A DETERMINATION OF THE STRUCTURE OF 4-(D-arabino-TETRA-HYDROXYBUTYL)-4-THIAZOLINE-2-THIONE

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ABSTRACT

The structure of 4-(D-arabino-tetrahydroxybutyl)-4-thiazoline-2-thione (1) was determined by means of synthesis, and was in agreement with the recent structural assignment by Jochims *et al.* Procedures of carbohydrate chemistry afforded typical derivatives of 1, and provided a total synthesis from D-glucose. The heterocyclic ring of 1 gave reactions characteristic of HS-C=N- and S=C-NH forms of a 4-thiazoline-2-thione. Periodate oxidation of 1 provided a route to the lowest homolog 11, which was alternatively prepared by a known method from the appropriate α -chloroketone and ammonium dithiocarbamate. An unequivocal preparation by a similar reaction with 3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-arabino-hexulose led to 1. The formation of carbohydrate-derived 4-thiazoline-2-thiones appears to be a general reaction of α -halo ketoses with ammonium dithiocarbamate.

INTRODUCTION

The title compound (1) is of particular interest, since it exhibits certain properties both of a carbohydrate and of a thione-substituted heterocycle that is capable of tautomerism. Zemplén *et al.*¹ reported 1 as a substance, melting at 218°, that can be separated in 2% yield from the products of the reaction of D-fructose with thiocyanic acid in hydrochloric acid solution. Jochims *et al.*² recently proposed the structure now assigned to 1. They reported that the reaction of 2-amino-2-deoxy-Dglucose with carbon disulfide yielded a 5-hydroxythiazolidine³, an example of a new class of compound. Subsequent dehydration and acetylation gave a tetraacetate that was identical with the tetraacetate of the substance reported¹ by Zemplén *et al.* The structures reported by Jochims and co-workers were based on elemental and spectral analyses and determination of molecular weight.

The procedure of Zemplén *et al.* had previously been applied to L-arabinose, D-fructose, D-galactose, D-glucose, D-lyxose, D-mannose, D-ribose, and D-xylose. The products were isolated in good yield, but, in some cases, there was uncertainty as to the structure⁴⁻⁶. Subsequent studies revealed these structures to be those of oxazolidine-2-thiones fused with furanoid or pyranoid ring-systems^{2,7-9}. The present article reports a structural determination based on the chemical properties

of 1, and an unequivocal synthesis of 1. The results obtained support the concurrent characterization² by Jochims *et al.*

RESULTS AND DISCUSSION

The reactions of 1 are typical of HS-C=N- and S=C-NH tautomers, and of primary and secondary hydroxyl groups. Although 1 is readily recrystallized from water, it is insoluble in the solvents commonly used in ebullioscopic or cryoscopic methods for determination of molecular weight. However, titration of 1 with standard sodium hydroxide or iodine solution permitted the determination of a neutralization equivalent and of an empirical formula. Treatment of 1 with sodium hydrogen carbonate plus an equivalent of sodium chloroacetate gave the S-alkylated derivative 2-(carboxymethyl)thio-4-(D-arabino-tetrahydroxybutyl)thiazole (2). Use of chlorodiphenylmethane in pyridine also afforded an S-derivative (3), but similar use of chlorotriphenylmethane in pyridine gave the trityl ether (4). Complete acetylation of 1 yielded the pentaacetate (5). Oxidation of 1 with iodine or ammonium persulfate afforded 2,2'-dithiobis[(4-D-arabino-tetrahydroxybutyl)thiazole] (6), and tritylation of this disulfide 6 gave a ditrityl ether (7).

The disulfide 6 was found to be cleaved readily by aqueous sodium hydroxide, carbonate, or hydrogen carbonate, to give 1 in approximately 82% yield; a by-product, 4-(D-*arabino*-tetrahydroxybutyl)thiazole (8), was also isolated (*ca.* 13%). Facile cleavage by alkali was also characteristic of the other thiazolyl disulfides encountered



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in the study. These reactions suggest that 1 contains three secondary hydroxyl groups, one primary hydroxyl group, and a tautomeric thiol-thione group.

Compound 1 showed a maximum absorption in the u.v. spectrum at 317 nm, comparable to that of 4-thiazoline-2-thione at 314 nm and to that of 4-methyl-4-thiazoline-2-thione at 321 nm, but in contrast to that of the saturated ring of thiazolidine-2-thione at 273 nm. The S-derivatives of 1 showed maximum absorption at 262–282 nm.

