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4-(D-*arabino*-TETRAHYDROXYBUTYL)-4-THIAZOLINE-2-THIONE. SYNTHESIS OF OPTICAL ISOMERS AND ANALOGS

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ABSTRACT

The previously reported[6], unequivocal synthesis of the title compound (**5a**) afforded a general method for the preparation of 4-substituted 4-thiazoline-2-thiones derived from fully acetylated α-halo ketoses. Such use of the α-halo ketoses (**1b**) or (**2b**) (as outlined in Method I of the Scheme) led to the crystalline L enantiomorph (**5b**) that, on cocrystallization with **5a**, gave the DL form (**5c**). By use of the α-bromo ketoses (**1d–1f**), further application of the method yielded amorphous, highly soluble, D-*xylo*, L-*xylo* (crude), and D-*gluco* analogs **5d–5f**, respectively. A *galacto*-1,4-bis-(4-thiazoline-2-thione) analog (**5g**), similarly obtained from the α-bromo ketose (**1g**), was crystalline, high-melting, and highly insoluble. By a modification of the procedure (Method II), treatment of the α-bromo ketoses (**1h–1i**) with the dithiocarbamic acid salts, derived from carbon disulfide and methylamine or 4-aminobutyric acid, led to the crystalline 4-thiazoline-2-thiones (**5h–5i**), respectively, that are also substituted at the *N*-hetero atom. Compounds intermediate in these syntheses are reported.

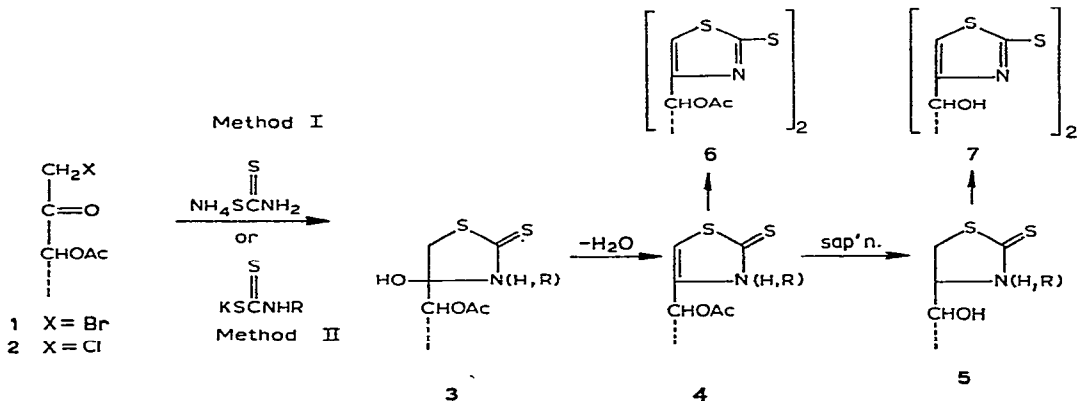
INTRODUCTION

The title compound (**5a**) was first reported by Zemplén *et al.*[1] to be isolable in a trace amount from the reaction of D-fructose with thiocyanic acid in hydrochloric acid solution. The major product obtained was shown to have an oxazolidine-2-thione structure fused to a pyranoid ring. Analogous oxazolidines were isolated[2–4] on similar treatment of L-arabinose, D-galactose, D-glucose, D-lyxose, D-mannose, D-ribose, and D-xylose. A ketose, D-fructose, was the only sugar of the series that was reported to yield a 4-thiazoline-2-thione when treated according to this procedure.

Recently, Jochims *et al.*[4,5] have proposed, on the basis of n.m.r. spectroscopic data, the structure now assigned to the title compound (**5a**). In their study, **5a** was obtained from the reaction of 2-amino-2-deoxy-D-glucose with carbon disulfide, *via* an intermediate 5-hydroxythiazolidine-2-thione that was subsequently dehydrated by refluxing for 16 h in pyridine. The reaction of α-amino carbonyl derivatives with carbon disulfide to form the new class of compounds, 5-hydroxythiazolidine-2-thiones, was reported to be general. Other 4-thiazoline-2-thiones derived from carbohydrates have, however, not yet been reported.

