Sulfoxide and Sulfone Derivatives of D-Xylothiopyranose[1]

ROY L. WHISTLER, T. VAN ES, AND R. M. ROWELL

Department of Biochemistry, Purdue University, Lafayette, Indiana

Received March 25, 1965

Oxidation of the tetraacetates of α- and β-D-xylothiopyranose with hydrogen peroxide in acetic acid produces the corresponding sulfones. Milder oxidation of methyl 2,3,4-tri-*O*-acetyl-α-and -β-D-xylothiopyranosides with sodium metaperiodate in methanol and water gives rise to the α and β diastereosomeric sulfoxides. Further oxidation of these intermediate sulfoxides with hydrogen peroxide in acetic acid yields the sulfones.

In the characterization of sugars with sulfur as the ring hetero atom, an overoxidation with sodium metaperiodate is observed.[2-4] This is due, mainly, to the oxidation of the heterocyclic sulfur atom to the intermediate sulfoxides, sulfone, and, probably, finally to the sulfonic acid if the reaction is continued for a long period of time.

The first sulfone to be prepared in the sugar series was made by Wrede and Zimmermann[5] in 1925. They oxidized the acetylated bis(β-D-glucopyranosyl) sulfide with potassium permanganate in acetic acid and obtained the bis(β-D-glucopyranosyl) sulfone.

Clingman and Richtmyer[6] showed that an underivatized thioglycoside could be oxidized to a sulfone with hydrogen peroxide in acetic acid without modification of the free hydroxyl groups. They obtained the sulfones of *p*-tolyl 1-thio-β-D-glucopyranoside and *p*-tolyl 1-thio-β-D-galactopyranoside.

Another class of sugar sulfones is produced by the oxidation of dithiomercaptals with peracids. Ammonium hydroxide degradation of these disulfone acetals is a general method for the conversion of an aldose to its next lower homolog.[7]

Micheel and Schmitz[8] described the first sugar sulfoxide, ethyl α-D-glucopyranosyl sulfoxide, obtained by oxidation of ethyl 1-thio-α-D-glucopyranoside with dilute aqueous hydrogen peroxide.

Other sugar sulfones and sulfoxides have been obtained by oxidation of 1-thioglycosides mostly from acetylated phenyl or acetylated substituted phenyl 1-thioglycosides.[9-15]

Sulfoxides and sulfones of sugars with sulfur in other positions than the glycosyl position have not been prepared.

To clarify the course of the oxidation of sulfur ring sugars, α and β anomers of fully acetylated D-xylothiopyranose and methyl D-xylothiopyranoside have been examined under conditions leading normally to either the sulfoxides or the sulfones.

Both the α and β anomers of 1,2,3,4-tetra-*O*-acetyl-D-xylothiopyranose are easily oxidized with hydrogen peroxide in glacial acetic acid at 25° to the sulfone stage. Under other mild oxidative conditions expected to lead normally to sulfoxides, such as with hydrogen peroxide in acetone,[16] chromic acid in pyridine,[17] or sodium metaperiodate in methanol–water,[18] only starting material is recovered (see Table I).

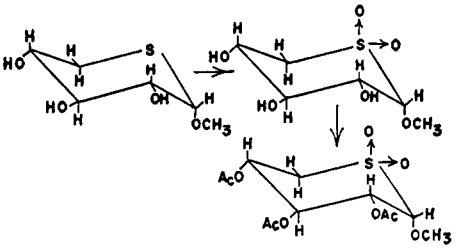

Figure 1.

Oxidation of either the α or β anomer of methyl 2,3,4-tri-*O*-acetyl-D-xylothiopyranoside with hydrogen peroxide in glacial acetic acid at 25° leads to the crystalline sulfone. Milder oxidation with metaperiodate in methanol and water produces the sulfoxides. The α-D anomer VII yields mainly one diastereoisomeric sulfoxide IX of $[\alpha]_D$ +134° and a trace of what seems to be the second isomer which can be separated by thin layer chromatography on silica gel G. Further oxidation of the principal sulfoxide or direct oxidation of methyl 2,3,4-tri-*O*-acetyl-α-D-xylothiopyranoside with hydrogen peroxide in glacial acetic acid yields the crystalline sulfone VIII. This sulfone can also be obtained directly by hydrogen peroxide oxidation of methyl α-D-xylothiopyranoside followed by acetylation (see Figure 1).

