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Note

The reaction of methyl 5-thio-3-*O*-toluene-*p*-sulfonyl-α-D-glucopyranoside and its triacetate with sodium azide

Najim A. Al-Masoudi [a,*] and Wolfgang Pfleiderer [b]

[a] *Chemistry Department, College of Science, University of Basrah, Basrah (Iraq)*
[b] *Facultät für Chemie, Universität Konstanz, Postfach 5560, D-7750 Konstanz (Germany)*

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There is considerable interest at present in nucleosides containing an azido residue[1–6] in their sugar moieties as potential agents for use against AIDS and related diseases. As part of a program on sulfur-in-the-ring sugars[7–11] together with their azido and amino analogues[12,13], the results of some azide displacement reactions are now reported.

Reaction of methyl 2,4,6-tri-*O*-acetyl-3-*O*-toluene-*p*-sulfonyl-α-D-glucopyranoside[8] (**1**) with sodium azide in boiling *N*,*N*-dimethylformamide gave the expected *allo*-azide **2** (10%) together with the 3-deoxyhexenopyranosides **3** (10%) and **4** (15%). The structures of **2–4** followed from their ^{1}H NMR spectra (Table I). Thus, the spectrum of **2** revealed only one large $J_{H,H}$ value ($J_{4,5}$ 12.0 Hz) in keeping with an α-allopyranoside in the $^4C_1$ conformation[7]. The lack of signals for H-2 and H-4 confirmed **3** and **4** to be the 2- and 3-enopyranosides, and the *J* values accorded with the expected $^5H_5$ and $^5H_1$ conformations, respectively. The *J* values for **3** were similar to those of the oxygen analogue[14]. The low yields of **2–4** were not unexpected. Displacements at C-3 of α-glucopyranoside derivatives are subject to a *syn*-diaxial interaction of the incoming nucleophile and the C-1 substituent, and the hexenopyranosides **3** and **4** are the products of relatively unfavourable *cis*-elimination reactions.

When methyl 5-thio-3-*O*-toluene-*p*-sulfonyl-α-D-glucopyranoside[8] (**5**) was subjected to azide displacement, the main product was the *gluco*-azide **6**, isolated as the triacetate **7** in modest yield. The *gluco* structure of **7** was indicated by the ^{1}H NMR spectrum ($J_{2,3} = J_{3,4} = 10.5$, $J_{4,5}$ 11.0 Hz). The observed displacement with retention of configuration must be the result of a double inversion. The possibility of an initial intramolecular displacement by sulfur is ruled out because the displacement on the triacetate **1** proceeded normally, albeit in low yield. A more likely explanation is that the tosylate **5** is converted first into either or both of the

* Corresponding author.

TABLE I

^{1}H NMR data (δ in ppm, J in Hz)

Compound	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6a}$	$J_{5,6b}$	H-6a $J_{6a,6b}$	H-6b	Other signals
2	4.50d	4.61dd	4.18dd	4.80dd	3.14ddd		4.35ddd	4.0dd	3.49 (OMe), 2.14,
	3.0	4.0	5.0	12.0	5.0	4.0	12.0		2.13, 2.12 (3 Ac)
3	5.71s		5.54d	5.60t	3.83dt		4.49dd	4.24dd	3.52 (OMe), 2.18
			3.0	8.8	5.0	4.0	11.0		(2 Ac), 2.13 (Ac)
4	5.60d	5.11dd	5.63d		3.47dt		4.50dd	4.34dd	3.50 (OMe), 2.18,
	3.5	2.5			5.0	4.0	11.0		2.07 (3 Ac)
7	4.66d	5.04dd	3.95dd	5.13dd	3.34ddd		4.33dd	4.05dd	3.45 (OMe), 2.18,
	3.0	11.0	11.0	11.0	5.0	3.5	12.0		2.17, 2.16 (3 Ac)
8	6.09d	5.39dd	4.0t	5.15t	3.45ddd		4.49dd	4.10dd	2.19, 2.17, 2.09,
	2.0	10.5	10.5	11.0	5.5	4.0	13.0		2.0 (4 Ac)

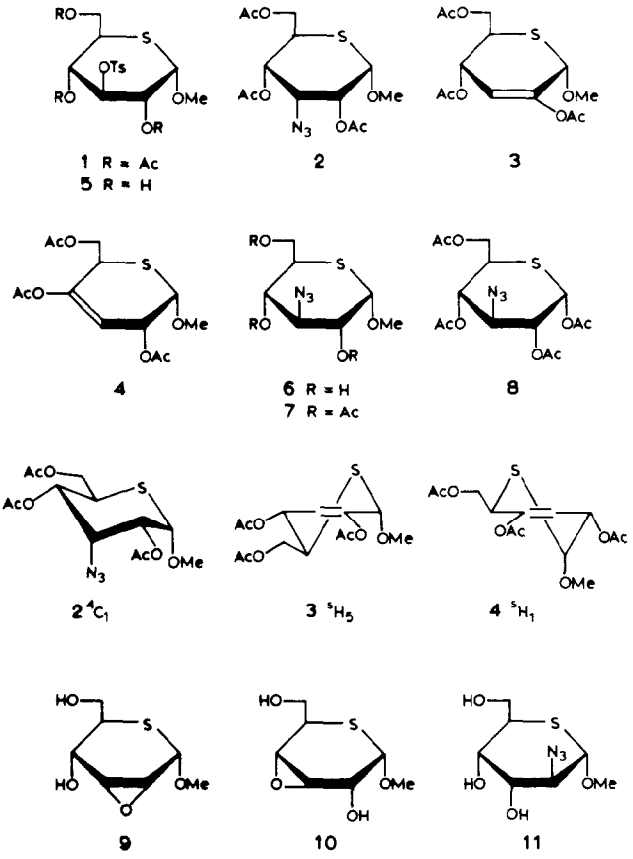
allo-epoxides **9** and **10**, which then undergo azide opening[12]. Some support for this explanation came from the observation that the 2,3-epoxide **9**[10] reacted with sodium azide in *N*,*N*-dimethylformamide to give, after acetylation, **7** as the major product. This result also is unusual since the *altro*-azide **11** might have been expected as the result of diaxial opening of the epoxide ring in **9** in the more favourable $^5H_5$ conformation. It has been shown in studies with the related *ribo*-epoxides[15] that C-2 of a 2,3-epoxide is relatively unreactive and ring opening occurs preferentially at C-3 presumably via the less favoured $^5H_5$ conformation. Acetolysis of **7** gave the α-tetra-acetate **8** ($J_{1,2}$ 2.0 Hz).

