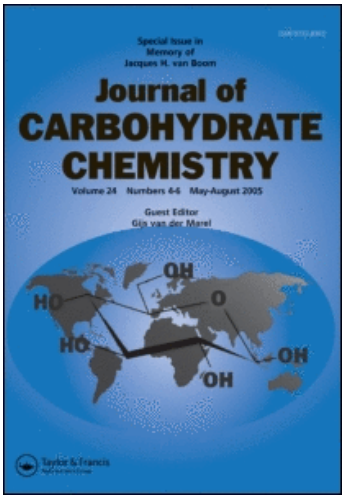

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A NEW SUGAR-DERIVED TETRAHYDROTHIAZEPINE OBTAINED BY THERMOLYSIS FROM PERACETYLATED 5-THIO-D-XYLOPYRANOSYL AZIDES

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ABSTRACT

Both α- and β-anomers of acetylated 5-thio-D-xylopyranosyl azide lead upon thermolysis to a new sugar-derived tetrahydrothiazepine. This compound arises from a ring expansion involving the preferred migration of the ring sulfur atom, which probably assists the decomposition of the azido group with departure of molecular nitrogen.

INTRODUCTION

Photolysis of glycosyl azides may result, depending upon the conditions and as shown by earlier works,[1,2] in various transformations and in particular in imine formation due to release of molecular nitrogen and migration (*1,2*-shift) of the anomeric hydrogen atom to the remaining nitrogen atom in the nitrene or nitrenoïde intermediate.[3] This method which constitutes a smooth route to derivatives of D-glycono-1,5-lactones[1] and, when the azido group is attached to a primary carbon atom, to sugar dialdoses,[4-6] takes advantage of the better migrating ability of hydrogen atoms over alkyl residues. Using acyclic azidoether models, the migrating ability of substituents in the course of photo-induced rearrangements has been established as follows: H >> CH_3 > Ph >> OR

since migration of alkoxy groups was not observed.[7] In contrast, upon thermolysis, azidothioethers give rise preferentially to migration of the thioaryl group.[8]

It is clear that the reactivity of simple glycosyl azides has not been fully explored and we showed recently that they can be converted in high yield to the corresponding sugar *N*-bromoiminolactones[9-11] on treatment with *N*-bromosuccinimide under free-radical conditions. We also showed that anomerically substituted glycopyranosyl azides[12-14] and in particular glycopyranosylidene diazides[15] can be easily prepared from the corresponding halogenated precursors. Their photolysis has been envisaged as a mild[16] route to new azasugars, a class of biologically active glycomimetics[17] which is receiving much attention. It was concluded that photolysis of α- and β-anomers of D-fructopyranosyl azide derivatives[14] and peracetylated 1-cyano glycopyranosyl azides[12] led predominantly to ring-expanded products resulting from the migration of the endocyclic carbon residue with retention of configuration. The same conclusion was reached when peracetylated and perbenzylated glycopyranosylidene diazides were subjected to photolysis.[18,19] In contrast, we found that methyl 1-azido-D-glucopyranosides rearranged upon photolysis with a preferential and stereocontrolled migration of the alkoxy groups.[20] Particularly noteworthy is the migration observed for the endocyclic oxygen atom to afford an oxazepine derivative which could be deacetylated uneventfully. Therefore, it was of interest to extend these investigations to the case of azido derivatives of the 5-thio series to get a closer insight in such rearrangements and to explore simple routes to unprecedented but potentially active structures.