Methyl 2,3,4-tri-*O*-acetyl-β-D-xylothiopyranoside (III), on oxidation with hydrogen peroxide in glacial acetic acid, also yields the expected sulfone (IV). Milder oxidation, however, with metaperiodate in methanol–water produces a mixture of the diastereoisomeric sulfoxides. The isomers are separated by chromatography on silica gel with chloroform–acetone as irrigant. Both are easily crystallized. One has a specific optical rotation in chloroform of $[\alpha]_D$ +27.2° and is designated as the α form V while the other with a specific optical rotation of $[\alpha]_D$ −133° is designated as the β form VI. The α and β forms appear to be produced in a ratio of about 3:1 as estimated visually by comparison of spot intensities of isomers separated by thin layer chromatography. Oxidation of each isomer with hydrogen peroxide in glacial acetic acid produces the sulfone IV, which also is obtained by direct hydrogen peroxide oxidation of the acetylated methyl β-D-xylothiopyranoside. (See Figure 2.)

(1) Journal Paper No. 2526 of the Purdue Agricultural Experiment Station, Lafayette, Ind. Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) R. L. Whistler and M. S. Feather, *Tetrahedron Letters*, **No. 15**, 667 (1962).
(3) D. L. Ingles and R. L. Whistler, *J. Org. Chem.*, **27**, 3896 (1962).
(4) R. W. Whistler and R. M. Rowell, *ibid.*, **29**, 1259 (1964).
(5) F. Wrede and W. Zimmermann, *Z. Physiol. Chem.*, **148**, 65 (1925).
(6) A. L. Clingman and N. K. Richtmyer, *J. Org. Chem.*, **29**, 1782 (1964).
(7) D. L. MacDonald, *Methods Carbohydrate Chem.*, **1**, 73 (1962).
(8) F. Micheel and H. Schmitz, *Ber.*, **72**, 992 (1939).
(9) H. Rheinboldt and E. Giesbrecht, *J. Am. Chem. Soc.*, **68**, 973 (1946).
(10) W. A. Bonner and R. W. Drisko, *ibid.*, **70**, 2435 (1948).
(11) B. Helferich and H. Schirp, *Ber.*, **86**, 547 (1953).
(12) G. Wagner and H. Kühmstedt, *Naturwissenschaften*, **46**, 425 (1959).
(13) G. Wagner and H. Kühmstedt, *Arch. Pharm.*, **294**, 147 (1961).
(14) G. Wagner and H. Pischel, *ibid.*, **296**, 576 (1963).
(15) G. Wagner and M. Wagler, *ibid.*, **297**, 206, 348, 358 (1964).
(16) S. Hunig and O. Boes, *Ann.*, **579**, 23 (1953).
(17) D. Edwards and J. B. Stenlake, *J. Chem. Soc.*, 3272 (1954).
(18) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1964).

TABLE I
PROPERTIES OF OXIDATION PRODUCTS

Compd.	Unoxidized		α-Sulfoxide		β-Sulfoxide		Sulfone	
	M.p., °C.	[α]D, deg.	M.p., °C.	[α]D, deg.	M.p., °C.	[α]D, deg.	M.p., °C.	[α]D, deg.
1,2,3,4-Tetra-*O*-acetyl-α-D-xylothiopyranose	100	+219	None		None		131	+62
1,2,3,4-Tetra-*O*-acetyl-β-D-xylothiopyranose	158	−49	None		None		194	−59
Methyl 2,3,4-tri-O-acetyl-β-D-xylothiopyranoside	122	−70.6	150	+27.2	206	−133	176	−69.3
Methyl 2,3,4-tri-*O*-acetyl-α-D-xylothiopyranoside	Sirup	+228	Trace		138	+134	148	+86

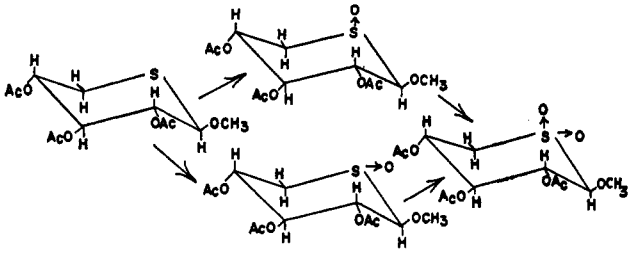

Figure 2.

