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THE ACTION OF BROMINE ON TETRA-*O*-ACETYL-1-*S*-ACETYL-1-THIO-β-D-GLUCOPYRANOSE. FORMATION AND DECOMPOSITION OF TETRA-*O*-ACETYL-β-D-GLUCOPYRANOSYLSULFENYL BROMIDE*†

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ABSTRACT

Treatment of either tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (**1**) or *tert*-butyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**6**) with a >3-molar excess of bromine in carbon tetrachloride or pure chloroform, at −10° for 1-3 min, gives tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide (**2**) in quantitative yield; prolonged exposure to bromine at room temperature converts the product **2** into tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**). Slow addition of bromine to the 1-thioglycoside **6** in carbon tetrachloride, or bromination of the thiolacetate **1** in reagent-grade chloroform, gives bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide (**4**), also obtainable by treating the sulfenyl bromide **2** with dry ethanol or with the 1-thioglycoside **6**. Oxidation of the disulfide **4** with *m*-chloroperoxybenzoic acid gives a mono-oxide derivative **5**, also obtainable by treating the sulfenyl bromide **2** with water or 95% ethanol. The disulfide **4** and its mono-oxide **5** were both converted into the bromide **3** by prolonged exposure to bromine at room temperature.

RESULTS AND DISCUSSION

It has been shown in earlier work from this laboratory that brief treatment of tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (**1**) with an excess of bromine in carbon tetrachloride gives the crystalline, unstable tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide[1] (**2**). The bivalent sulfur atom in this derivative displays electrophilic character and can attack various types of electron-rich centers[2−4]. The present report describes a detailed study of reactions leading to the sulfenyl bromide **2** and to its subsequent decomposition by the reagent or by various solvents. A convenient procedure for preparing **2** in quantity is also described.

Preparation of the sulfenyl bromide **2** by bromination of the thiolacetate **1** in

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carbon tetrachloride for 5 min at room temperature, as described in the original report[1], gives crystalline product when the reaction is performed on a scale of 250–500 mg, but erratic results are obtained when the scale of the preparation is increased, or other solvents are used; side-products appear to be formed concurrently with **2**, and decomposition of **2** may take place during attempted isolation. In order to establish optimal conditions for the preparation of **2**, and to determine the nature of any side-products, the course of the reaction of **1** with bromine was followed by n.m.r. spectroscopy. The n.m.r. technique was chosen in preference to thin-layer chromatography (t.l.c.) for monitoring the reaction, because the highly reactive sulfenyl bromide **2** would almost certainly undergo decomposition in contact with the chromatographic adsorbent. Detailed n.m.r. spectral correlations of acetylated 1-thioaldopyranoses[5] and acetylated glycosyl halides[6] have been made in this laboratory, and the presence of either of these species in the reaction mixture could be detected readily by the presence of characteristic spectral signals.

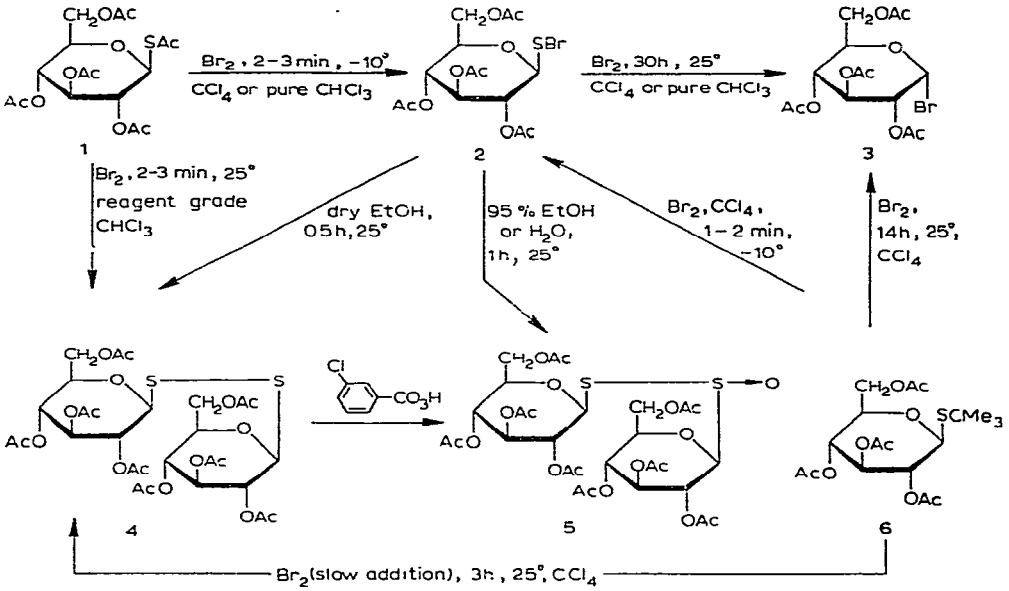
Treatment of the thiolacetate **1** in carbon tetrachloride at ~40° with a 3-molar excess of bromine caused complete cleavage of the *S*-acetyl group from **1** within 1 min, as shown by the disappearance of the 3-proton singlet at τ 7.59 (SAc)[5] observed in the spectrum of **1**, and the appearance of a signal corresponding to acetyl bromide at τ 7.19. Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**) was definitely absent from the reaction mixture at this stage, because no low-field doublet (for H-1 of **3**) was observed in the spectrum. The spectrum was consistent with the product's being the sulfenyl bromide **2**, and this supposition is supported by the data from elemental analysis and the reactivity of the product isolated, which clearly establish that it is **2** and not bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide (**4**). The n.m.r. spectra of the sulfenyl bromide **2** and the disulfide **4** differ only in minor details, and in neither case can the H-1 signal be observed clearly to the low-field side of the "envelope" of signals for the methine protons, because the sulfur atom at C-1 exerts a much smaller deshielding effect than an oxygen or halogen atom[5].