EXPERIMENTAL

Melting points were determined with a Buchi apparatus, and are uncorrected. The ^{1}H NMR spectra were recorded with a Bruker WM 250 spectrometer on solutions in $CDCl_3$ (internal Me_4Si). Optical rotations were determined with a Perkin–Elmer Type 141 polarimeter. The purity of products was monitored by TLC on Kieselgel 60 (Merck).

*Reactions with sodium azide.—(a) Methyl 2,4,6-tri-*O*-acetyl-5-thio-3-*O*-toluene-*p*-sulfonyl-α-*D*-glucopyranoside* (**1**). A solution of **1** (1.14 g) in *N*,*N*-dimethylformamide (50 mL) containing sodium azide (0.35 g) was heated under reflux for 7 h, then concentrated in vacuo. The residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (7:3 toluene–EtOAc) of the syrupy residue on silica gel gave, first, methyl 2,3,6-tri-*O*-acetyl-5-thio-α-*D*-*erythro*-hex-2-enopyranoside (**3**), isolated as a syrup (74 mg, 10%); $[\alpha]_D$ +54° (*c* 1.17, $CHCl_3$). Mass spectrum: *m/z* 318.0795 (M^+) ($C_{13}H_{18}O_7S$ calcd 318.0773).

Eluted second was methyl 2,4,6-tri-*O*-acetyl-3-deoxy-5-thio-α-*D*-hex-3-enopyranoside (**4**), isolated as a syrup (112 mg, 15%); $[\alpha]_D$ +152° (*c* 1.11, $CHCl_3$). Mass spectrum: *m/z* 318.0800 (M^+) ($C_{13}H_{18}O_7S$ calcd 318.0773).



Further elution gave methyl 2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-5-thio-α-D-allopyranoside (**2**), isolated as a syrup (80 mg, 10%); $[\alpha]_D$ +160° (*c* 1.0, $CHCl_3$). Mass spectrum: *m/z* 319.3532 ($M^+ - N_3$) ($C_{13}H_{19}N_3O_7S$ calcd 319.3442).

*(b) Methyl 5-thio-3-*O*-toluene-*p*-sulfonyl-α-*D*-glucopyranoside (**5**).* A solution of **5** (1.0 g) in *N,N*-dimethylformamide (50 mL) containing sodium azide (1.11 g) was heated under reflux for 2.5 h, then concentrated in vacuo. The residue was treated with pyridine (35 mL) and Ac_2O (20 mL) for 2 days at room temperature. Work-up in the usual way and column chromatography (19:1 CH_2Cl_2–MeOH) of the product on silica gel (120 g) afforded methyl 2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-5-thio-α-D-glucopyranoside (**7**; 0.36 g, 36%); mp 85–86°C (from di-isopropyl ether–ether); $[\alpha]_D$ +208° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{19}N_3O_7S$: C, 43.23; H, 5.30; N, 11.63%. Found: C, 43.31; H, 5.32; N, 11.69.

*(c) Methyl 2,3-anhydro-5-thio-α-D-allopyranoside (**9**).* A solution of **9** (0.50 g) and sodium azide (0.35 g) in *N,N*-dimethylformamide (20 mL) was heated under reflux for 3 h, then concentrated in vacuo. The residue was treated with dry pyridine (30 mL) and Ac_2O (15 mL) for 2 days at room temperature, and the mixture was

worked-up in the usual manner. Column chromatography (7:3 toluene–EtOAc) of the residue (0.83 g) on silica gel gave **7** (0.66 g, 71%), identical with the product in (*b*).

*1,2,3,4,6-Tetra-O-acetyl-3-azido-3-deoxy-5-thio-α-*D*-glucopyranose* (**8**).—The glycoside **7** (0.33 g) was added to a stirred mixture of Ac_2O (25 mL), acetic acid (0.5 mL), and concd H_2SO_4 (0.1 mL) at 0°C. After storage for 48 h at room temperature, the mixture was partitioned between CH_2Cl_2 and cold, satd aq $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (4:1 toluene–EtOAc) of the syrupy residue on silica gel afforded **8** (0.11 g, 31%); $[\alpha]_D$ +128° (*c* 0.75, $CHCl_3$). Mass spectrum: *m/z* 330.2693 ($M^+ - OAc$) ($C_{14}H_{19}N_3O_8S$ calcd 330.2675).

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