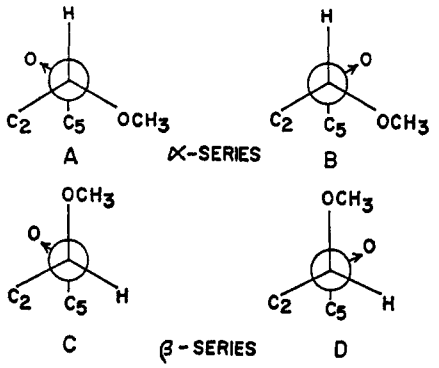

Figure 3.

While it is not possible from this work to assign configurations to the sulfoxides, a postulation of structure might logically develop from consideration of the relative yields of isomers obtained. From methyl α-D-xylothiopyranoside acetate, one isomeric sulfoxide is obtained in large yield while the other diastereoisomer is produced in very small amounts. Consideration of the relative disposition of the nonbonding orbitals of the glycosidic oxygen and sulfoxide oxygen might suggest greater ease of formation and stability of structure A compared to structure B leading to a predominance of A. The more readily formed structure would therefore have the sulfoxide oxygen somewhat in the *endo* form while the less easily formed structure B would have the oxygen in the more *exo* position to the sugar ring. In methyl β-D-xylothiopyranoside acetate, either sulfoxide oxygen is about equally *gauche* with the glycosidic oxygen, as shown in C and D, and both are obtained. Some additional stability might be reasoned here for the *exo* form D in so far as the sulfoxide oxygen would bisect the hydrogens on C-5. (See Figure 3.)

Experimental

Analytical Methods.—Sulfoxides were separated by chromatography on silica gel[19] columns, 2.8 × 60 cm. Two grams of the sulfoxide mixture in 10 ml. of chloroform–acetone (6:1 v./v.) was placed on the column and then irrigated with the same chloroform–acetone mixture. Purity of crystalline products was determined by thin layer chromatography on silica gel G[20] coated microscope slides irrigated with chloroform–acetone (12:1 v./v.). R_f values are reported in this irrigant. Location of components was obtained by spraying with 5% sulfuric acid in ethanol and charring until permanent spots were visible. A spray reagent of hydriodic acid specifically sensitive to sulfoxides[21] was used in the preparation and identification of the sugar sulfoxides. Acetyl groups were detected by a spray reagent of ferric hydroxamate.[22]

1,2,3,4-Tetra-*O*-acetyl-α-D-xylothiopyranose Sulfone (I).—To a mixture of 20 ml. of glacial acetic acid and 8 ml. of 30% hydrogen peroxide was added 2 g. of 1,2,3,4-tetra-*O*-acetyl-α-D-xylothiopyranose.[23] The reaction mixture was allowed to stand at 25° for 48 hr., then diluted with 100 ml. of distilled water. The solution was extracted three times with 50-ml. portions of chloroform and the combined chloroform extracts were washed with cold 5% sodium bicarbonate solution followed by two water washings. After drying the chloroform solution over sodium sulfate, it was concentrated to dryness and compound I was crystallized from dilute alcohol, yield 1.70 g., m.p. 130–131°, $[\alpha]^{20}D$ +62° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{13}H_{18}O_{10}S$: C, 42.6; H, 4.92. Found: C, 42.9; H, 4.95.

Compound I, dissolved in carbon tetrachloride, showed peaks in the infrared spectrum at 1330 and 1145 cm.$^{-1}$ which are characteristic for asymmetric and symmetric sulfone stretching vibrations in C–SO_2–C-type compounds.[24]

1,2,3,4-Tetra-*O*-acetyl-β-D-xylothiopyranose Sulfone (II).—To a mixture of 20 ml. of glacial acetic acid and 8 ml. of 30% hydrogen peroxide was added 2 g. of 1,2,3,4-tetra-*O*-acetyl-β-D-xylothiopyranose.[23] The reaction mixture was allowed to stand at 25° for 48 hr., then diluted with 100 ml. of distilled water. Compound II crystallized from the aqueous mixture and was removed by filtration. Recrystallization from ethanol gave 1.60 g., m.p. 193–94°, $[\alpha]^{20}D$ −59° (*c* 1.0, chloroform). It also showed infrared bands at 1330 and 1145 cm.$^{-1}$.

Anal. Found: C, 42.6; H, 4.72.

Methyl 2,3,4-tri-*O*-acetyl-β-D-xylothiopyranoside (III) was prepared by the method of Whistler and Van Es.[25] The R_f value was 0.71.