When the reaction mixture was kept at 40°, the initial product **2** began to decompose after 3–4 min, with the formation of the glycosyl bromide **3**, and conversion of **2** into **3** was complete in 1 hour, as shown by the n.m.r. spectrum.

For the conversion of **1** into **2**, at least a 3-molar excess of bromine, added in one portion, was required. When smaller proportions of bromine were used, starting material (**1**) could still be detected, even after several minutes of reaction.

A convenient method for the preparation of the sulfenyl bromide **2** on a 50–100 millimolar scale, giving a quantitative yield of crystalline product, consisted in conducting the bromination in carbon tetrachloride for 2–3 min at −10° and evaporating the solvent and excess reagent rapidly at 30° with a vacuum pump. The product was analytically pure without recrystallization, and could be kept for an extended time at the temperature of liquid nitrogen. The compound could be recovered from solutions in nonhydroxylic solvents, but was rapidly decomposed by traces of moisture or hydroxylic solvents; solutions prepared for optical rotatory measurements became more levorotatory on storage, probably because of moisture-

catalyzed decomposition. Although the sulfenyl bromide **2** and the disulfide **4** (a product of decomposition of **2**) can be differentiated from each other by the pattern



of acetyl-group signals in their n.m.r. spectra, a more convenient method for distinguishing **2** from **4** was by i.r. spectroscopy (see Fig. 1).

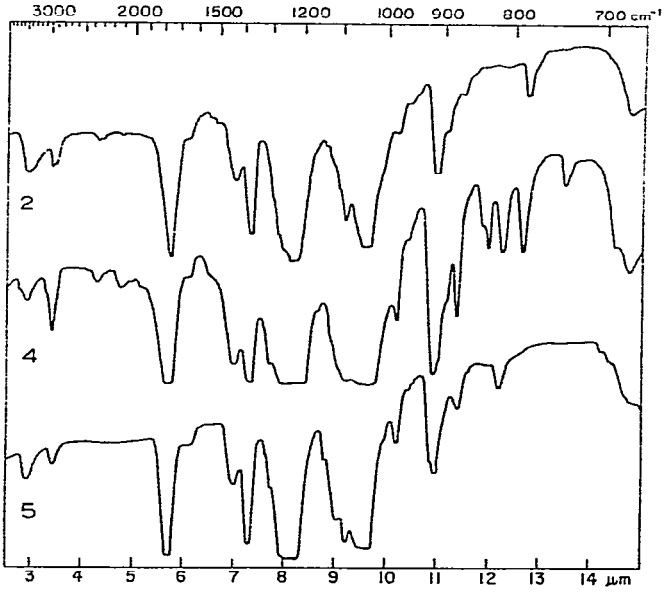


Fig. 1. The i.r. spectra (KBr pellet) of tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide (**2**), bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide (**4**), and bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide mono-oxide (**5**).

Quantitative conversion of the thiolacetate **1** into crystalline **2** could be effected under identical conditions by use of pure chloroform (free from water and ethanol) as the solvent; the product was identified as **2** by physical data and by treatment with cyclohexene to give the crystalline adduct, *trans*-2-bromo-1-(tetra-*O*-acetyl-β-D-glucopyranosylthio)cyclohexane[3,4]. Another route to the sulfenyl bromide **2** involves treatment of *tert*-butyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**6**) in carbon tetrachloride with a large excess of bromine for 1–2 min at −10°; the reaction gives crystalline **2** in quantitative yield. The product was characterized by physical data and by treatment with benzenethiol to give phenyl tetra-*O*-acetyl-β-D-glucopyranosyl disulfide[3,4].

Treatment of the thiolacetate **1**, the sulfenyl bromide **2**, or the 1-thioglycoside **6** in carbon tetrachloride with a large excess of bromine for an extended period (30–60 h) at room temperature gave the glycosyl bromide **3**, as indicated by n.m.r. spectroscopy and confirmed by isolation of **3**.