In an independent study, the structure of the title compound (**5a**) was also

determined[6] by degradation to known derivatives and by an unequivocal synthesis. By use of the latter synthesis, as outlined in Method I of the Scheme, **5a** was obtained from the reaction of 3,4,5,6-tetra-*O*-acetyl-1-bromo-1-deoxy-D-*arabino*-hexulose (**1a**) with ammonium dithiocarbamate, *via* a 4-hydroxythiazolidine-2-thione intermediate **3a**. Ready dehydration of **3a** to **4a**, followed by removal of the *O*-acetyl groups, afforded the title compound (**5a**). Earlier literature also reported[7,8] an



a D-*arabino*
b L-*arabino*
c DL-*arabino*
d D-*xylo*
e L-*xylo*
f D-*gluco*
g *galacto*-1,4-bis
h D-*arabino*; R = Me
i L-*arabino*; R = $(CH_2)_3CO_2H$

SCHEME

The series **a**–**e**, **h**, and **i** have a tetrahydroxy(or acetoxy)butyl chain, the series **f** has a pentahydroxy (or acetoxy)pentyl chain, and the series **g** has a 1,2,3,4-tetrahydroxy(or acetoxy)butane-1,4-diyl chain

extension of the synthesis by a modification of the procedure. By the latter route, treatment of an α-halo ketone with a dithiocarbamic acid salt (derived from carbon disulfide and an alkyl- or arylamine, or an amino acid) gave 4-thiazoline-2-thiones substituted at the *N*-hetero atom. It appeared probable that these sequences of reactions (*i.e.*, as outlined in Methods I and II) could be used as a procedure of significant scope for the preparation of 4-thiazoline-2-thiones from carbohydrates. The present article reports application of these methods to preparation of the optical isomers, and certain analogs, of the title compound (**5a**).

The unequivocal synthesis[6] of **5a** largely provided a parallel route to the enantiomorph (**5b**) by known methods of carbohydrate chemistry. The starting point for the preparation of **5b** was L-arabinose. Oxidation with bromine by the method of Fieser *et al.*[9], and isolation of the product from isopropyl alcohol, afforded L-arabinono-1,4-lactone (in 89% yield). Addition of the lactone to methanolic potassium hydroxide[10] gave potassium L-arabinonate (83%); this was acetylated with acetic anhydride and hydrogen chloride to yield tetra-*O*-acetyl-L-arabinonic acid[11] (54%). Thionyl chloride[12] converted the latter into tetra-*O*-acetyl-L-arabinoyl chloride[13] (85%), whereupon treatment with diazomethane yielded 3,4,5,6-tetra-*O*-acetyl-1-

deoxy-1-diazo-L-*arabino*-hexulose[13] (84%). Addition of hydrogen bromide or chloride furnished 3,4,5,6-tetra-*O*-acetyl-1-bromo-1-deoxy-L-*arabino*-hexulose (**1b**) or the 1-chloro derivative (**2b**), respectively. Use of α-halo ketoses **1b** or **2b** permitted synthesis (see Method I) of the intermediate 4-hydroxythiazolidine-2-thione (**3b**) by the ammonium dithiocarbamate method. Acidic dehydration of **3b** gave the acetylated thiazoline structure **4b**, and deacetylation of **4b** yielded 4-(L-*arabino*-tetrahydroxybutyl)-4-thiazoline-2-thione (**5b**). Thiones **4b** and **5b**, on mild oxidation, characteristically yielded the respective disulfides (**6b**) and (**7b**). Cocrystallization of the corresponding enantiomorphs afforded the racemates (**1c**), (**2c**), and (**4c–6c**). All of the products of these reactions were obtained in crystalline form.

4-(D-*xylo*-Tetrahydroxybutyl)-4-thiazoline-2-thione (**5d**), unlike its diastereoisomer (**5a**), is soluble in cold water and in ethanol, and resisted crystallization. Previously, oxidation of tetra-*O*-acetyl-*aldehydo*-D-xylose, obtained from the corresponding diethyl dithioacetal by thiol cleavage[14], was reported by Major and Cook[15] to yield crystalline tetra-*O*-acetyl-D-xylonic acid. The corresponding crystalline acid chloride was obtained by Wolfrom *et al.*[14]. In the present work, the last two intermediates were used satisfactorily as syrups. Treatment of the acid chloride with diazomethane yielded crystalline 3,4,5,6-tetra-*O*-acetyl-1-deoxy-1-diazo-D-*xylo*-hexulose[14]. However, subsequent treatment with hydrogen bromide afforded an α-bromo ketose (**1d**), which crystallized below 0°. Use of **1d** according to Method I gave the product (**5d**) *via* the crystalline, intermediate 4-hydroxythiazolidine and thiazoline structures **3d** and **4d**, respectively. A similar route to the enantiomorph, 4-(L-*xylo*-tetrahydroxybutyl)-4-thiazoline-2-thione (**5e**), required preparation of the new intermediate, L-xylose diethyl dithioacetal (**8**). Other new compounds employed in the preparation were tetra-*O*-acetyl-L-xylose diethyl dithioacetal (**9**), 3,4,5,6-tetra-*O*-acetyl-1-deoxy-1-diazo-L-*xylo*-hexulose (**11**), and their respective racemates, (**10**) and (**12**).

