21.72

[a]In deuterium oxide. [b]In chloroform-*d*.

the coupling constants and the multiplicities of the signals are in full agreement with the assignments made.

The assignments for the ^{13}C-n.m.r. spectra of compounds **1–3** are shown in Table II, where the chemical shifts for methyl α-D-galactopyranoside[10] are also included. The ^{13}C chemical shifts of the anomeric carbon atoms of **1** and **3** appear at δ 97.35 and 99.44, respectively. As it is known[11,12] that the tosylation of a hydroxyl group produces an upfield shift of 2–3 p.p.m. of the signal for the β-carbon atom, the upfield shift of 2.09 p.p.m. shown by the anomeric carbon atom of compound **1** is attributed to the tosylation of the hydroxyl group located at C-2 of this compound.

For the same reason, the signal of the anomeric carbon atom of compound **2** appears at higher field than that of **3** (97.54 p.p.m.). Interestingly, the introduction of a tosyloxy group at C-3 does not give rise to a γ-effect.

From the remaining signals of the carbon atoms belonging to the pyranoside ring in **1**, that at δ 77.75 is assigned to C-2, taking into consideration that sulfonyla-

tion[12,13] produces a deshielding effect of 6–13 p.p.m. at the α-carbon atom. When this signal is compared with the chemical shift of C-2 in methyl α-D-galactopyranoside (see Table II), a deshielding effect of 7 p.p.m. is observed. For the same reason, for compound **3**, the signal at δ 80.83 is assigned to C-3, which would suffer a deshielding effect of ~9 p.p.m.

For compound **2**, the signals at δ 73.42 and 76.43 are assigned to C-2 and C-3, respectively, as both of them would experience a strong α-deshielding and a strong β-shielding effect.

EXPERIMENTAL

General. — Melting points were measured with an Electrothermal melting-point apparatus and are uncorrected. Optical rotations were measured with a Hilger–Watts polarimeter. Evaporations were performed *in vacuo*, the bath temperature being kept below 45°. Proton n.m.r. spectra (100 MHz) were recorded, and integrated, with a Varian HA-100 spectrometer. The ring-proton region was also recorded at 270 MHz, with a spectrometer built at the University of British Columbia with Nicolet parts. Tetramethylsilane was used as the internal reference standard, and the concentration of the samples was 6–8% in deuteriochloroform. Coupling constants were measured on 250- or 500-Hz sweep-width spectra. ^{13}C-N.m.r. spectra were recorded with a CFT-20 spectrometer, for solutions (10–15%) of the compounds in deuteriochloroform; chemical shifts are given relative to internal tetramethylsilane. The spectra were recorded with complete proton-decoupling. Column chromatography was performed on silica gel Merck 60. The homogeneity of compounds was verified by t.l.c. on glass plates coated with 250-μm layers of Silica Gel HF_{254} (Merck), with solvents (v/v) *A* (3:2 benzene–ethyl acetate) and *B* (3:2 petroleum ether–ethyl acetate).

*Methyl 2,6-di-*O-p-*tolylsulfonyl-α-*D-*galactopyranoside* (**1**). — To a stirred solution, cooled in ice–water, of methyl α-D-galactopyranoside (4.55 g, 2.35 mmol) in anhydrous pyridine (30 mL) was added a solution of *p*-toluenesulfonyl chloride (9.85 g, 5.17 mmol) in anhydrous pyridine (15 mL), dropwise, during 2 h, and the mixture was stirred for 22 h at room temperature. The pyridine was evaporated off, the residual syrup was taken up in chloroform (200 mL), and the solution washed successively with cold 0.25M sulfuric acid, 5% aqueous sodium hydrogencarbonate solution, and water, and evaporated. The residual syrup was dissolved in boiling 95% ethanol; on cooling, the solution yielded **1** (2.73 g), m.p. 150–151.5°. A sample recrystallized from the same solvent had m.p. 151–152°, $[\alpha]_D^{17}$ +75° (*c* 0.6, pyridine); lit.[4] m.p. 148°, $[\alpha]_D$ +68° (*c* 2.0, pyridine); ^{1}H-n.m.r. ($CDCl_3$): δ 2.45 (s, 6 H, CH_3, tosyl), 3.24 (s, 3 H, OCH_3), 3.92–4.06 (m, 3 H, H-3,4,5), 4.15 (dd, 1 H, $J_{5,6'}$ 7.0, $J_{6,6'}$ 10.5 Hz, H-6'), 4.22 (dd, 1 H, $J_{5,6}$ 5.5, $J_{6,6'}$ 10.5 Hz, H-6), 4.56 (dd, 1 H, $J_{2,1}$ 3.0, $J_{2,3}$ 9.0 Hz, H-2), 4.61 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), and 7.20–7.80 (m, 8 H, aromatics).