Methyl 2,3,4-Tri-*O*-acetyl-β-D-xylothiopyranoside Sulfone (IV).—To a mixture of 10 ml. of glacial acetic acid and 4 ml. of 30% hydrogen peroxide was added 1 g. of the triacetate III. The mixture was allowed to stand at 25° for 48 hr. and diluted with 75 ml. of distilled water. Compound IV crystallized from the solution and was removed by filtration. Recrystallization from ethyl acetate solution by addition of hexane yielded 0.91 g., m.p. 176°, $[\alpha]^{21}D$ −69.3° (*c* 1.17, chloroform), R_f 0.46.

Anal. Calcd. for $C_{12}H_{18}O_9S$: C, 42.6; H, 5.33; S, 9.47. Found: C, 42.7; H, 5.21; S, 9.55.

Methyl 2,3,4-Tri-*O*-acetyl-β-D-xylothiopyranoside α- and β-Sulfoxides (V and VI).—To 24 ml. of methanol was added 1.12 g. of compound III and the solution was cooled to 0°. To this was added 0.86 g. of sodium metaperiodate dissolved in 6 ml. of distilled water. The mixture was stirred at 5° for 48 hr. followed by dilution with 50 ml. of distilled water and worked up as de-

(19) J. T. Baker Chemical Co., Phillipsburg, N. J.

(20) Brinkmann Instruments Inc., Westbury, N. Y. 11590.

(21) J. F. Thompson, W. N. Arnold, and C. J. Morris, *Nature*, **197**, 380 (1963).

(22) M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **40**, 1043 (1962).

(23) J. C. P. Schwarz and K. C. Yule, *Proc. Chem. Soc.*, 417 (1961).

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

(25) R. L. Whistler and T. Van Es, *J. Org. Chem.*, **28**, 2303 (1963).

scribed for I. The evaporated residue was crystallized from a mixture of ethyl acetate–hexane to give 0.87 g. Thin layer chromatography showed that the crystalline material obtained was composed of three different compounds. The fastest moving component was unreacted starting material, R_f 0.71. The other two components, R_f 0.28 and 0.18, were separated by column chromatographic fractionation as described earlier. The compound V, of R_f 0.28 from the chromatographic column and crystallized from ethyl acetate on addition of hexane, had m.p. 149–150°, $[\alpha]^{24}D$ +27.2° (*c* 1.95, in chloroform).

Anal. Calcd. for $C_{12}H_{18}O_8S$: C, 44.7; H, 5.59; S, 9.94. Found: C, 44.4; H, 5.54; S, 9.68.

The compound VI of R_f 0.18 on similar crystallization had m.p. 203°, $[\alpha]^{24}D$ −133° (*c* 2.1, chloroform).

Anal. Found: C, 44.9; H, 5.55; S, 9.63.

Both sulfoxides showed intensification of the peak at 1040 cm.$^{-1}$ due to the C–SO–C group.[24]

To 250 mg. of each sulfoxide were added 3 ml. of glacial acetic acid and 0.5 ml. of 30% hydrogen peroxide and the oxidation was allowed to continue at 25° for 48 hr. On dilution with 15 ml. of distilled water, each gave crystals of sulfone IV, m.p. 193–194°, R_f 0.46.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranoside (VII).—To 40 ml. of dry pyridine was added 6 g. of methyl α-D-xylothiopyranoside[3] and to this solution, cooled to 0°, was added slowly 30 ml. of acetic anhydride. After standing at 25° for 24 hr. it was poured into 500 ml. of ice and water. The water solution was extracted four times with 100-ml. portions of chloroform and the combined extracts were washed sequentially with bicarbonate solution, a dilute copper sulfate solution, and finally with water. The chloroform was dried over sodium sulfate and removed under reduced pressure. The sirup obtained (7.8 g.) did not crystallize, $[\alpha]^{20}D$ +228° (*c* 1.0, chloroform), R_f 0.71.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranoside Sulfone (VIII).—To a mixture of 10 ml. of glacial acetic acid and 4 ml. of 30% hydrogen peroxide was added 1 g. of the triacetate VII. The mixture was allowed to stand at 25° for 48 hr., then diluted with 75 ml. of distilled water, and worked up as described for I. Crystallization of the residue from water gave 0.95 g., m.p. 147–148°, $[\alpha]^{20}D$ +86° (*c* 1.0, chloroform), R_f 0.64.

Anal. Calcd. for $C_{12}H_{18}O_9S$: C, 42.6; H, 5.32; OCH_3, 9.16. Found: C, 42.7; H, 5.00; OCH_3, 9.38.

