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Note

Synthesis and properties of 2,3,4,6-tetra-*O*-acetyl-5-thio-α- and -β-D-glucopyranosyl bromide*

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5-Thio-D-glucopyranose[1] has interesting biochemical and pharmacological properties[2] and has become commercially available. We now describe the synthesis and some properties of the crystalline, acetylated glycosyl bromides.

Reaction of 1,2,3,4,6-penta-*O*-acetyl-5-thio-αβ-D-glucopyranose[3] (**1** and **2**) with 30% hydrogen bromide in acetic acid gave a mixture of the anomeric glycosyl bromides, from which the α-bromide **3** (main product) and β-bromide **4** were isolated crystalline by chromatography on silica gel. This behaviour contrasts with that well known for 1,2,3,4,6-penta-*O*-acetyl-αβ-D-glucopyranose, which gives only the α-glycosyl bromide. An oily 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranosyl bromide was used in the synthesis of 5-thio-D-glucopyranosyl phosphate[4]. Since anomeric glycosyl halides have not hitherto been reported for thio sugars, their properties are of interest.

The structures of **3** and **4** were confirmed by ^{1}H- and ^{13}C-n.m.r. spectroscopy. Table I compares ^{1}H-n.m.r. data for the 5-thio-D-glucose derivatives **1**–**4** with those for 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[5] (**5**). The $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ values are all in the range of 9.0–10.2 Hz, as expected for *trans*-diaxial protons and consistent with $^4C_1$(D) conformations. A $^4C_1$(D) conformation in the crystal state has been confirmed[6] for **1**. The higher $J_{1,2}$ values for **3** and **4** as compared to **1** and **2** reflect the lower electronegativity of Br-1 as compared to AcO-1. A similar effect may be invoked to explain why the $J_{1,2}$ value for **5** is higher than that for **3**, since sulfur is less electronegative than oxygen. This effect of the sulfur atom is most pronounced on the anomeric protons, for example, H-1 of **3** resonates 1 p.p.m. to higher field than H-1 of the oxygen analogue **5**. The relatively low-field positions of the H-3 resonances for the α-bromides **3** and **5** may be attributed to the deshielding effect of Br-1, which is syn-diaxial to H-3.

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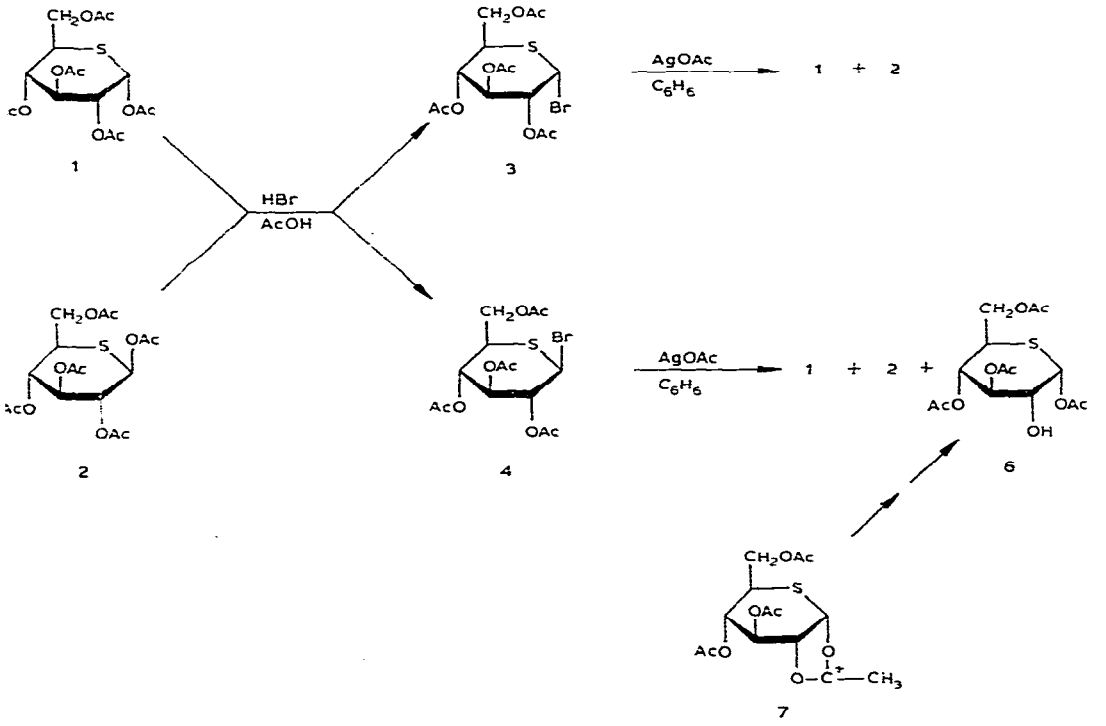