The course of the reaction of the thiolacetate **1** with a large excess of bromine at −10° was changed completely when reagent-grade chloroform (containing 0.75% of ethanol and, possibly, some water) was used as the solvent. After 2 min of reaction, there was formed a product, isolated crystalline in 79% yield, that was identical with a sample of bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide (**4**) that had been prepared from **1** by *S*-deacetylation followed by oxidative dimerization. The same product was also formed in high yield when the 1-thioglycoside **6** in carbon tetrachloride was treated dropwise with bromine during 3 h. It may be supposed that, in the latter reaction, bromine reacts with **6** to give the sulfenyl bromide **2**, which then reacts with excess 1-thioglycoside **6** to give the disulfide **4** and *tert*-butyl bromide. Such a reaction

$$2+6 \rightarrow 4+Me_3CBr$$

would be facilitated by the ease of heterolysis of the C-1–S bond in **6** during attack of the electrophilic sulfur atom of **2** on the nucleophilic sulfur atom of **6**. Support for this mechanism is provided by the observation that, in carbon tetrachloride, compound **2** reacts with **6** to give the disulfide **4** in high yield, and a volatile *tert*-butyl derivative is produced.

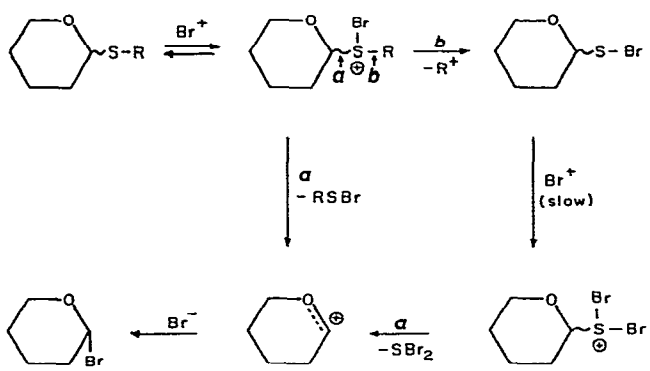
The sulfenyl bromide **2** was decomposed rapidly by dry ethanol, and the major product of reaction after 0.5 h at 25° was the disulfide **4**; none of the sulfenyl bromide **2** could be detected. Water, also, caused rapid decomposition of the sulfenyl bromide **2**, but in this case the principal crystalline product, isolated in 59% yield, was a compound having the empirical formula $C_{28}H_{38}O_{19}S_2$, corresponding to a mono-oxide of the disulfide **4**; compound **4** was obtained concurrently, in 6% yield. The mono-oxide migrated more slowly than **4** on t.l.c., and was absent from the product of reaction of **2** with dry ethanol. Separation of the mono-oxide from the disulfide **4** could be effected readily, because of the extremely low solubility of the former in cold ethanol. The n.m.r. spectra of **4** and the mono-oxide were very closely similar, and differed noticeably only in the pattern of the acetyl-group signals at high resolution; the two compounds were readily differentiated, however, by their i.r. spectra (see Fig. 1) and X-ray powder diffraction patterns.

Oxidation of the disulfide **4** with *m*-chloroperoxybenzoic acid gave a mono-oxide derivative identical with that obtained by treating **2** with water. An excess of the oxidant did not appear to cause oxidation to a more highly oxygenated derivative. Treatment of the sulfenyl bromide **2** with 95% ethanol gave a mixture of the mono-oxide and the disulfide **4**.

The mono-oxide may be formulated either as a sulfenic anhydride (R–S–O–S–R) or as a thiolsulfinate [R–S–S(O)–R]; the formulation R–O–S–S–R is excluded by the n.m.r. data. By analogy with work on simple compounds of related structure[7], the thiolsulfinate structure (**5**) may be considered the more probable, although this supposition has not been proved rigorously. A compound having structure **5** should be capable of existence in two diastereoisomeric forms. In various preparations of the mono-oxide, the crude product had a melting point much lower than that of the product after recrystallization from hot ethanol. Possibly, the crude product was a different structural isomer of the mono-oxide, or a mixture of diastereoisomers[7] of **5**.

Bromination of either the disulfide **4** or the mono-oxide **5** in carbon tetrachloride for 1 day at 35° gave the bromide **3** in high yield. The disulfide **4** was not decomposed under the brief conditions of reaction used for preparing the sulfenyl bromide **2** from **1** or **6**, and only slight conversion of **4** into **3** was observed in the experiment in which the 1-thioglycoside **6** was converted into **4** by slow addition of bromine during 3 h at 25°.

Formation of the sulfenyl bromide **2** from the *tert*-butyl thioglucoside **6**, as well as from the thiolacetate **1**, lends support to the mechanistic rationale (see Scheme I) originally proposed[1] for the formation of **2**, based on the heterolysis of an inter-



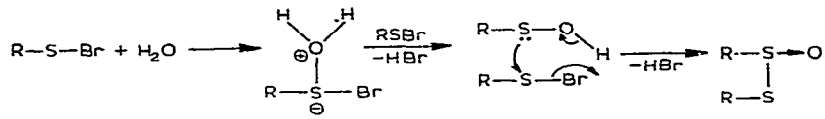
Scheme I

mediate bromosulfonium ion at point *b*, if R^+ is a cation more stable than the glycosyl cation that would result from scission at point *a*. The fact that the reaction requires more than one molecule of bromine per molecule suggests that the actual transition-state may involve an additional molecule of bromine that interacts with the bromosulfonium ion. Conversion of the sulfenyl bromide **2** into the bromide **3** is, predictably,

a slower process than formation of **2**, because the sulfur atom in **2** would be expected to be much less susceptible to attack by (positive) bromine than the sulfur atom in **1** or **6**.