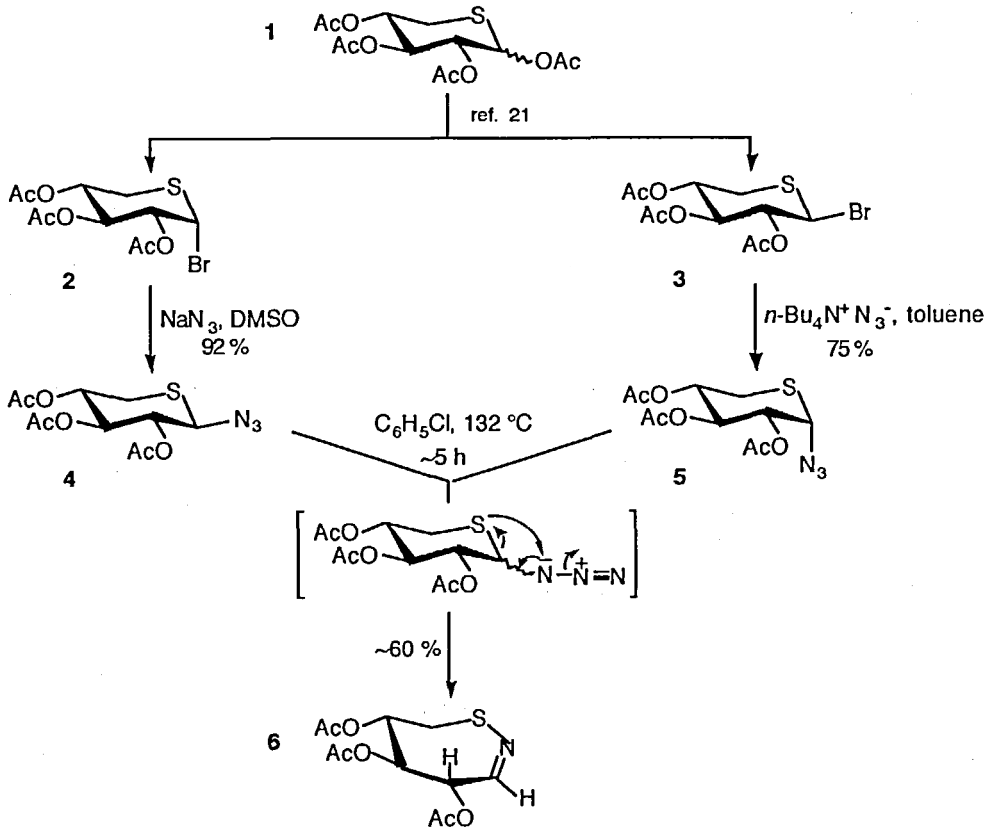
RESULTS AND DISCUSSION

The known 1,2,3,4-tetra-*O*-acetyl-5-thio-D-xylopyranose[21] can be converted efficiently to the corresponding anomeric bromides which both are stable and crystalline materials.[21] On treatment with azide anion, they were converted in high yield to the new 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl azides with inversion of the anomeric configuration. The Walden inversion observed for the conversion of **3** to **5** accounts for an S*N*2 mechanism which should also operate for the transformation of **2** into **4**. In effect, the applied conditions are against the formation of a thiocarbenium ion, which, however, may lead to the 1,2-*trans* azidosugar **4** due to the C-2 acetoxy group participation. In contrast with our previous observations with natural sugar azido

derivatives, photolysis of **4** and **5** were found to be sluggish and poorly selective, so we resorted to thermolysis which proved more effective. In effect, heating to reflux a chlorobenzene solution of the substrates for ~5 h resulted in an almost complete conversion of **4** and **5** to afford a new major compound and minor unidentified byproducts. No differences in substrate reactivity and reaction selectivity could be detected depending upon the anomeric configuration of the starting material. Compound **6** was isolated by flash chromatography in a 33 % yield from **4**. Due to partial decomposition of **6** at the purification stage, the isolated yield was lower than expected from TLC plates appearance. Interpretations of ^{1}H NMR spectra of the reaction mixtures indicated a ~60 % yield of **6** from **4** and ~75 % from **5**. No evidence supporting the formation of **6** by photolysis was found.