TABLE I

^{1}H-N.M.R. DATA FOR 5-THIO-D-GLUCOSE DERIVATIVES[a]

Compound	*Chemical shifts (δ) and multiplicities of signals*							
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*OAc*
1	6.11 d	5.21 q	5.41 t	5.30 t	3.56 o	4.35 q	4.04 q	2.20, 2.09, 2.06, 2.03, 2.00
2	5.92 d	5.39 t	5.12 t	5.33 t	3.33 o	4.35 q	4.15 q	2.09, 2.08, 2.04, 2.03, 2.01
3	5.58 d	4.93 q	5.58 t	5.33 t	3.71 o	4.49 q	4.13 q	2.10, 2.09, 2.06, 2.03
4	4.76	5.40 t	5.05 t	5.38 t	3.32 o	4.31 q	4.13 q	2.10, 2.09, 2.05, 2.01
5[c]	6.62 d	4.82 q	5.59 t	5.14 t	4.28	4.29 q	4.16 q	2.09, 2.03, 2.01
	Coupling constants (Hz)[b]							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	
1	2.9	9.7	9.7	10.2	4.7	2.9	12	
2	8.5	9.0	9.0	9.5	5.5	3.7	12	
3	3.5	9.5	9.5	10.2	4.7	2.9	12	
4	10.0	9.5	9.5	9.0	5.5	3.5	12	
5[c]	3.9	10.0	9.5	9.5	~4.0	~6.0	~12	

[a]100 MHz (CDCl$_3$, internal Me$_4$Si). [b]First order. [c]2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide from ref. 5.

TABLE II

^{13}C-CHEMICAL SHIFTS AND ^{13}C–^{1}H COUPLING CONSTANTS OF 5-THIO-D-GLUCOPYRANOSE DERIVATIVES[a]

Compound	*C-1* $J_{1,H-1}$	*C-2* $J_{2,H-2}$	*C-3* $J_{3,H-3}$	*C-4* $J_{4,H-4}$	*C-5* $J_{5,H-5}$	*C-6* $J_{6,H-6}$
1	70.5	71.7[b]	73.0[b]	70.5	39.8	60.9
	162.0	154.8	162.0	154.3	143.1	151.2[c]
2	71.4	73.2[b]	72.7	71.1[b]	41.5	61.7
	164.8	157.3	159.3	156.5	141.5	149.8[c]
3	52.4	74.1	71.6[b]	71.2[b]	41.7	60.5
	167.2	149.7	145.6	145.6	141.9	151.2[c]
4	43.1	75.9	73.4[b]	71.4[b]	45.8	60.7
	166.7	167.4	157.1	159.4	144.0	150.6[c]
5[d]	86.5	70.4[b]	72.0[b]	67.0	70.0[b]	60.8
	185	148	148	150	150	147

[a]Carbon–proton coupling constants for **1** and **2** were determined directly, whereas those of **3** and **4** were determined by an indirect method[19] and hence are subject to greater error (see Experimental). [b]Assignments may be reversed. [c]An average value of the two $J_{6,H-6}$ coupling constants. [d]Values from ref. 7.

The ^{13}C-n.m.r. data for **1** to **4** are compared with those of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[7] (**5**) in Table II. Substitution of S for O dramatically affects the ring-carbon resonances, particularly those of C-1. Thus, for the β-bromide **4**, the C-1 signal has the highest chemical shift. Likewise, the C-1,H-1 coupling constants are much smaller for the sulfur derivatives, as expected from the decreased electronegativity of sulfur. The difference between $J_{C-1,H-1}$ for the anomeric bromides (**3** and **4**) and acetates (**1** and **2**) is only 1.5 and −2.8 Hz, respectively, whereas it is 10 Hz for the oxygen analogues and hence can be used for anomeric assignment[7]. Similar observations have been reported by Perlin *et al.*[9,10].