The glycosylsulfenyl bromide **2** appears to be intermediate in stability between the extremely reactive alkylsulfenyl bromides[8] and the stable arylsulfenyl bromides[8].

A plausible route for formation of the mono-oxide **5** in the reaction of **2** with water would involve hydrolysis of one molecule of **2** to the sulfenic acid, followed



by reaction of the latter with a second molecule of **2** to give the thiolsulfinate. In the reaction with ethanol, it is conceivable that the observed disulfide **4** may arise by the reaction of a molecule of an ethyl sulfenate with a molecule of the sulfenyl bromide, with formation of ethyl hypobromite by sulfur–oxygen bond-cleavage, since the

$$R\text{–}S\text{–}Br + EtOH \xrightarrow[-HBr]{} R\text{–}S\text{–}OEt \xrightarrow[R\text{–}S\text{–}Br]{} R\text{–}S\text{–}S\text{–}R + EtOBr$$

Et–O bond would not be susceptible to abstraction of the Et group by bromide ion. These rationalizations have not been proved experimentally.

Reactions of the sulfenyl bromide **2** with thiols, amines, and alkenes are described in the accompanying paper[4].

EXPERIMENTAL

General. — Evaporations were performed under diminished pressure. Strict precautions were taken to prevent ingress of moisture in all of the bromination experiments. Specific rotations were measured in a 2-dm tube. Melting points were determined with a Thomas–Hoover Unimelt apparatus. I.r. spectra were recorded with a Perkin–Elmer "Infracord" Model 137 i.r. spectrophotometer, unless specified otherwise. N.m.r. spectra were recorded at 60 or 100 MHz with Varian A-60 or HA-100 n.m.r. spectrometers; chemical shifts refer to an internal standard of tetramethylsilane (τ = 10.00). Ultraviolet spectra were recorded with a Bausch and Lomb "Spectronic 505" recording spectrometer. Microanalyses were made by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities. T.l.c. was performed with Silica Gel G (E. Merck, Darmstadt, Germany), activated at 120°, as the adsorbent, 3:1 (v/v) dichloromethane–ether as the developer, and sulfuric acid as the indicator. Column chromatography was performed with Silica Gel Davison (60–200 mesh,

Davison Division of the W. R. Grace Co., Baltimore, Md.), activated at 120°, as the adsorbent, with 100 g of adsorbent per g of the mixture to be separated. Columns were packed by allowing a slurry of the adsorbent in the eluent (3:1 dichloromethane–ether) to settle under gravity, and elution was effected without application of pressure or suction. The reagent-grade chloroform (J. T. Baker Chemical Co., Phillipsburg, N. J.) used was stated to contain 0.75% of ethanol. Purified chloroform, free from ethanol and water, was obtained by passing reagent-grade chloroform through a column of neutral, Woelm alumina immediately before use. The petroleum ether used was a fraction having b.p. 60–110°.

*N.m.r. spectral study of the reaction of tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-*D*-glucopyranose* (**1**) *in carbon tetrachloride with bromine.* — A suspension of the thiol-acetate[9] **1** (126 mg) in carbon tetrachloride (1 ml) was prepared in an n.m.r. sample tube, and a small drop of tetramethylsilane was added. The spectrum at 60 MHz showed a 3-proton singlet at τ 7.59 (SAc), peaks (12 protons) at τ 7.92, 7.98, and 8.00 (OAc), and no signals below τ 4.5. From a stock solution of bromine (15.60 g; 5.0 ml) in carbon tetrachloride (20 ml) a 250-μl aliquot (corresponding to 3.1 moles of bromine per mole of **1**) was added by means of a syringe to the suspension of **1** at ~40°. The suspended material dissolved rapidly. A scan of the n.m.r. spectrum was initiated 60 sec after addition of the bromine, and was completed 100 sec afterwards. The spectrum showed no signals below τ 4.5, but the SAc signal had disappeared completely and a 3-proton singlet at τ 7.19 had appeared (acetyl bromide in carbon tetrachloride shows its proton signal at τ 7.19). A 12-proton multiplet was observed at τ ~7.9 (OAc). The spectrum was rescanned 200 sec after the addition of the bromine; this scan, completed 100 sec later, resembled the previous one, except that a low-intensity doublet at τ 3.33, having $J_{1,2}$ 4.0 Hz (H-1 of the glycosyl bromide **3**), was present. The latter signal increased in intensity with time, and, after 1 h, it had an integrated intensity of one proton (relative to the 12-proton signal at τ ~7.9). At this time, the spectrum was identical with that of the glycosyl bromide **3** in carbon tetrachloride, except for the additional 3-proton singlet at τ 7.19 (AcBr). The reaction solution was evaporated to dryness, and the residue was dissolved in carbon tetrachloride. The n.m.r. spectrum of the solution was unchanged, except that the signal at τ 7.19 had disappeared.

When the experiment was performed with a 1.5-molar excess of bromine, the spectrum indicated that some starting material **1** was present, even after 10–20 min of reaction.