The structure of compound **6** was convincingly supported by NMR spectroscopy which showed, in NOE difference spectra, enhancements for protons H-2 and H-3 upon selective irradiation of the H-1 proton, as expected if the carbon chain was preserved in the rearrangement process. The H-1 proton appeared as a deshielded doublet with a small vicinal coupling (δ 7.62 ppm, $J_{1,2}$ = 2.3 Hz). A good agreement was also found between the measured ^{13}C chemical shifts, assigned on the basis of a 2D HSQC decoupled ^{13}C NMR spectrum, and those calculated for the tetrahydrothiazepine derivative **6**. The structure of the ring-expanded product **6** obtained from both anomer **4** and **5** shows that upon thermolysis, migration involved primarily the sulfur atom as already reported for acyclic azidothioether models,[8] regardless of the anomeric configuration of the substrates. As compared to the case of alkyl azides, the thermal decomposition of azidothioethers was found to occur at lower temperatures (~180 °C and ~120 °C respectively).[8] Considering this difference and kinetic data strongly in favor of a nonionic and nonnitrene type process occurring in the thermolysis of azidothioethers, this reaction was explained by a concerted process in which the sulfur atom assists the departure of molecular nitrogen[8] and our results completely support this interpretation (Scheme). Earlier work also shows that only *azidoacetal*-related precursors are prone to stereocontrolled rearrangements[20] when subjected to photolysis since this treatment triggers migration of the endocyclic carbon atom in sugar-derived *azidoethers*.[12,14] This is in contrast to the preferred migration of a thioalkyl residue, observed when acyclic[8] and cyclic *azidothioethers* are subjected to thermolysis.

While a refined interpretation of the studied azidosugar rearrangements will be proposed soon, it is noteworthy that thermolysis of both α and β acetylated 5-thio-D-xylopyranosyl azides led by ring expansion and in ~60 % yield to a new sugar-derived tetrahydrothiazepine derivative, a representative of an unknown class of compounds which is under further investigations.



Scheme

EXPERIMENTAL

General methods. The NMR spectra were obtained from deuteriochloroform solutions with tetramethylsilane as the internal reference using a BRUKER AM 300 spectrometer, unless otherwise indicated. Chemical shifts (δ) are given in ppm, couplings (J) are expressed in Hertz.

2,3,4-Tri-*O*-acetyl-5-thio-β-D-xylopyranosyl azide (4). A suspension of sodium azide (0.39 g, 6 mmol) in dry DMSO (10 mL) was stirred at room temperature until complete dissolution (~ 45 min). After addition of 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide **2** (1.07 g, 3 mmol), stirring was continued for 4-5 h whereupon TLC monitoring showed the complete conversion of the substrate (R_f ~0.42, diethyl

ether-petroleum ether 1:1v/v) into a new compound visible as a more polar spot on the plates (R_f ~0.31, same eluent). The solution which was diluted with diethyl ether (50 mL) was washed with water (25 mL). The aqueous phase was extracted with diethyl ether (50 mL) and the ethereal phases were combined, washed with water (4 x 20 mL) to yield, after drying (Na_2SO_4) and concentration under vacuum a white solid (0.93 g). Crystallisation from diethyl ether-petroleum ether afforded two crops of pure **4** (0.87 g, 92% yield) as a fluffy white material. mp 123 °C; $[\alpha]_D$ -53° (*c* 0.45, chloroform); IR (KBr): ν N_3 2100 cm^{-1}; ^1H NMR δ 5.15 (t, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 5.0 - 5.1 (m, 2H, $J_{4,5e}$ = ~3.7 Hz, H-3, H-4), 4.49 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 2.95 (dd, 1H, $J_{5a,5e}$ = 13.7 Hz, H-5e), 2.71 (m, 1H, $J_{4,5a}$ = 10.5 Hz, H-5a), 2.09, 2.03, 2.03 (2s, 9H, acetyl); (C_6D_6) δ 5.28 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 5.02 (t, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 4.98 (m, 1H, $J_{4,5e}$ = ~4 Hz, H-4), 3.66 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 2.24 (dd, 1H, $J_{4,5a}$ = 10.5 Hz, H-5e), 2.00 (m, 1H, $J_{5e,5a}$ = 13.6 Hz, H-5a), 1.68, 1.63, 1.57 (3s, 9H, acetyl); ^{13}C NMR (50 MHz) δ 169.7, 169.6, 169.3 (C=O), 73.80, 72.47, 71.88, 63.04 (C-1 to C-4), 28.55 (C-5), 20.74, 20.55, 20.49 (CH_3).

Anal. Calcd for $C_{11}H_{15}N_3O_6S$: C, 41.64; H, 4.76; N, 13.24; O, 30.25; S, 10.10. Found: C, 41.80; H, 4.54; N, 13.15; O, 30.27; S, 9.83.

