Note

Synthesis and n.m.r. spectra of substituted methyl 6-deoxy-6-halo-α-D-glucopyranosides

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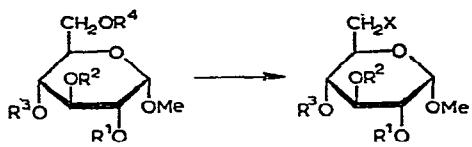
An improved method for the displacement of carbohydrate sulfonates was recently reported[1]. Utilizing this improved method, which we modified slightly in order to adapt it as a routine preparative procedure, we undertook the synthesis of several substituted methyl 6-deoxy-6-halo-α-D-glucopyranosides and present here their n.m.r. spectra.

Exploratory experiments with compounds **1–5** established that displacement of a 6-sulfonic ester required with chloride, bromide, and iodide ion 4 to 14, 1,



Compound	R^1	R^2	R^3	R^4	*Compound*	R^1	R^2	R^3	*Halogen, X*
1	BzO	BzO	BzO	Tzs	**6**	BzO	BzO	BzO	Cl, Br, I
2	Ts	BzO	BzO	Ts	**7**	Ts	BzO	BzO	Cl, Br, I
3	Ms	Ac	Ac	Ms	**8**	Ms	Ac	Ac	Cl, Br, I
4	Ac	Ac	Ac	Ts	**9**	Ac	Ac	Ac	Cl, Br, I
5	BzO	BzO	Ms	Ms	**10**	BzO	BzO	Ms	Cl, Br, I

and 0.25 h, respectively. These rates agree qualitatively with the listed nucleophilicities of the halides[2]. With either bromide or iodide ions no difference was noted in the displacement of a 6-methanesulfonate or 6-*p*-toluenesulfonate group, whereas, with chloride ion, displacement of the 6-methanesulfonyloxy group needed from 4 to 7 h (compounds **3** and **5**), and the 6-*p*-tolylsulfonyloxy group needed from 7 to 14 h (compounds **1**, **2**, and **4**).

By heating for 100 to 150 times the time needed to displace a 6-methanesulfonyloxy group in compound **5**, the 4-methanesulfonyloxy group is displaced by bromide and iodide ions but not by chloride ion. However, the slow displacement was incomplete, and the product proved to be a mixture of the 4-deoxy-4-halo derivatives

having the D-*gluco* and D-*galacto* configurations[1]. All attempts to displace with halides the 2-methanesulfonyloxy group in compound **3** and the 2-*p*-tolylsulfonyloxy group in compound **2** were unsuccessful.

N.m.r. spectra. — In Table I are recorded the ^{1}H n.m.r. spectra of the methyl 6-deoxy-6-halo-α-D-glucopyranosides. Unfortunately, no single solvent would resolve all of the proton signals. When chemical shifts were compared, only the δ-values in the same solvent were used.

TABLE I

CHEMICAL SHIFTS OF RING PROTONS[a] IN METHYL 6-DEOXY-6-HALO-HEXOSIDES

Compound		*Chemical shifts (δ), p.p.m. from internal Me_4Si, with 100-mMHz spectra*						
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*[b]H-6,6′*	*Solvent*
6	Cl	5.52	5.77	6.59	6.00	4.58	4.00	P
	Br	5.17	5.41	6.48	5.56	4.16	3.28	B
	I	5.16	5.42	6.49	5.48	4.99	3.09	B
7	Cl	5.10	4.61	5.89	5.34	4.22	3.64	C
	Br	5.09	4.61	5.89	5.29	4.20	3.47	C
	I	5.08	4.62	5.89	5.19	3.99	3.29	C
8	Cl	5.02	4.63	5.48	5.03	4.04	3.61	C
	Br	5.01	4.63	5.47	4.97	4.02	3.43	C
	I	5.00	4.62	5.46	4.86	3.79	3.22	C
9	Cl	4.96	4.84	5.43	5.00	4.03	3.72	A
	Br	4.96	4.84	5.43	4.96	3.99	3.58	A
	I	4.92	4.78	5.36	4.78	3.79	3.18	C
10	Cl	5.05	5.24	6.25	4.87	3.92	3.69	B
	Br	5.43	5.66	6.44	5.40	4.30	3.98	P
	I	5.01	5.23	6.23	4.67	3.69	3.36	B

[a]Solvents were: C chloroform-*d*, A acetone-d_6, B benzene-d_6, P pyridine-d_5. [b]H-6,6′ ring-protons resonances were measured as a group.

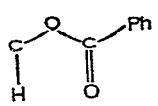
In Table I the chemical shift of the H-4, H-5, and H-6,6′ signal (within any one halogen series) exhibits a regular downfield shift (related to the electronegativity of the halogen[3]), on going from I to Br to Cl, of approximately:

	H-4	H-5	H-6,6′
I → Cl	+0.15	+0.25	+0.35
I → Br	+0.10	+0.20	+0.19.

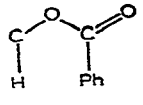
The uniform variation (Δ0.08 δ) between the anomeric-proton signal in the **7** and **8** halogen series suggests that in the **7** halogen series the 2-OTs aromatic ring and the anomeric proton are oriented in the same plane, on a time-average basis. Guthrie and coworkers[4] have pointed out that chemical shifts in methyl 2-*O*-tosyl-β-D-

glucopyranoside indicate that the methoxyl group and the aromatic ring are at right angles.