The type of heterocyclic ring in 1 and the position of substitution were indicated by typical reactions. Preparative, periodate oxidation of 1 or 6 yielded the disulfide (9), which showed, in its i.r. spectrum, absorption for an aldehyde group. Alkaline cleavage of the disulfide 9 yielded the thione (10). The aldehydes 9 and 10 formed Schiff-base derivatives. Reduction of 10 with potassium borohydride provided 4-(hydroxymethyl)-4-thiazoline-2-thione (11), the lowest homolog of 1. Oxidation of 11 under mild conditions gave the disulfide (12). Base-catalyzed, conjugate addition at the nitrogen hetero atom of 4-thiazoline-2-thiones has been shown to be a characteristic reaction of the heterocyclic system¹⁰. Treatment of 11 with 3-buten-2-one in this way afforded the adduct (13), which showed, in its u.v. spectrum, maximum absorption at 321 nm. Alternatively, 11 was prepared by a known, synthetic method¹¹ for 4-thiazoline-2thiones. By this procedure, the reaction of 1-acetoxy-3-chloro-2-propanone and ammonium dithiocarbamate gave a typical intermediate¹², 4-(acetoxymethyl)-4-hydroxythiazolidine-2-thione (14). Facile, acidic dehydration of 14 gave the 4-thiazoline structure (15), and subsequent alkaline hydrolysis of 15 gave 11. The observed proper-



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ties of 11 as obtained from 1 by way of periodate oxidation, and by the synthesis from an α -halo ketone and ammonium dithiocarbamate, were the same.

The configuration of the tetrahydroxybutyl substituent in 1 was confirmed by preparation by known methods of carbohydrate chemistry. D-Glucose in aqueous, methanolic potassium hydroxide was oxidized with oxygen to afford potassium D-arabinonate¹³(76%) which, after acetylation with acetic anhydride-hydrogen chloride, yielded tetra-O-acetyl-D-arabinonic acid¹⁴ (48%). Thionyl chloride¹⁵ converted the latter into tetra-O-acetyl-D-arabinonoyl chloride¹⁶ (85%) which, on treatment with diazomethane, yielded 3,4,5,6-tetra-O-acetyl-1-deoxy-1-diazo-D-arabino-hexulose¹⁷ (84%). Subsequent addition of hydrogen bromide to the diazo ketone in ether provided 3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-arabino-hexulose¹⁷ (85%). Use of the latter α -bromo ketone permitted synthesis, by the ammonium dithiocarbamate method, of a 4-thiazoline-2-thione bearing a 4-substituent of known configuration.



The intermediate, 4-hydroxy-4-(D-*arabino*-tetraacetoxybutyl)thiazolidine-2-thione (16) was isolated, and was readily dehydrated to give 4-(D-*arabino*-tetraacetoxybutyl)-4-thiazoline-2-thione (17). The tetraacetate 17 was independently obtained by Jochims and co-workers² from the more stable 5-hydroxythiazolidine by boiling the latter for 16 h in pyridine. Oxidation of 17 under mild conditions gave the disulfide 18. Hydrolysis of either 17 or the precursor 16 gave 1. The overall yield from D-glucose was 17%; all products were obtained crystalline. The observed properties of 1, as prepared from D-fructose by the method of Zemplén *et al.*⁴ and from the α -bromo ketose derived from D-glucose, were the same.

The preferred method of synthesis of 4-thiazoline-2-thiones derived from carbohydrates depends largely upon the availability of the starting material. Of the required ketoses, only D-fructose has been reported to have been used for this purpose by the method of Zemplén *et al.*⁴ The procedure of Jochims *et al.*² via a 5-hydroxythiazolidine has been reported to be a general reaction of α -amino carbonyl compounds with carbon disulfide. The method described here, via a 4-hydroxythiazolidine, has been found to have significant application. Homologs of **1**, prepared from α -halo ketoses by this method, will be described in a subsequent paper.

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EXPERIMENTAL

Melting points, determined in thin-walled capillary tubes, are corrected. Infrared spectra were recorded for potassium bromide disks on a Baird Atomic spectrophotometer, Model NK-1, having sodium chloride optics; and ultraviolet spectra on a Cary spectrophotometer, Model 11-M. Specific rotations were determined in a 2-dm polarimeter tube.