The sulfone showed infrared bands at 1330 and 1145 cm.$^{-1}$.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranoside Sulfoxide (IX).—To 7 ml. of methanol was added 0.56 g. of compound VII and the solution was cooled to 0°. To this was added a solution to 0.43 g. of sodium metaperiodate in 3 ml. of distilled water. The mixture was stirred at 5° for 48 hr. followed by dilution with 30 ml. of distilled water and was worked up as described for compound I. The evaporated residue was crystallized from ethyl acetate–hexane to give 0.32 g., m.p. 137–138°, $[\alpha]^{20}D$ +134° (*c* 1.0, chloroform), R_f 0.27.

Anal. Calcd. for $C_{12}H_{18}O_8S$: C, 44.7; H, 5.59; OCH_3, 9.62. Found: C, 44.8; H, 5.42; OCH_3, 9.63.

The sulfoxide showed infrared absorption at 1040 cm.$^{-1}$.

To 3 ml. of glacial acetic acid and 0.5 ml. of3 0% hydrogen peroxide was added 250 mg. of IX. The solution was allowed to stand at 25° for 48 hr., diluted with 15 ml. of distilled water, and worked up as described for compound II. Crystallization from water gave the sulfone VIII, m.p. 147°, R_f 0.64.

Methyl α-D-Xylothiopyranoside Sulfone (X).—To 6 ml. of glacial acetic acid and 2 ml. of 30% hydrogen peroxide was added 0.79 g. of methyl α-D-xylothiopyranoside.[3] The mixture was allowed to stand at 25° for 1 week. Evaporation under reduced pressure gave a sirup which was chromatographically pure and had infrared peaks at 1330 and 1145 cm.$^{-1}$. Acetylation with acetic anhydride in pyridine gave the known acetylated sulfone VIII.

Acknowledgment.—The authors gratefully acknowledge Grant No. RO1 Am 06782-03 MCHA from the Department of Health, Education, and Welfare which helped support this work.

1,6-Anhydro-5,6-dideoxy-6-mercapto-β-D-*xylo*-hexofuranose[1]

ROY L. WHISTLER AND BRANKO URBAS

Department of Biochemistry, Purdue University, Lafayette, Indiana

Received April 1, 1965

5,6-Dideoxy-6-thioacetyl-D-*xylo*-hexofuranose is prepared from 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose by tosylation and displacement of the tosyloxy group with thioacetate. Hydrolysis removes the isopropylidene group. Extended treatment of this compound in acidic methanol or acidic water leads to the title compound, a cyclic system formed by nucleophilic displacement of the conjugate acid group at C-1 with attachment of the sulfur from C-6.

Experience has shown that sulfur, when located as a thiol on either C-4 or C-5 of a sugar, preferentially enters the ring under normal glycoside-forming conditions in acidic methanol.[2] It is interesting that this preference to react with the carbonyl function and to participate as the ring hetero atom persists even when the position of sulfur is on C-4, and leads to selective formation of the furanose over the normally expected pyranose ring.[3]

The high reactivity of acidic alkyl mercaptans with sugar carbonyl functions is well known from the formation of dialkyl dithiols. Under the same acidic conditions alcohols form glycosides. Preferential participation of a thiol group at C-4 of an aldose to give a five-membered ring under normal Fischer glycoside-forming conditions is facilitated by the ease with which sulfur forms smaller bond angles than oxygen.

In examining a further aspect of the introduction of sulfur into sugar rings, an initial exploration has been made of the possibility of introducing sulfur into a seven membered sugar ring. Seven-membered rings are not easily formed with oxygen and do not occur in detectable amounts under normal Fischer glycoside-forming conditions. A seven-membered ring containing sulfur might be more stable than an oxygen-containing seven-membered ring owing to the somewhat greater flexibility of sulfur bond angles.

This laboratory recently found a route to the preparation of 5-deoxy-D-*xylo*-hexose.[4] Hence it was of interest to prepare 5,6-dideoxy-6-thioacetyl-D-*xylo*-hexofuranose to see whether this sugar, with the formation of the normal pyranose ring blocked, would form the unstable furanose ring on oxygen or the normally still less stable seven-membered ring on sulfur.

(1) Journal Paper No. 2525 of the Purdue Agricultural Experiment Station, Lafayette, Ind.

(2) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962).

(3) R. L. Whistler, W. E. Dick, T. R. Ingle, R. M. Rowell, and B. Urbas, *J. Org. Chem.*, **29**, 3723 (1964).

(4) R. E. Gramera, T. R. Ingle, and R. L. Whistler, *ibid.*, **29**, 2074 (1964).