In further use of the method, treatment of 3,4,5,6,7-penta-*O*-acetyl-1-bromo-1-deoxy-D-*gluco*-heptulose (**1f**) according to Method I gave the 4-hydroxythiazolidine (**3f**). Dehydration of **3f** yielded the acetylated thiazoline (**4f**), which gave a disulfide (**6f**). Deacetylation of **4f** afforded 4-(D-*gluco*-pentahydroxypentyl)-4-thiazoline-2-thione (**5f**) as a glass that was soluble in ethanol and in water.

A bis(4-thiazoline-2-thione) compound (**5g**) was prepared from 3,4,5,6-tetra-*O*-acetyl-1,8-dibromo-1,8-dideoxy-*galacto*-2,7-octodiulose (**1g**) *via* the bis(4-hydroxythiazolidine-2-thione) intermediate (**3g**). Simultaneous, rapid dehydration and deacetylation of **3g** in sodium hydroxide solution, and subsequent acidification, gave crystalline 4,4′-(*galacto*-1,2,3,4-tetrahydroxybutane-1,4-diyl)-bis(4-thiazoline-2-thione) (**5g**) directly.

4-Thiazoline-2-thiones substituted at the *N*-hetero atom were obtained from certain carbohydrates by the reactions outlined in Method II. As an example of this approach, treatment of α-bromo ketose **1a** with the dithiocarbamic acid salt derived from methylamine, carbon disulfide, and potassium acetate led to intermediates **3h** and **4h** (syrup), and to the product, 3-methyl-4-(D-*arabino*-tetrahydroxybutyl)-4-

thiazoline-2-thione (**5h**). By the same method, treatment of **1b** with the dithiocarbamic acid salt derived from 4-aminobutyric acid gave, *via* intermediates **3i** and **4i** (syrup), the analogous product, 3-(3-carboxypropyl)-4-(L-*arabino*-tetrahydroxybutyl)-4-thiazoline-2-thione (**5i**).

On the basis of these results, it is expected that chain-lengthened 4-thiazoline-2-thiones may be obtained *via* α-halo ketoses **1** and **2** that are derived from homologous precursors, *e.g.*, 3,4,5,6,7,8-hexa-*O*-acetyl-1-deoxy-1-diazo-D-*glycero*-D-*gulo*-octose[16], 3,4,5,6,7,8,9-hepta-*O*-acetyl-1-deoxy-1-diazo-D-*erythro*-L-*manno*-nonulose[17], etc. The simplest analog of the heterocyclic series, namely, 4-hydroxymethyl-4-thiazoline-2-thione, was reported previously[6].

The heterocyclic forms of the products and their corresponding intermediates described herein were given structural assignments by analogy, and by the similarity of their u.v. or i.r. spectra to those of compounds previously reported. Characteristic data obtained for the new compounds are given in the experimental section.

EXPERIMENTAL

U.v. spectra between 210 and 400 nm were determined with a Perkin–Elmer Model 202 Recording Spectrophotometer, with 1-cm silica cuvettes. Appropriate blank corrections were made for all determinations of optical absorbance. Melting points were determined in open, soft-glass capillaries in an oil bath, and are corrected. Optical rotations were measured with a Rudolph polarimeter by using a 2-dm polarimeter tube.

3,4,5,6-Tetra-O-*acetyl-1-bromo-1-deoxy*-L-arabino-*hexulose* (**1b**). — The following preparation is based on the general method previously reported[18] for the synthesis of the D enantiomorph (**1a**). 3,4,5,6-Tetra-*O*-acetyl-1-deoxy-1-diazo-L-*arabino*-hexulose[13] (13.4 g) was suspended in 400 ml of anhydrous ether, and dry hydrogen bromide was passed into the mixture until the resulting evolution of nitrogen ceased. The solution formed was successively washed with water at 5° and with excess aqueous sodium hydrogen carbonate. The dried (sodium sulfate) organic layer was concentrated *in vacuo*, and the solution diluted with petroleum ether. The crystals which formed on cooling were collected; yield 13.3 g (87%), m.p. 66–67°, unchanged on recrystallization from ether–petroleum ether; $[\alpha]_D^{23}$ −65 ±2° (*c* 4, chloroform).

Anal. Calc. for $C_{14}H_{19}BrO_9$: C, 40.9; H, 4.7; Br, 19.4. Found; C, 41.0; H, 4.8; Br, 19.4.

When the washing steps were omitted from the procedure, the product obtained decomposed on prolonged storage.

3,4,5,6-Tetra-O-*acetyl-1-bromo-1-deoxy*-DL-arabino-*hexulose* (**1c**). — Cocrystallization of **1b** and the D enantiomorph[18] (**1a**) (1.0 g of each) from ether–petroleum ether, and subsequent recrystallization, gave the optically inactive form, yield 1.7 g (85%), m.p. 92°, $[\alpha]_D^{23}$ 0 ±1° (*c* 4, chloroform).

Anal. Calc. for $C_{14}H_{19}BrO_9$: Br, 19.4. Found: Br, 19.2.