2,3,4-Tri-*O*-acetyl-5-thio-α-D-xylopyranosyl azide (5). 2,3,4-Tri-*O*-acetyl-5-thio-β-D-xylopyranosyl bromide **4** (176 mg, 0.5 mmol) was added to a solution of tetra-*n*-butylammonium azide[22] (710 mg, 2.5 mmol, 5 eq) in toluene (5 mL) at 0 °C. After stirring for 2 h at room temperature, TLC monitoring showed the complete transformation of the starting material (R_f 0.4) to a new compound (R_f 0.45 in diethyl ether-petroleum ether 1:1 v/v). Water (10 mL) was added and the separated aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic phases were washed with distilled water (3 x 10 mL), dried over Mg_2SO_4, then concentrated under vacuum to afford a residue (157 mg) which crystallized from diethyl ether as a colourless solid (119 mg; 75 % yield). mp 90 °C; $[\alpha]_D$ +392° (*c* 0.98, chloroform); IR (KBr): ν N_3 2100 cm^{-1}; ^1H NMR (300.13 MHz) δ 5.38 (t, 1H, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 5.12 - 4.99 (m, 3H, H-1, H-2, H-4), 3.02 (dd, 1H, $J_{5a,5e}$ = 13.2 Hz, $J_{5a,4}$ = 11.1 Hz, H-5a), 2.79 (ddd, 1H, $J_{1,5e}$ = 1.1 Hz, $J_{4,5e}$ = 4.8 Hz, H-5e), 2.08, 2.04, 2.03 (3s, 9H, acetyl); (C_6D_6) δ 5.68 (t, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 9.9 Hz, H-3), 5.22 (dd, 1H, $J_{1,2}$ = 3.2 Hz, H-2), 5.18 (ddd, $J_{4,5e}$ = 4.6 Hz, $J_{4,5a}$ = 11.3 Hz, H-4), 4.30 (dd, 1H, $J_{1,5e}$ = 1.1 Hz, H-1), 2.62 (dd, 1H, $J_{5a,5e}$ = 13.3 Hz, H-5a), 2.27 (ddd, 1H, H-5e), 1.76, 1.71, 1.70 (3s, 9H, acetyl)); ^{13}C NMR (75.5 MHz) δ 169.86, 169.75, 169.47 (C=O), 73.86, 72.44, 69.58 (C-2 to C-4), 62.64 (C-1), 25.87 (C-5), 20.73, 20.63, 20.51 (CH_3).

Anal. Calcd for $C_{11}H_{15}N_3O_6S$: C, 41.64; H, 4.76; N, 13.24; O, 30.25; S, 10.10. Found: C, 41.77; H, 4.85; N, 13.12; O, 30.05; S, 10.13.

Photolysis of 2,3,4-Tri-*O*-acetyl-5-thio-α- and β-D-xylopyranosyl azide 5 and 4. A solution of compound **4** or **5** (32 mg, 0.1 mmol) in dry benzene (1 mL) placed in a quartz tube (1 cm diameter) maintained at ~1 cm of a medium-pressure mercury lamp (Hanovia 450 W) was irradiated with unfiltered UV light until the starting material disappeared (~8 h). A parallel experiment was carried out using acetonitrile as the solvent. In each case, TLC plates eluted with ethyl acetate-hexane 1:1 v/v showed essentially polar compounds (R_f 0) resulting most probably from decomposition of fragile photoproducts observed at the first stage of the reaction (R_f 0.52 and 0.45). According to TLC examination, the more mobile compound (R_f 0.52) appeared to be more stable than the other (R_f 0.45), which was hardly visible when irradiation was prolonged for a few hours.