The α-bromide **3** has λ_{max}^{EtOH} 246 nm (ε 1,840), and the β anomer **4** λ_{max}^{EtOH} 208 nm (ε 680), and these absorptions should be useful for diagnostic purposes. The 246-nm band in the α anomer may reflect overlap of one of the C-1–Br antibonding orbitals (*e.g.*, π^*_{CBr}) with the axially oriented, lone-pair orbital (n_s) of the sulfur. Theoretical treatment indicates that the overlap of these bonding and antibonding orbitals is responsible for the anomeric effect, and that it is smaller for sulfur than for oxygen due to the longer C–S bond[11]. Our observation that some β-bromide **4** was formed and that it did not mutarotate, whereas the oxygen analogue[12] and other β-halides[13] do, confirms a decrease in the anomeric effect for the sulfur analogues. For **1** in the crystal state, the C-1–S and C-5–S bonds are not shortened by the anomeric effect[6,14].

The reaction of glycosyl bromides with silver acetate in boiling benzene, or in acetic acid or acetic anhydride at room temperature, is subject to neighboring-group participation and *trans*-acetates are formed from *trans*-halides[13,15]. When the α-bromide **3** was treated with silver acetate in boiling benzene, a 1:1 mixture of **1** and **2** was obtained. The β-bromide **4** reacted faster than **3**, yielding 28% of a 1:1

mixture of **1** and **2** together with 1,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranose (**6**) and other products. The structure of **6** was indicated by the n.m.r. data. For a solution in $CDCl_3$, the hydroxyl doublet collapsed to a singlet on irradiation of the H-2 resonance and was therefore due to HO-2 (see Experimental).

The absence of stereochemical control in the displacement reactions of **3** and **4** could be due to stereoelectronic factors[16]. The interaction of the unshared electron orbitals on the sulfur atom with the antibonding orbital is attenuated because of the greater C–S distance. Thus, the lower solvolysis rate of 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide as compared to the corresponding oxygen analogue[17] could be due to the stereoelectronic effect. An ineffective participation by the lone-pair orbital could lead to diminished neighboring-group participation[18] of AcO-2 in **3**. Although some dioxenium ion **7** is formed during the displacement reactions of **4**, the regiospecificity of its opening has been lost as shown by the formation of **6** due to traces of water in the reaction mixture. The diminished lone-pair participation in the ring opening of the dioxenium ion may also be responsible for the multiple products obtained by Shin and Perlin[9] on treatment of 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-galactopyranosyl bromide with methanol and silver carbonate.

EXPERIMENTAL

General. — Melting points (uncorrected) were determined by the capillary method. I.r. spectra were obtained with a Perkin–Elmer 457 spectrophotometer, and ^{1}H- and ^{13}C-n.m.r. spectra (internal Me_4Si) with a Varian XL-100 instrument operating in the F.t. mode at 100 and 25.2 MHz, respectively; ^{13}C peaks were assigned by off-resonance proton decoupling[19]. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. T.l.c. was performed on Merck MF-254 silica gel, with detection by u.v. light or by charring with sulfuric acid.

Tetra-O-acetyl-5-thio-D-glucopyranosyl bromides (**3** *and* **4**). — To a solution of 1,2,3,4,6-penta-*O*-acetyl-5-thio-αβ-D-glucopyranose (200 mg, 0.4 mmol) in dichloromethane (2 mL) was added 30% HBr in acetic acid (0.5 mL). The solution was stored at 0° for 24 h, the solvent was evaporated, and traces of acetic acid were removed by repeated evaporation of toluene from the residue; t.l.c. (ether–light petroleum, 2:1) then indicated products with R_F 0.50 and 0.37. The mixture was eluted from a column (1.3 × 17 cm) of silica gel with ether–light petroleum (2:1), to give the α-bromide (13 mg) and a mixture (146 mg; combined yield of **3** and **4**, 76%). Recrystallisation of the mixture from ether–light petroleum gave needles of the β-bromide **4**, m.p. 102–104°, $[\alpha]_D^{20}$ −6.5° (*c* 1, chloroform); ν_{max}^{KBr} 1735 (ester C=O), 1222 (C-O, acetates), and 1030 cm^{-1} (C-O esters).

Anal. Calc. for $C_{14}H_{19}BrO_8S$: C, 39.35; H, 4.48. Found: C, 39.50; H, 4.55.

The mother liquor from the above recrystallisation (enriched in the faster-moving α anomer) was eluted from a column (1.3 × 17 cm) of silica gel with ether–light petroleum (2:1), to give **3** (55 mg; R_F 0.5) and an αβ-mixture (28 mg).

Recrystallisation of the α-bromide from hexane gave material with m.p.

59–61°, $[\alpha]_D^{20}$ +227° (*c* 1, chloroform); ν_{max}^{KBr} 1735 (ester C=O), 1222 (C–O, acetates), and 1030 cm^{-1} (C–O, esters).