3,4,5,6-Tetra-O-*acetyl-1-chloro-1-deoxy*-L-arabino-*hexulose* (**2b**). — 3,4,5,6-Tetra-*O*-acetyl-1-deoxy-1-diazo-L-*arabino*-hexulose[13] (10.0 g) was treated by the

procedure used for the preparation of **1b**, except that hydrogen chloride was employed instead of hydrogen bromide. Recrystallization from ether–petroleum ether gave a pure product, yield 9.1 g (89%), m.p. 76–77°, $[\alpha]_D^{23}$ −68 ±2° (*c* 4, chloroform).

Anal. Calc. for $C_{14}H_{19}ClO_9$: C, 45.9; H, 5.2; Cl, 9.7. Found: C, 45.9; H, 5.6; Cl, 9.4.

3,4,5,6-Tetra-O-*acetyl-1-chloro-1-deoxy*-DL-arabino-*hexulose* (**2c**). — Cocrystallization of equal amounts of **2b** and the D enantiomorph[18] from ether–petroleum ether, followed by recrystallization, gave the racemate, m.p. 101°, $[\alpha]_D^{23}$ 0 ±1° (*c* 4, chloroform).

Anal. Calc. for $C_{14}H_{19}ClO_9$: C, 45.9; H, 5.2; Cl, 9.7. Found: C, 45.6; H, 5.5; Cl, 9.7.

4-Hydroxy-4-(L-arabino-*tetraacetoxybutyl)thiazolidine-2-thione* (**3b**). — *Treatment* of **2b** (20.2 g) with ammonium dithiocarbamate (7.2 g) by the general method previously described for the preparation of 4-hydroxythiazolidine-2-thiones[19] and for the D enantiomorph[6] (**3a**) in solution in acetone–water gave **3b**, yield 19.8 g (85%). Recrystallized from ether, the product had m.p. 146–147°, λ_{max}^{MeOH} 243, 276 nm (ε 7,500, 15,900).

Anal. Calc. for $C_{15}H_{21}NO_9S_2$: C, 42.5; H, 5.0; N, 3.3; S, 15.1. Found: C, 42.8; H, 5.0; N, 3.2; S, 14.9.

Use of the bromo derivative (**1b**) as the α-halo ketone, instead of the chloro derivative (**2b**), gave similar results.

4-Hydroxy-4-(D-xylo-*tetraacetoxybutyl)thiazolidine-2-thione* (**3d**). — Treatment of 3,4,5,6-tetra-*O*-acetyl-1-deoxy-1-diazo-D-*xylo*-hexulose[14] (13.5 g) in ether with hydrogen bromide by the method used for the preparation of **1b** gave a product that crystallized from cold ether, but that was a melt at room temperature. Evaporation of the ether afforded **1d** as a syrup.

Treatment of the latter syrup with ammonium dithiocarbamate (4.6 g) by the procedure used to prepare **3b** yielded **3d**, 12.6 g (80%). Recrystallized from 2 liters of ether by evaporation of the solvent, the product had m.p. 153°, λ_{max}^{MeOH} 243, 277 nm (ε 6,900; 14,400).

Anal. Calc. for $C_{15}H_{21}NO_9S_2$: C, 42.5; H, 5.0; N, 3.3; S, 15.1. Found: 42.5; H, 5.0; N, 3.5; S, 14.7.

3,4,5,6-Tetra-O-*acetyl-1-deoxy-1-diazo*-L-xylo-*hexulose* (**11**). — Treatment of tetra-*O*-acetyl-L-xylonyl chloride (26.0 g), in the form of a syrup, with diazomethane according to the procedure described[14] for the preparation of the D enantiomorph afforded **11** as pale-yellow crystals, yield 17.0 g (58%), m.p. 125–126°, unchanged on recrystallization from ether; $[\alpha]_D^{24}$ −47 ±2° (*c* 4, chloroform).

Anal. Calc. for $C_{14}H_{18}N_2O_9$: C, 46.9; H, 5.1; N, 7.8. Found: C, 46.7; H, 5.1; N, 7.9.

3,4,5,6-Tetra-O-*acetyl-1-deoxy-1-diazo*-DL-xylo-*hexulose* (**12**). — Cocrystallization of equal amounts of **11** and the D enantiomorph[14] from ether–petroleum ether, and subsequent recrystallization, gave the optically inactive form, m.p. 122°, $[\alpha]_D^{24}$ 0 ±1° (*c* 4, chloroform).

Anal. Calc. for $C_{14}H_{18}N_2O_9$: C, 46.9; H, 5.1; N, 7.8. Found: C, 46.8; H, 5.0; N, 7.5.