*Preparation of tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide* (**2**). — *A. From* **1** *in carbon tetrachloride.* To a suspension of tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose[9] (**1**, 20.00 g, 49.2 mmoles) in anhydrous carbon tetrachloride (200 ml) cooled to about −10° was added a solution of bromine (9.0 ml, 176 mmoles) in carbon tetrachloride (40 ml) and the mixture was stirred for 2–3 min at about −10°. Volatile materials were then rapidly removed on a rotary evaporator at ~30°/< 10 torr, to give **2** as a pale-yellow, crystalline residue, yield 22.27 g (102%), m.p. 102–104°, $[\alpha]_D^{15}$ −66.7 ±1° (*c* 2.1, tetrahydrofuran) changing to −11.4 ±1° after 14 h; λ_{max}^{KBr}

(see Fig. 1) 5.72 (OAc), 11.20 μm (axial H at C-1), SAc absent[9]; n.m.r. data (100 MHz, chloroform-*d*): τ 4.55–5.02 (3-proton multiplet), 5.35 (1-proton multiplet) (H-1,2,3,4), τ 5.63–5.99 (2-proton multiplet, H-6), τ 6.14 (1-proton multiplet, H-5)[5], τ 7.90, 7.92, 7.97, 8.00 (12 protons, acetyls).

Anal. Calc. for $C_{14}H_{19}BrO_9S$: C, 37.93; H, 4.32; Br, 18.03; S, 7.23. Found: C, 37.99; H, 4.39; Br, 17.52; S, 7.51.

The product gave an X-ray powder diffraction pattern identical with that previously reported[1]. Rapid recrystallization of the product from carbon tetrachloride gave an almost quantitative recovery of **2**, having physical constants essentially identical with those of the material first isolated. T.l.c. of **2** showed a principal component having R_F 0.45 and minor components having R_F 0.76, 0.71, and 0.29, although none of these components could actually be attributed to **2** itself, because of the probability that **2** undergoes decomposition on the adsorbent.

Compound **2** prepared by the above procedure was used in all preparations described in this paper, unless stated otherwise.

B. From **1** *in purified chloroform.* A solution of the thiolacetate **1** (2.048 g, 5.04 mmoles) in purified chloroform (50 ml) was cooled to −10°, and a solution of bromine (1.5 ml, 29 mmoles) in purified chloroform (8.5 ml) was added. The mixture was kept for 1 min at −10°, and then evaporated rapidly at 30° to give a pale-yellow, crystalline residue; yield 2.153 g (96%), m.p. 103–105°, $[\alpha]_D^{19}$ −74 ±1° (*c* 2.2, chloroform), becoming more levorotatory after several hours. By mixed m.p., i.r. and n.m.r. spectra, and X-ray powder diffraction data, the product was identical with the sulfenyl bromide **2** prepared by procedure *A*.

A suspension of **2** (prepared in purified chloroform from 2.13 g of the thiolacetate **1**) in carbon tetrachloride (50 ml) was treated with cyclohexene (1 ml) in carbon tetrachloride (9 ml), and the mixture was kept for 1 h at 25°; it was then washed successively with water (100 ml), saturated aqueous sodium hydrogen carbonate solution (100 ml), and water (100 ml), dried (magnesium sulfate), and evaporated. The residual syrup was crystallized from ether–petroleum ether to give colorless, stout needles, yield 1.532 g (56%), m.p. 82–88°. Purification of the product by column chromatography gave pure *trans*-2-bromo-1-(tetra-*O*-acetyl-β-D-glucopyranosylthio)cyclohexane, m.p. 88–89° (identical with an authentic sample[3,4] by mixed m.p. and comparative i.r. and n.m.r. spectra), together with a small amount of the disulfide derivative **4**.

C. From tert-*butyl tetra*-O-*acetyl*-1-*thio*-β-D-*glucopyranoside*[5,10] (**6**) *in carbon tetrachloride.* To a solution of the 1-thioglycoside **6** (516 mg, 1.23 mmoles) in carbon tetrachloride (20 ml) at −10° was added bromine (0.75 ml, 15 mmoles); after 1.5 min at −10°, the mixture was rapidly evaporated at 30° to give the sulfenyl bromide **2** as a yellow, crystalline solid, yield 548 mg (101%), m.p. 97–99°. By comparative i.r. and n.m.r. spectra, and by X-ray powder diffraction data, this product was identical with **2** prepared by methods *A* or *B*.

To a suspension of the product (463 mg) in carbon tetrachloride (40 ml) was added a solution of benzenethiol (0.5 g) in carbon tetrachloride (9.5 ml), and the

mixture was kept for 1 h at 25°. The resulting solution was washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated to dryness, and the residue was crystallized from ethanol–petroleum ether to give phenyl tetra-*O*-acetyl-β-D-glucopyranosyl disulfide[3,4], yield 200 mg (34%), m.p. 123–125°, identical with an authentic sample[3,4] by mixed m.p., comparative i.r. and n.m.r. spectra, and X-ray powder diffraction data[4].