A comparison of the spectra of **7** and **8** showed an interesting deshielding effect[5]. The difference in chemical shift between the H-1, H-2, and H-6,6′ resonances was small ($< \Delta 0.08\ \delta$) whereas the difference between the H-3, H-4, and H-5 resonances was moderate, reasonably uniform, and decreased progressively; thus, $\Delta\delta$ H-3 +0.42; H-4, +0.32; and H-5, +0.19. The major differences between the **8** and **7** series was a 2-*O*-mesyl group *vs.* a 2-*O*-tosyl group and a 3,4-di-*O*-acetyl *vs.* a 3,4-di-*O*-benzoyl group. Inspection of molecular models offers an explanation for this deshielding. In form **A** the aligning of the benzoyl carbonyl group with the hydrogen



A



B

atom would cause a downfield shift, and in form **B** the aligning of the phenyl ring with the hydrogen atom would also cause a downfield shift (the $PhCO_2$-group was considered to be coplanar because of resonance effects). Since *ortho*-hydrogen atoms on the aromatic ring and the deshielded proton would give rise to severe crowding, form **B** was not considered a reasonable conformation. A carbonyl-induced shift shown in **A** would account for the shifts observed; thus, in the **7** series the 2-*O*-Ts group and 4-*O*-benzoyl group would restrict the free rotation of the 3-*O*-benzoyl group and permit its C=O group to become aligned with H-3; also the 3-*O*-benzoyl and 6-halomethyl group would restrict the free rotation of the 4-*O*-benzoyl group and its C=O group would be aligned with H-4. However, as the 6-halomethyl group is smaller than the 3-*O*-benzoyl group, the rotation of the 4-*O*-benzoyl group would not be so restricted as is the 3-*O*-benzoyl group, and deshielding of H-4 would be less than that of H-3. The deshielding experienced by H-5 indicates that the C=O group of the 4-*O*-benzoyl group does align to some degree with H-5. These carbonyl-induced shifts come from steric restriction on the free rotation of the benzoyl group, and undoubtedly arise from the accumulation of bulky substituents on the glucopyranoside ring.

EXPERIMENTAL

General procedures. — Although the starting sulfonic esters are known, we found the procedures reported either long or inconvenient, and mention here improved procedures without detailing the preparation of compounds **1**, **2**, and **3**. The reported preparations[6] of compound **1** involved tritylation, benzoylation, detritylation, and tosylation of methyl α-D-glucopyranoside. When a unimolar tosylation and subsequent benzoylation was carried out in the same vessel, crystalline **1** was isolated readily in 65% yield from methyl α-D-glucopyranoside. By using the benzylthiocarbonyl

blocking group, Willard *et al.*[7] developed a multi-step procedure to prepare compound **2**. Dimolar tosylation of methyl α-D-glucopyranoside according to the procedure of Jarý *et al.*[8] yielded a syrup that by t.l.c. examination showed to be a mixture of starting glucoside, and mono-, di-, and tritosylated material, with the ditosyl fraction predominating. Benzoylation of this syrup in pyridine and workup gave crystalline **2** in 69% yield from methyl α-D-glucopyranoside. Partial mesylation[9] of methyl α-D-glucopyranoside was found more convenient when conducted at 0°; the period for adding mesyl chloride was extended to 14–16 h. Methyl 2,6-di-*O*-methylsulfonyl-α-D-glucopyranoside was isolated in a yield comparable with that published[9]. Acetylation with acetic anhydride in pyridine and workup gave compound **3**.

T.l.c. was carried out on Silica Gel G* as previously reported[10], with the appropriate solvent system. Experimental methods described earlier were followed[1].

Standard procedure for displacement. — In 300 ml of toluene was placed the starting sulfonate (3–5 g) and the appropriate lithium halide and hexamethylphosphoramide (HMPA); molar ratios of sulfonate: LiX:HMPA were 1:6:6 to 7. The mixture was heated to reflux with stirring and maintained for 0.25, 1, or 17 h, depending on whether the halide was I, Br, or Cl. After the reaction mixture had been cooled to 5°, it was washed with three 50-ml portions of ice–water, dried ($MgSO_4$), and concentrated under vacuum (aspirator) to a syrup or crystalline material. This

TABLE II

YIELD, MELTING POINTS, AND OPTICAL ROTATIONS OF METHYL 6-DEOXY-6-HALO-α-D-GLUCOPYRANOSIDES

Compound	*Halogen*	*Yield, %*	*M.p., degrees*	$[\alpha]_D^{22-23}$, *2% in chloroform*	*References*
6	Cl	92	131.8	+54	
	Br	88	117.5	+51	11a, 12
	I	92	104	+37	13
7	Cl	82	167	+31	
	Br	88	156.5	+26	
	I	89	179.5	+40	
8	Cl	86	167.7	+147	
	Br	71	174.3	+130	
	I	84	158.5	+120	
9	Cl	70	99	+160	11b, 11c, 14
	Br	77	117	+128	11a, 14
	I	83	149	+110	11d, 11e, 15
10	Cl	86	164.7	+152	
	Br	84	180d	+155	
	I	74	191	+128	

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

material was dissolved in a minimum amount of boiling 95% ethanol and the solution allowed to cool to room temperature, during which time crystals deposited. The crystals were separated by filtration, washed with a small portion of ice-cold 95% ethanol, and air dried.

All air-dried samples melted within 1° of their reported final melting-points (Table II). Yields (Table II) were reported for the air-dried crystals. Optical rotations (Table II) were determined in chloroform at 22–23° on analytically pure samples.

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