4-Hydroxy-4-(L-xylo-*tetraacetoxybutyl)thiazolidine-2-thione* (**3e**). — Treatment of **11** (14.3 g) in ether solution with hydrogen bromide by the procedure used for synthesizing **1b** gave **1e** as a syrup. Treatment of the syrup with ammonium dithiocarbamate (4.9 g) by the procedure used to prepare the D enantiomorph (**3d**) gave **3e**, yield 15.3 g (91%, from **11**). Recrystallized from ether, the product had m.p. 152–153°, λ_{max}^{MeOH} 244, 277 nm (ε 7,200, 15,100).

Anal. Calc. for $C_{15}H_{21}NO_9S_2$: C, 42.5; H, 5.0; N, 3.3; S, 15.1. Found: C, 42,7; H. 5.2; N, 3.7; S, 14.8.

4-Hydroxy-4-(D-gluco-*pentaacetoxypentyl)thiazolidine-2-thione* (**3f**). — The following preparation of **3f** by a previously reported[20] method depends on the interaction of a suspension of the reagents in ether. The procedure used for the preparation of **3b** by interaction of the reagents in solution in acetone–water is, on the basis of comparative reaction times and yields, a preferred method.

A suspension of 3,4,5,6,7-penta-*O*-acetyl-1-bromo-1-deoxy-D-*gluco*-heptulose[18] (25.0 g) and ammonium dithiocarbamate (5.7 g) in ether (300 ml) was stirred for 3 days at reflux temperature. The solid phase was collected, and washed with water. Evaporation of the ether phase afforded a solid residue. The combined solids, precipitated twice from ethanol, gave an amorphous product, yield 9.0 g (35%), λ_{max}^{MeOH} 245, 277 nm (ε 6,500, 13,600),

Anal. Calc. for $C_{18}H_{25}NO_{11}S_2$: C, 43.6; H, 5.1; N, 2.8; S, 12.9. Found: C, 43.7; H, 4.9; N, 2.7; S, 12.9.

4,4'-(galacto-*1,2,3,4-Tetraacetoxybutane-1,4-diyl)-bis(4-hydroxythiazolidine-2-thione*) (**3g**). — Treatment of 3,4,5,6-tetra-*O*-acetyl-1,8-dibromo-1,8-dideoxy-*galacto*-2,7-octodiulose[21] (10.0 g) with ammonium dithiocarbamate (5.5 g) by the procedure used for the preparation of **3b** gave **3g**, separated in three crops, yield 8.8 g (84%). Recrystallized from acetone–water, the product melted at above 300°, λ_{max}^{MeOH} 243, 277 nm (ε 12,900, 25,200).

Anal. Calc. for $C_{18}H_{24}N_2O_{10}S_4$: C, 38.8; H, 4.3; N, 5.0; S, 23.0. Found: C, 39.2; H, 4.0; N, 4.7; S, 22.6.

4-Hydroxy-3-methyl-4-(D-arabino-*tetraacetoxybutyl)thiazolidine-2-thione* (**3h**) — The following preparation is based upon a previously reported[7], general method for the synthesis of 4-hydroxythiazolidine-2-thiones from amines. Carbon disulfide (8.8 ml) was added, dropwise, to a stirred solution (cooled in an ice bath) of potassium acetate (14.2 g) and methylamine (40% in water, 11.2 g) in methanol (100 ml). Stirring and cooling were continued for 3 h. 3,4,5,6-Tetra-*O*-acetyl-1-bromo-1-deoxy-D-*arabino*-hexulose[18] (**1a**) in methanol (100 ml) was added to the stirred, cooled reaction mixture during 30 min. The mixture was kept overnight at room temperature, diluted with water and concentrated *in vacuo*, precipitating **3h**, yield 29.3 g (92%). Two recrystallizations from methanol–water (77% recovery) gave a pure product, m.p. 148–149°, λ_{max}^{MeOH} 253, 273 nm (ε 9,600, 15,800).

Anal. Calc. for $C_{16}H_{23}NO_9S_2$: C, 43.9; H, 5.3; N, 3.2; S, 14.7. Found: C, 43.5; H, 5.3; N, 3.1; S, 14.3.

3-(3-Carboxypropyl)-4-hydroxy-4-(L-arabino-*tetraacetoxybutyl)-thiazolidine-2-thione* (**3i**). — A previously reported[8] modification of the procedure of the foregoing experiment permitted use of an amino acid in this synthesis. Thus, treatment of the dithiocarbamic acid salt, obtained from the reaction of 4-aminobutyric acid (8.7 g) with potassium hydroxide (4.8 g) and carbon disulfide (4.4 ml) in methanol (50 ml), with **1b** (15.0 g) gave **3i** as an amorphous solid, yield 17.0 g (92%). The product was extracted into ether, and the extract was treated with powdered charcoal, filtered, and dried (sodium sulfate). Evaporation of the filtrate *in vacuo* gave a glass, λ_{max}^{MeOH} 255, 276 nm (ε 8,800, 14,400).