Bromination of thio derivatives **1**, **2**, *and* **6** *for an extended time. — A. Bromination of thioacetate* **1**. To a suspension of the thioacetate **1** (2.33 g, 5.73 mmoles) in carbon tetrachloride (60 ml) was added bromine (2 ml, ~39 mmoles) in carbon tetrachloride (8 ml), and the mixture was kept for 30 h at 25° and then evaporated to dryness. The product was crystallized from ether–petroleum ether to give tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**), yield 2.09 g (89%), m.p. 87–88°, indistinguishable from an authentic sample of **3** by mixed m.p., and by i.r. and n.m.r. spectra. T.l.c. of the mother liquors showed a single component, having chromatographic characteristics indistinguishable from those of **3**.

The preceding experiment was repeated, but with purified chloroform as the solvent. The results were identical with those given for the reaction in carbon tetrachloride, and the crystalline bromide **3** was isolated in 90% yield.

B. Bromination of sulfenyl bromide **2**. A suspension of **2** (2.62 mmoles, prepared from 1.065 g of thiolacetate **1**) in carbon tetrachloride (50 ml) was treated with bromine (2 ml, ~39 mmoles) in carbon tetrachloride (8 ml), and the mixture was kept for 30 h at 25°. The resultant, orange solution was evaporated to a syrup that was crystallized from ether–petroleum ether to give the bromide **3**, yield 492 mg (46%), m.p. 87–88°, indistinguishable from authentic **3** by mixed m.p. and by i.r. and n.m.r. spectra. T.l.c. of the mother liquors showed the presence of a major component having the mobility of **3**, and a minor component having R_F 0.45.

C. Bromination of 1-thioglycoside **6**. To a suspension of the 1-thioglycoside **6** (534 mg, 1.27 mmoles) in carbon tetrachloride (20 ml) was added bromine (1.5 ml, 29 mmoles). The resultant, clear solution was kept for 60 h at 25°, and evaporated to dryness; a solution of the resultant syrup in dichloromethane was washed with aqueous sodium hydrogen carbonate, dried (magnesium sulfate), decolorized with carbon, and evaporated to a syrup. Crystallization of the syrup from ether–petroleum ether gave the bromide **3**, yield 167 mg (32%), m.p. 82–85°, identical with an authentic sample of **3** by t.l.c. and i.r. and n.m.r. spectra. T.l.c. of the mother liquors indicated that **3** was the principal component; a minor component had R_F 0.46.

When the reaction was followed by n.m.r. spectroscopy at ~40°, the 9-proton signal at τ 8.61 for the *tert*-butyl group of **6** was absent 1 min after the addition of bromine, and the spectrum showed no signal below τ 4.5. A 9-proton signal at τ 8.19 was observed. After 14 h, the spectrum showed a 1-proton doublet at 3.27, $J_{1,2}$ 4.1 Hz, and was closely similar to that of the bromide **3**, except for the presence of the 9-proton singlet at τ 8.19.

*Preparation of bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide* (**4**). — The general procedure of Richtmyer, Carr, and Hudson[11] was used, except that the starting

material employed was tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (**1**, 10.05 g) instead of tetra-*O*-acetyl-β-D-glucopyranosyl ethylxanthate. The product was obtained as colorless needles, yield 8.014 g (89%), having m.p. 140–141°, $[\alpha]_D^{21}$ −157 ±0.5° (*c* 5.5, chloroform) [lit.[11] m.p. 142–143°, $[\alpha]_D^{20}$ −156° (chloroform)]; R_F 0.44; λ_{max}^{KBr} (see Fig. 1) 5.76 (OAc), 11.17 μm (axial H at C-1); λ_{max}^{EtOH} 250 (ε 450), 206 nm (900); n.m.r. data (100 MHz, chloroform-*d*): τ 4.61–5.01 (3-proton multiplet), 5.28–5.37 (1-proton multiplet) (H-1,2,3,4), τ 5.55–5.87 (8-peak multiplet, H-6), τ 6.20 (H-5), τ 8.85, 8.88, 8.96, and 8.98 (3-proton singlets, acetyls); X-ray powder diffraction data: 13.00 vs (1), 9.74 vw, 7.94 m, 7.44 vw, 6.98 w, 5.72 s (3), 5.02 m, 4.72 m, 4.08 s (2), 3.89 m, 3.54 w.

Anal. Calc. for $C_{28}H_{38}O_{18}S_2$: C, 46.28; H, 5.27; S, 8.82. Found: C, 46.22; H, 5.00; S, 8.64.

Formation of the disulfide **4** *by bromination of thiolacetate* **1** *in reagent-grade chloroform.* — A solution of **1** (1.16 g, 2.85 mmoles) in reagent-grade chloroform (8.5 ml) was cooled to about −10°, and a solution of bromine (1.5 ml, 29 mmoles) in reagent-grade chloroform (8.5 ml) was added. After 2 min at −10°, the solution was rapidly evaporated at 30°. Crystallization of the resultant syrup from ether–petroleum ether, and recrystallization from the same solvent mixture, gave the disulfide **4**, yield 0.82 g (79%), m.p. 142–143°, identical by mixed m.p., t.l.c., i.r. and n.m.r. spectra, and X-ray powder diffraction pattern with an authentic sample of **4**.