Anal. Found: C, 39.38; H, 4.45.

Reactions with silver acetate. — (*a*) A solution of **3** (35 mg, 0.08 mmol) in dry benzene (10 mL) was boiled under reflux for 1 h in the presence of silver acetate (26 mg, 0.16 mmol), filtered, and concentrated. The residue was eluted from silica gel (5 g) with ether–light petroleum (2:1), to give the αβ-penta-acetate (27 mg, 84%), the ^{1}H-n.m.r. spectrum of which contained doublets for H-1α at δ 6.11 ($J_{1,2}$ 2.9 Hz) and H-1β at δ 5.92 ($J_{1,2}$ 8.5 Hz); αβ-ratio, 1:1.

(*b*) A solution of **4** (35 mg, 0.08 mmol) in dry benzene (10 mL) was boiled under reflux for 1 h in the presence of silver acetate (26 mg, 0.18 mmol). Work-up and chromatography, as described in (*a*), gave the αβ-penta-acetate (9 mg, 28%; αβ-ratio, 1:1), and a mixture (13 mg, 44%) of 1,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranose (**6**) and an unidentified product (probably 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranose). Crystallisation of the mixture from ether–light petroleum gave **6** (6 mg), m.p. 131–133°, $[\alpha]_D^{22}$ +268° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): δ 6.02 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), ~4.1 ($J_{2,3}$ 9 Hz, H-2 overlapped by H-6′), 5.25 (q, 1 H, $J_{3,4}$ 7 Hz, H-3), 5.36 (t, 1 H, $J_{4,5}$ 9 Hz, H-4), 3.50 (m, 1 H, $J_{4,5}$ 9 Hz, H-5), 4.41 (q, 1 H, $J_{5,6}$ 5 Hz, H-6), 4.06 (q, 1 H, $J_{6,6'}$ 12 Hz, H-6′), 2.07, 2.08, 2.11, 2.20 (4 s, 12 H, 4 Ac), and 2.39 (d, 1 H, $J_{2,OH}$ 8 Hz, collapsed to a s on irradiation at δ 4.1, exchangeable with D_2O, HO-2).

Anal. Calc. for $C_{14}H_{20}O_9S$: C, 46.15; H, 5.53. Found: C, 46.31; H, 5.33.

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REFERENCES

1 R. L. Whistler and W. C. Lake, *Methods Carbohydr. Chem.*, 6 (1972) 286–296.
2 M. Chen and R. L. Whistler, *Misc. Pap. Landbouwhogesch. Wageningen*, 12 (1976) 17–28.
3 U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, 34 (1969) 97–100.
4 R. L. Whistler and J. H. Stark, *Carbohydr. Res.*, 13 (1970) 15–21.
5 D. Horton and W. N. Turner, *J. Org. Chem.*, 30 (1965) 3387–3394.
6 W. Korytnyk, M. Hanchak, S. Valentekovich-Horvath, J. Vitali, and R. Parthasarathy, *Abstr. Int. Symp. Carbohydr. Chem., Xth*, Sydney, Australia, 1980, p. 31.
7 K. Bock and C. Pedersen, *J. Chem. Soc., Perkin Trans. 2*, (1974) 293–297.
8 B. Coxon, *Ann. N.Y. Acad. Sci.*, 222 (1973) 952–970.
9 J. E. N. Shin and A. S. Perlin, *Carbohydr. Res.*, 76 (1979) 165–176.
10 V. S. Rao and A. S. Perlin, *Carbohydr. Res.*, 92 (1981) 141–148.
11 S. Wolfe, M.-H. Whangbo, and D. J. Mitchell, *Carbohydr. Res.*, 69 (1979) 1–26.
12 F. Weygand, H. Ziemann and H. J. Bestmann, *Chem. Ber.*, 91 (1958) 2534–2537.
13 W. Korytnyk and J. A. Mills, *J. Chem. Soc.*, (1959) 636–649.
14 C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, 4 (1969) 39–97.
15 R. S. Tipson, *J. Biol. Chem.*, 130 (1939) 55–59.
16 R. U. Lemieux, K. B. Hendriks, R. V. Stick, and K. James, *J. Am. Chem. Soc.*, 97 (1975) 4056–4062.
17 R. L. Whistler and T. Van Es, *J. Org. Chem.*, 28 (1963) 2303–2304.
18 R. U. Lemieux and O. Hindsgaul, *Carbohydr. Res.*, 82 (1980) 195–206.
19 J. C. MacDonald and M. Mazurek, *J. Magn. Reson.*, 28 (1977) 181–190.