Anal. Calc. for $C_{19}H_{27}NO_{11}S_2$: C, 44.8; H, 5.4; N, 2.8; S, 12.6. Found: C, 44.6; H, 5.4; N, 2.6; S, 12.3.

4-(L-arabino-*Tetraacetoxybutyl)-4-thiazoline-2-thione* (**4b**). — Acid dehydration of **3b** (6.0 g) by the procedure reported[6] earlier for the preparation of the D enantiomorph (**4a**) gave the 4-thiazoline-2-thione **4b**, yield 3.9 g (69%). Recrystallized from ether, the product had m.p. 169°, λ_{max}^{MeOH} 317 nm (ε 12,300), $[\alpha]_D^{24}$ +80 ±1° (*c* 2, chloroform).

Anal. Calc. for $C_{15}H_{19}NO_8S_2$: C, 44.4; H, 4.7; N, 3.5; S, 15.8. Found: C, 44.6; H, 4.7; N, 3.2; S, 15.7.

4-(DL-arabino-*Tetraacetoxybutyl)-4-thiazoline-2-thione* (**4c**). — Cocrystallization of equal amounts of **4b** and the D enantiomorph[6] (**4a**) from ether, and subsequent recrystallization, afforded the racemic product, m.p. 173–174°, λ_{max}^{MeOH} 317 nm (ε 12,500), $[\alpha]_D^{24}$ −2 ±2° (*c* 2, chloroform).

Anal. Calc. for $C_{15}H_{19}NO_8S_2$: C, 44.4; H, 4.7; N, 3.5; S, 15.8. Found: C, 44.7; H, 4.5; N, 3.3; S, 15.7.

4-(D-xylo-*Tetraacetoxybutyl)-4-thiazoline-2-thione* (**4d**). — Dehydration of **3d** (9.4 g) by heating it to 185° gave an amorphous product, yield 8.2 g (94%). Reprecipitation, twice, from ether–petroleum ether gave **4d** as a glass, λ_{max}^{MeOH} 317 nm (ε 12,700), $[\alpha]_D^{24}$ +129 ±2° (*c* 4, chloroform).

Anal. Calc. for $C_{15}H_{19}NO_8S_2$: C, 44.4; H, 4.7; N, 3.5; S, 15.8. Found: C, 44.2; H, 4.6; N, 3.4; S, 15.4.

4-(L-xylo-*Tetraacetoxybutyl)-4-thiazoline-2-thione* (**4e**). — Dehydration of **3e** and reprecipitation of the resulting product by the procedure used in the foregoing experiment gave an amorphous product (**4e**), λ_{max}^{MeOH} 317 nm (ε 13,000), $[\alpha]_D^{24}$ −131 ±2° (*c* 4, chloroform).

Anal. Calc. for $C_{15}H_{19}NO_8S_2$: C, 44.4; H, 4.7; N, 3.5; S, 15.8. Found: C, 44.0; H, 4.8; N, 3.2; S, 16.1.

4-(D-gluco-*Pentaacetoxypentyl)-4-thiazoline-2-thione* (**4f**). — Dehydration of **3f** and subsequent reprecipitation of the resultant product by the procedure used for the preparation of **4d** gave the amorphous 4-thiazoline-2-thione (**4f**), λ_{max}^{MeOH} 317 nm (ε 14,000), $[\alpha]_D^{24}$ +133 ±2° (*c* 4, chloroform).

Anal. Calc. for $C_{18}H_{23}NO_{10}S_2$: C, 45.3; H, 4.9; N, 2.9; S, 13.4. Found: 45.6; H, 5.0; N, 2.8; S, 13.8.

4-(L-arabino-*Tetrahydroxybutyl)-4-thiazoline-2-thione* (**5b**). — By repetition of the method used for the preparation of the D enantiomorph[6] (**5a**), a solution of **4b** (8.3 g) and potassium hydroxide (8.3 g) in water (40 ml) was boiled for 2 min, cooled, and made acidic with concentrated hydrochloric acid. The resulting, crystalline precipitate was collected, and rinsed with cold water (10 ml); yield 4.2 g (88%). Recrystallization from water gave pure **5b**, m.p. 218°, λ_{max}^{MeOH} 317 nm (ε 13,800), $[\alpha]_D^{20}$ +80 C, ±2° (*c* 1, *N,N*-dimethylformamide).

Anal. Calc. for $C_7H_{11}NO_4S_2$: C, 35.4; H, 4.7; N, 5.9; S, 27.0. Found: C, 35.6; H, 4.9; N, 5.7; S, 26.6.