T.l.c. of the mother liquors revealed a principal component having the mobility of **4**, and traces of two additional components having the mobilities of the bromide **3** and the starting material **1**. In a repetition of the experiment, the yield of crystalline **4** was 77%.

Formation of the disulfide **4** *by slow bromination of the 1-thioglycoside* **6**. — Bromine (0.35 ml, ~7 mmoles) was added dropwise during 3 h to a solution of **6** (544 mg, 1.29 mmoles) in carbon tetrachloride (30 ml), and the reaction was monitored by t.l.c. At the end of the 3-h period, only a trace of **6** remained, and the major component corresponded to the disulfide **4**; a trace of a product having R_F 0.39 was also present. Evaporation of the solution, and crystallization of the residue from ether–petroleum ether, gave the disulfide **4**, yield 358 mg (76%), m.p. (one recrystallization) 140–141°, identical with authentic **4** by mixed m.p., i.r. and n.m.r. spectra, and X-ray powder diffraction pattern.

Fractional recrystallization of the mother liquors gave 13.4 mg (2.5%) of the starting material **6**.

Reaction of the sulfenyl bromide **2** *with 1-thioglycoside* **6** *to give the disulfide* **4**.— A suspension of **2** (1.151 g, 2.60 mmoles) in carbon tetrachloride (50 ml) was mixed with a solution of **6** (1.060 g 2.52 mmoles) in carbon tetrachloride (20 ml) and the mixture was shaken for 16 h at room temperature. The resultant, clear solution was washed successively with aqueous sodium hydrogen carbonate and water, dried (magnesium sulfate), and evaporated to dryness. Crystallization of the residue from ethanol–petroleum ether gave the disulfide **4**; yield (in three crops) 1.314 g (70%),

identical with an authentic sample by t.l.c., mixed m.p., i.r. and n.m.r. spectra, and X-ray powder diffraction pattern.

T.l.c. of the mother liquors showed a major component corresponding to **4**, and a minor component corresponding to **6**.

An aliquot of the reaction mixture after 16 h was examined by n.m.r. spectroscopy at 60 MHz. The 9-proton singlet at τ 8.61 ($SCMe_3$) present in the spectrum of the starting 1-thioglycoside **6** had diminished to low intensity, and a sharp singlet at τ 8.19, corresponding to *tert*-butyl bromide formed, was observed. The reaction mixture was evaporated, and the residue was dissolved in carbon tetrachloride. The signal at τ 8.19 (Me_3CBr) was no longer observable in the n.m.r. spectrum of this solution.

Reaction of the sulfenyl bromide **2** *with dry ethanol to give the disulfide* **4**. — Dry ethanol (50 ml) was added to the sulfenyl bromide **2** (prepared from 1.90 g of **1**), and the yellow reaction-mixture was kept for 20–30 min at room temperature; white needles were then present, and t.l.c. indicated the presence of a single component, R_F 0.53, corresponding to the disulfide **4**. No component having R_F 0.39 (corresponding to the oxide **5**) was detected. To the reaction mixture was added 50 ml of saturated aqueous sodium hydrogen carbonate solution, and the mixture was concentrated to remove ethanol. The resulting aqueous suspension was extracted with two 50 ml portions of dichloromethane, and the extracts were combined, washed with water, dried (magnesium sulfate), and evaporated. Crystallization of the residue from ethanol gave the disulfide **4**, yield 847 mg (50%), m.p. (after recrystallization from ethanol) 141–142°, identical with authentic **4** by t.l.c. and X-ray powder diffraction pattern.

T.l.c. of the mother liquors showed a major component having the mobility of the disulfide **4**, and traces of components having R_F 0.77 and 0.12. No component corresponding to the oxide **5** (R_F 0.39) was present.

The experiment was repeated with sulfenyl bromide **2** (from 2.32 g of **1**) in dry ethanol (50 ml). After 20 min, the white needles of **4** that had formed were filtered off; yield 548 mg (26%), m.p. 142–143°. The filtrate was collected in a flask containing *α*-toluenethiol (1 ml) in dry ethanol (10 ml). After 10 min at 25°, t.l.c. of the mixture showed no component having the mobility (R_F 0.88) of benzyl tetra-*O*-acetyl-*β*-D-glucopyranosyl disulfide[3,4], indicating that the sulfenyl bromide **2** had been completely decomposed by ethanol within 20 min.