*Methyl 2,3,6-tri-*O-p-*tolylsulfonyl-α-*D-*galactopyranoside* (**2**). — The mother

liquor from the crystallization of **1** was evaporated, and the resulting syrup was dissolved in boiling methanol. On cooling, the solution yielded 0.52 g of **2**, m.p. 140–141°. A sample recrystallized from the same solvent had m.p. 142–143°, $[\alpha]_D^{17}$ +109.7° (*c* 1.08, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 2.42 (s, 3 H, tosyl), 3.24 (s, 3 H, OCH_3), 4.02 (t, 1 H, H-5), 4.15 (d, 2 H, H-6,6′, spacing 1.5 Hz), 4.24 (dd, 1 H, $J_{4,3}$ 3.0, $J_{4,5}$ 1.0 Hz, H-4), 4.62 (dd, 1 H, $J_{2,1}$ 3.3, $J_{2,3}$ 10.0 Hz, H-2), 4.73 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.75 (dd, 1 H, $J_{3,4}$ 3.0, $J_{3,2}$ 10.0 Hz, H-3), and 7.20–7.80 (m, 12 H, aromatics).

Anal. Calc. for $C_{28}H_{32}O_{12}S_3$: C, 51.21; H, 4.91; S, 14.64. Found: C, 51.30; H, 4.98; S, 14.44.

Evaporation of the mother liquor from the crystallization of **2** gave a syrup which was chromatographed on a column of silica gel (330 g) with solvent *B*; 20-mL fractions were collected.

Fractions 50–80 yielded, after evaporation, and crystallization of the residue from ethanol, compound **2** (1.63 g; total yield 2.15 g, 17.2%), m.p. 138–140°. Fractions 150–200 gave, after the same treatment, compound **1** (0.60 g; total yield of **1**, 3.33 g, 26.6%).

*Methyl 3,6-di-*O*-p-tolylsulfonyl-α-*D*-galactopyranoside* (**3**). — Evaporation of fractions 245–310 gave a syrup; this was dissolved in hot ethanol, affording **3** on cooling (0.25 g, 2.0%), m.p. 89–90°. A sample recrystallized from the same solvent had the same m.p., $[\alpha]_D^{18}$ +82.2° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 2.44 (s, 6 H, CH_3, tosyl), 3.35 (s, 3 H, OCH_3), 3.94 (dd, 1 H, $J_{2,1}$ 3.8, $J_{2,3}$ 10.0 Hz, H-2), 3.98 (t, 1 H, $J_{5,6} = J_{5,6'} = 6.0$ Hz, H-5), 4.12 (dd, 1 H, $J_{4,3}$ 3.0, $J_{4,5}$ 1.0 Hz, H-4), 4.15 (dd, 1 H, $J_{6',5}$ 6.5, $J_{6,6'}$ 11.0 Hz, H-6′), 4.56 (dd, 1 H, $J_{3,4}$ 3.0, $J_{3,2}$ 10.0 Hz, H-3), 4.73 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), and 7.3–7.8 (m, 8 H, aromatics).

Anal. Calc. for $C_{21}H_{26}O_{10}S_2 \cdot H_2O$: C, 48.45; H, 5.42; S, 12.31. Found: C, 48.47; H, 5.43; S, 12.08.

ACKNOWLEDGMENTS

This research was supported by the Dirección de Investigaciones Científicas y Tecnológicas de la UTE. The authors thank Prof. G. G. S. Dutton (University of British Columbia) for his interest and encouragement, and Prof. L. D. Hall and the Chemistry Department of the University of British Columbia for facilities provided one of the authors (A. Z.) in order to obtain ^{1}H-n.m.r. spectra while he was working under a Fellowship of a joint program of NRC-Canada–CIDA.

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