4-(DL-arabino-*Tetrahydroxybutyl)-4-thiazoline-2-thione* (**5c**). — Corystallization of equal amounts of **5b** and the D enantiomorph[6] (**5a**) from water, followed by recrystallization, gave the optically inactive form, m.p. 197°, λ_{max}^{MeOH} 317 nm (ε 13,700), $[\alpha]_D^{20}$ 0 ±1° (*c* 1, *N,N*-dimethylformamide).

Anal. Calc. for $C_7H_{11}NO_4S_2$: C, 35.4; H, 4.7; N, 5.9; S, 27.0. Found: C, 35.0; H, 4.8; N, 5.7; S, 26.9.

4-(D-xylo-*Tetrahydroxybutyl)-4-thiazoline-2-thione* (**5d**). — A solution of **4d** (5.4 g) and potassium hydroxide (5.4 g) in water (25 ml) was boiled for 2 min, cooled, acidified with hydrochloric acid, and evaporated *in vacuo* to dryness. The amorphous residue was extracted with ethanol, and the extract was evaporated to dryness *in vacuo*, affording a glass, yield 2.5 g (81%). The product, soluble in water, ethanol, and acetone, had λ_{max}^{MeOH} 317 nm (ε 11,200).

Anal. Calc. for $C_7H_{11}NO_4S_2$: C, 35.4; H, 4.7. Found: C, 35.8; H, 5.0.

Treatment of **4e** by the method used in the foregoing experiment gave a residue that resisted crystallization. The crude L enantiomorph (**5e**) so obtained had λ_{max}^{MeOH} 317 nm (ε 11,800).

4-(D-gluco-*Pentahydroxypentyl)-4-thiazoline-2-thione* (**5f**). — Treatment of **4f** (3.0 g) by the procedure used in the foregoing experiment afforded a quantitative yield of **5f** as a syrup that was soluble in water, λ_{max}^{MeOH} 317 nm (ε 12,100).

Anal. Calc. for $C_8H_{13}NO_5S_2$: C, 35.9; H, 4.9. Found: C, 35.6; H, 5.1.

4,4'-(galacto-*1,2,3,4-Tetrahydroxybutane-1,4-diyl)bis(4-thiazoline-2-thione*) (**5g**). — Simultaneous dehydration and deacetylation of the 4-hydroxythiazolidine **3g** (4.6 g), by the procedure used for the preparation of **5b**, gave the product (**5g**) directly, yield 2.0 g (71%). The product was dissolved in aqueous sodium carbonate, and the solution was treated with powdered charcoal, filtered, and the filtrate acidified with hydrochloric acid. The resulting, lustrous flakes were collected, and had m.p. 253°, $\lambda_{max}^{HCONMe_2}$ 317 nm (ε 24,800), $[\alpha]_D^{23}$ 0 ±1° (*c* 2, *N,N*-dimethylformamide).

Anal. Calc. for $C_{19}H_{12}N_2O_4S_4$: C, 34.5; H, 3.4; N, 7.9; S, 36.4. Found: C, 34.1; H, 3.6; N, 7.7; S, 36.5.

The product was soluble in acetone and *N,N*-dimethylformamide, and insoluble in chloroform, methanol, or water.

3-Methyl-4-(D-arabino-*tetrahydroxybutyl)-4-thiazoline-2-thione* (**5h**). — The

4-hydroxythiazolidine (**3h**) (17.0 g) was suspended in 400 ml of 50 M hydrochloric acid, and the mixture was refluxed for 1 h. Evaporation of the resulting solution yielded a syrup that resisted crystallization. A solution of the syrup and potassium hydroxide (17.0 g) in water (85 ml) was stirred for 4 min at 75°, cooled, and acidified with hydrochloric acid. After a small amount of gum had separated, the solution was treated with powdered charcoal, filtered, and evaporated to dryness. Extraction of the residue with ethanol, and subsequent concentration of the extract, gave a crystalline precipitate, yield 5.0 g, in two crops (51%, from **3h**). Recrystallization from ethanol gave **5h** as white flakes, m.p. 181°, λ_{max}^{MeOH} 313 nm (ε 15,000), $[\alpha]_D^{25}$ −56 ±2° (*c* 2, water).

Anal. Calc. for $C_8H_{13}NO_4S$: C, 38.2; H, 5.2; N, 5.6; S, 25.5. Found: C, 38.5; H, 5.3; N, 5.3; S, 25.9.

The product was soluble in ethanol, methanol, and water, and insoluble in ether.

3-(3-Carboxypropyl)-4-(D-arabino-*tetrahydroyxbutyl-4-thiazoline-2-thione* (**5i**). — The acid dehydration of the 4-hydroxythiazolidine (**3i**) (11.8 g) by the procedure used in the foregoing experiment gave a syrupy product. Treatment of the syrup by the saponification procedure used for the preparation of **5h**, and subsequent acidification, gave a product that crystallized from the aqueous reaction mixture during several weeks at room temperature. Recrystallized from water during several days at room temperature, pure **5i** had m.p. 160°, λ_{max}^{MeOH} 317 nm (ε 13,200), $[\alpha]_D^{25}$ +39 ±2° (*c* 2, water).