*Bis(tetra-*O*-acetyl-β-*D*-glucopyranosyl) disulfide mono-oxide* (**5**) *by oxidation of disulfide* **4** *with* m-*chloroperoxybenzoic acid*. — A solution of the disulfide **4** (264 mg, 360 *μ*moles) and *m*-chloroperoxybenzoic acid (49 mg, 80% pure by g.l.c., 230 *μ*moles of oxidant) in chloroform (50 ml) was kept at 25°. After 40 min, t.l.c. indicated the presence of two components, R_F 0.51 and 0.39, in approximately equal amounts; no change was noted after 4 h. Additional oxidant (~50 mg, 230 *μ*moles) was added, and after 1 h, t.l.c. indicated no significant change in the mixture; it was therefore washed successively with aqueous sodium hydrogen carbonate solution (50 ml) and water (50 ml), dried (magnesium sulfate), and evaporated to dryness, and the residue was triturated with ethanol (10 ml), whereupon the mono-oxide **5** crystallized as

colorless, microscopic needles, yield 110 mg (41%), m.p. 150–151°. Recrystallization from hot ethanol gave pure **5**, m.p. 152.5–153°, $[\alpha]_D^{22}$ −52.1 ±1° (*c* 2.5 chloroform); R_F 0.39; λ_{max}^{KBr} (see Fig. 1) 5.72 μm (OAc); n.m.r. data (100 MHz, chloroform-*d*): τ 4.36–5.18 (multiplets, H-1,2,3,4), τ ~5.76 (multiplet, H-6), τ ~6.17 (multiplet, H-5), τ 7.90, 7.95, 7.96, and 7.98 (singlets, acetyls); X-ray powder diffraction data: 11.86 s (2,2), 10.45 s (2,2), 7.68 s (2,2), 5.43 s (3,3), 5.07 m, 4.95 s (3,3), 4.67 vw, 4.44 vs (1), 4.29 w.

The product **5** had extremely low solubility in cold ethanol, in contrast to the disulfide **4**, which was moderately soluble; the two compounds were readily separable because of this difference.

Reaction of the sulfenyl bromide **2** *with water to give the disulfide mono-oxide* **5**. — A suspension of **2** (prepared from 1.043 g of **1**) in carbon tetrachloride (40 ml) was shaken with water (3 ml) for 40 min at 25°. The solvents were evaporated from the resultant white suspension, the residue was dissolved in dichloromethane (100 ml), and the solution was washed successively with saturated aqueous sodium hydrogen carbonate solution and water, dried (magnesium sulfate), and evaporated to a syrup. Addition of ethanol to the syrup caused immediate crystallization, to give the oxide **5**, yield 560 mg (59%), m.p. 151°, identical with an authentic sample by t.l.c., i.r. and n.m.r. spectra, and X-ray powder diffraction data.

T.l.c. of the mother liquors showed that essentially all of the oxide **5** had been removed by crystallization, but a component having the mobility (R_F 0.51) of the disulfide **4** was present. Column-chromatographic fractionation of the mother liquors gave the disulfide **4**, yield 60 mg (6%), m.p. 140°, identical with an authentic sample by t.l.c., i.r. and n.m.r. spectra, and X-ray powder diffraction pattern.

Reaction of the sulfenyl bromide **2** *with 95% ethanol to give the disulfide* **4** *and the mono-oxide* **5**. — To the sulfenyl bromide **2** (prepared from 2.317 g of **1**) was added 95% ethanol (40 ml) at room temperature. The mixture became clear after a few min, and then became turbid and deposited white, fluffy needles. After 8 h, the reaction mixture was processed as in the preceding experiment, to give the mono-oxide **5**, yield 1.239 g (59%), m.p. (after recrystallization from hot ethanol) 151–152°, identical with an authentic sample by mixed m.p., i.r. and n.m.r. spectra, and X-ray powder diffraction pattern.

The mother liquors from the reaction contained a single component, chromatographically identical with the disulfide **4**; t.l.c. of the initial reaction-product indicated that **4** and **5** were present in approximately equal amounts.

The foregoing experiment and the preceding one were repeated several times, either by the procedure described or by directly filtering off the product that crystallized from the reaction mixture. Frequently, the ethanol-insoluble product initially obtained had a melting point lower than that of the material obtained after recrystallization from hot ethanol; values of 101–103°, 111–113°, 113–114°, 132–134°, and 138–139° were observed in different experiments. In each instance, the product was free from the disulfide **4** (t.l.c.), and after refluxing with ethanol, recrystallization

gave the oxide **5** having m.p. 152.5–153°, with recoveries of ~60%. A dimorph of **5**, having m.p. 157–158°, was also encountered.

Bromination of the disulfide **4** *to give the bromide* **3**. — To a suspension of **4** (196 mg, 270 μmoles) in carbon tetrachloride (30 ml) was added bromine (1.5 ml, ~29 mmoles), and the resultant solution was kept for 23 h at ~35°. The solution was evaporated to dryness at 30°, carbon tetrachloride was added to, and evaporated from, the residue, and the latter was dissolved in dry chloroform-*d*. The n.m.r. spectrum of the solution was identical with that[6] of the bromide **3**, and the integrated intensities of the H-1 signal (τ 3.25, $J_{1,2}$ 4.0 Hz) and of the acetyl-group signals were in the ratio 1:12. T.l.c. of the solution showed a principal component (R_F 0.80) chromatographically indistinguishable from **3**; very minor side-products, having R_F 0.42, 0.31, 0.29, 0.20, and 0.1, were also present.

Bromination of the mono-oxide **5** *to give the bromide* **3**. — The mono-oxide **5** (133 mg, 180 μmoles) was treated with bromine (1.5 ml, ~29 mmoles) by exactly the procedure used in the preceding experiment, and identical results were obtained.

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