Thermolysis of 2,3,4-Tri-*O*-acetyl-5-thio-β-D-xylopyranosyl azide 4. A solution of compound **4** (160 mg, 0.5 mmol) in freshly distilled chlorobenzene (15 mL) was introduced into a flask equipped with a cooling device. Boiling under argon for about 5 h resulted, as shown by TLC monitoring of the reaction, in almost complete conversion of the starting azide (R_f 0.66, ethyl acetate-hexane 1:1 v/v) to a more polar product (R_f 0.56, ethyl acetate-hexane 1:1) along with traces of polar byproducts. Evaporation of the solvent under vacuum (~3mm Hg) led to a brown syrup (157 mg) which, upon examination by ^{1}H NMR, was shown to contain essentially **6** (~60 %) as well as traces of unchanged azide, chlorobenzene and unidentified byproducts. Flash chromatography on silica gel with ethyl acetate-petroleum ether-triethylamine 30:70:1 v/v as the eluent led to **6**, either pure (36 mg) or in admixture (18 mg) with a slightly less mobile (R_f ~0.53) and less abundant compound (~2:1 ratio by ^{1}H NMR) which was not identified. The total isolated yield for **6** (~33 % taking into account both fractions) was lower than expected. Although the purity of the main crop of compound **6** was proved by NMR spectroscopy, examination by TLC showed two spots (R_f 0.56 and 0.19) on the plates developed with ethyl acetate-hexane 1:1 v/v. Observation of this new, more polar compound which was not isolated can account for the loss arising at the purification stage. After pure **6** was stored for 2 years in a freezer under normal atmosphere, its spontaneous transformation to two polar compounds (R_f ~0.19 and 0.12) was observed, probably as a result of reaction with water.

6: colourless syrup; IR (film): 1750 cm^{-1}, ν C=O, 1605 cm^{-1} (weak), ν C=N; $[\alpha]_D^{22}$ -36.5 (*c* 0.5 chloroform); ^{1}H NMR δ 7.62 (d, 1H, $J_{1,2}$ = 2.3 Hz, H-1), 5.81 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 5.40 (dd, 1H, $J_{3,4}$ = 6.0 Hz, H-3), 5.31 (dt, 1H, $J_{4,5a}$ = 6.1 Hz, $J_{4,5e}$ = 2.5 Hz, H-4), 3.02 (dd, 1H, $J_{5a,5e}$ = 15.4 Hz, H-5a), 3.60 (dd, 1H, H-5e), 2.14, 2.10, 2.07 (3s, 9H, acetyl). Irradiation of the H-1 proton at 7.62 ppm resulted in 4.2 and 1.9 % enhancements of the H-2 and H-3 signals, respectively, in NOE difference spectra. ^{13}C NMR: The

resonances of the carbon atoms were unambiguously assigned by a 2D HSQC decoupled ^{13}C spectrum. They are close to the chemical shifts calculated by the ChemWindows program (values in italics): δ 169.75, 169.24, 169.12, *171.0* (C=O), 159.49, *163.7* (C-1), 69.80, *69.10* (C-2), 71.02, *74.0* (C-3), 73.80, *73.1* (C-4), 37.64, *31.8* (C-5), 20.78, 20.53, 20.50, *17.6* (CH_3); MS e.i. 289, 1% $[M]^+$, 229, 1% $[M-60]^+$, 187, 2% $[M-60-42]^+$, 169, 1% $[M-120]^+$, 145, 4% $[M-60-84]^+$, 127, 12% $[M-120-42]^+$; MS (CI, NH_3) 290 $[M+1]^+$, 307 $[M+18]^+$.

Anal. Calcd for $C_{11}H_{15}NO_6S$ (289.30): C, 45.67; H, 5.23; N, 4.84; O, 33.18; S, 11.08. Found: C, 45.79; H, 5.41; N, 4.85; O, 32.49; S, 10.48.

Thermolysis of 2,3,4-Tri-*O*-acetyl-5-thio-α-D-xylopyranosyl azide 5. Compound **5** (66.3 mg, 0.2 mmol) was heated in chlorobenzene (5 mL) for 5 h whereupon TLC monitoring showed its almost complete transformation to tetrahydrothiazepine **6**, and formation of minor byproducts. Evaporation of chlorobenzene under reduced pressure and examination of the residue by ^1H NMR led to an estimated 75 % yield for compound **6**.

Photolysis of compound 6. Exposure of a benzene solution (0.5 mL) of compound **6** (16 mg) to unfiltered UV light showed its complete transformation mainly to a more polar compound (R_f 0.09) within ~45 min. This compound was not detected (TLC) upon photolysis of **4** and **5**.

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