Anal. Calc. for $C_{11}H_{17}NO_6S_2$: C, 40.9; H, 5.3; N, 4.3; S, 19.8. Found: C, 41.2; H, 5.2; N, 4.2; S, 19.6.

2,2'-Dithiobis[(4-L-arabino-*tetraacetoxybutyl)thiazole*] (**6b**). — Oxidation of **4b** (3.0 g) in 50% aqueous methanol (250 ml), by the iodine method previously reported[6] [used for the preparation of the D enantiomorph (**6a**)] gave the disulfide, yield 2.3 g (77%). Recrystallized from ether, the product had m.p. 146°, λ_{max}^{MeOH} 266 nm (ε 9,100), $[\alpha]_D^{24}$ +13 ±1° (*c* 4, chloroform).

Anal. Calc. for $C_{39}H_{36}N_2O_{16}S_4$: N, 3.5; S, 15.9. Found: N, 3.2; S, 15.6.

2,2'-Dithiobis[(*4*-DL-arabino-*tetraacetoxybutyl)thiazole*] (**6c**). — A solution of equal amounts of **6b** and the D enantiomorph[6] (**6a**) in ether was evaporated. The resulting racemate resisted crystallization, and had λ_{max}^{MeOH} 266 (ε 9,400), $[\alpha]_D^{24}$ 0 ±1° (*c* 4, chloroform).

Anal. Calc. for $C_{30}H_{36}N_2O_{16}S_4$: C, 44.5; H, 4.5; N, 3.5; S, 15.9. Found: C, 44.5; H, 4.3; N, 3.3; S, 15.7.

2,2'-Dithiobis[(*4*-D-gluco-*pentaacetoxypentyl)thiazole*] (**6f**). — Oxidation of **4f** (4.8 g) by the procedure used for the preparation of **6b** gave **6f**, yield 3.8 g (80%). Recrystallized from ether, the disulfide had mp.. 88°, λ_{max}^{MeOH} 267 nm (ε 9,200).

Anal. Calc. for $C_{36}H_{44}N_2O_{20}S_4$: C, 45.4; H, 4.7; N, 2.9; S, 13.5. Found: C, 45.2; H, 4.6; N, 3.0; S, 13.1.

2,2'-Dithiobis[(*4*-L-arabino-*tetrahydroxybutyl)thiazole*] (**7b**). — Oxidation of **5b** (2.4 g) by the procedure previously reported[6] [used for the preparation of the

D enantiomorph (**7a**)] gave a quantitative yield of the disulfide. Washed with boiling water, the product had m.p. 210°.

Anal. Calc. for $C_{14}H_{29}N_2O_8S_4$: C, 35.6; H, 4.3; N, 5.9; S, 27.1. Found: C, 35.2; H, 4.0; N, 5.6; S, 27.1.

L-*Xylose diethyl dithioacetal* (**8**). — Treatment of a solution of L-xylose (20.0 g) in 24 ml of hydrochloric acid with 20 ml of ethanethiol, according to the procedure previously reported[22] for the preparation of D-xylose diethyl dithioacetal, gave **8**, yield 21.2 g (64%). Recrystallized from ethanol, the product had m.p. 63–64°, $[\alpha]_D^{20}$ $+70 \pm 1°$ (*c* 1, chloroform).

Anal. Calc. for $C_9H_{29}O_4S_2$: C, 42.1; H, 7.9; S, 25.0. Found: C, 41.8; H, 7.9; S, 24.6.

Tetra-O-*acetyl*-L-*xylose diethyl dithioacetal* (**9**). — Acetylation of **8** (14.0 g) in pyridine (50 ml) with acetic anhydride (100 ml), by the procedure previously reported[22] for the preparation of the D enantiomorph, gave **9**, yield 22.0 g (95%). Recrystallized from methanol–water, the product had m.p. 49–50°, $[\alpha]_D^{25}$ $-13 \pm 1°$ H, (*c* 4, chloroform).

Anal. Calc. for $C_{17}H_{28}O_8S_2$: C, 48.1; H, 6.7; S, 15.1. Found: C, 47.8; 6.6; S, 15.6.

Tetra-O-*acetyl*-DL-*xylose diethyl dithioacetal* (**10**). — Cocrystallization of equal amounts of **9** and the D enantiomorph[22] from ethanol–water, and subsequent recrystallization, gave the optically inactive form, m.p. 47°, $[\alpha]_D^{24}0$ $\pm 1°$ (*c* 4, chloroform).

Anal. Calc. for $C_{17}H_{28}O_8S_2$: C, 48.1; H, 6.7; S, 15.1. Found: C, 48.0; H, 6.8; S, 15.0.

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