4-(p-arabino-Tetrahydroxybutyl)-4-thiazoline-2-thione (1). — Modification of the method of Zemplén et al.¹ provided 1. To a stirred solution of D-fructose (1,080 g, 6 moles) and potassium thiocyanate (600 g, 6.18 moles) in water (240 ml) was added hydrochloric acid (7.2 moles), in portions during 30–40 min, with cooling to 20–30°. The mixture was cooled for 30 min longer, nucleated with 1, and kept overnight at room temperature; solids were precipitated. Crushed ice (500 g) was added, and the mixture was stirred for 2 h in an ice bath. The solids remaining, which were collected and rinsed with cold water, weighed 42 g. (Oxazolidine-2-thiones can be separated by concentration of the filtrate².) Excess sodium carbonate was added, with stirring, to a suspension of the crude product in water (400 ml), and the resultant solution was stirred with powdered charcoal, and filtered. Acidification with hydrochloric acid precipitated 1. Recrystallized from water (650 ml), the product weighed 28 g (2%); m.p. 218° (lit.¹ m.p. 218°); λ_{max}^{MeOH} 317 nm (ε 13,700); λ_{max} (aqueous sodium hydroxide, pH 11) 293 nm (ε 9,600); pK_a²⁵ 7.05–7.10 (0.01N solution); solubility 0.25 g/100 ml of water at 25°, and 5 g/100 ml at 100°; $[\alpha]_D^{25} - 77 \pm 2°$ (c 1, N,N-dimethylformamide)].

2-(Carboxymethyl)thio-4-(D-arabino-tetrahydroxybutyl)thiazole (2). — To a boiling mixture of 1 (23.7 g, 0.1 mole), sodium chloroacetate (12.8 g, 0.11 mole), and water (130 ml) was added sodium hydrogen carbonate (10 g) in portions. The resulting solution was boiled for 5 min, cooled, and acidified with hydrochloric acid to give 2, yield 27.5 g (93%), m.p. 151°. Recrystallized from water, it had λ_{max}^{MeOH} 277 nm (ε 6,600), [α]_D²⁵ -143 ±1° (c 1, N,N-dimethylformamide).

Anal. Calc. for C₉H₁₃NO₆S₂: C, 36.6; H, 4.4; N, 4.7; S, 21.7. Found: C, 36.5; H, 4.5; N, 4.8; S, 21.5.

2-(Diphenylmethyl)thio-4-(D-arabino-tetrahydroxybutyl)thiazole (3).—A solution of 1 (23.7 g, 0.1 mole), chlorodiphenylmethane (20.3 g, 0.1 mole), and pyridine (175 ml) was kept for 2 days at room temperature. After removal of most of the pyridine *in vacuo*, with warming, and dilution to 1 liter with an excess of aqueous hydrochloric acid, precipitation occurred, to give 14.2 g of crude 3. (Concentration of the filtrate yielded 10.7 g of unreacted 1). Two recrystallizations from ethanol gave pure 3, yield 11 g (27%), m.p. 157°. λ_{max}^{MeOH} 282 nm (ε 7,500); $[\alpha]_D^{25} - 52 \pm 1$ (c 1, N.N-dimethylformamide).

Anal. Calc. for C₂₀H₂₁NO₄S₂: C, 59.5; H, 5.2; N, 3.5; S, 15.9. Found: C, 59.8; H, 5.4; N, 3.5; S, 15.6.

4-[D-arabino-2,3,4-Trihydroxy-1-(trityloxy)butyl]-4-thiazoline-2-thione (4). — Treatment of 1 with chlorotriphenylmethane for 7 days by the preceding method

gave 4 (25%); recrystallized from chloroform-petroleum ether, it had m.p. (unsharp) ca. 100°; $\lambda_{\text{max}}^{\text{HCONMe2}}$ 328 nm (ε 12,300); $[\alpha]_{D}^{25}$ -37 ±2° (c 1, N,N-dimethyl-formamide).

Anal. Calc. for C₂₆H₂₅NO₄S₂: C, 65.1; H, 5.3; N, 2.9; S, 13.4. Found: C, 65.2; H, 5.4; N, 2.7; S, 13.2.

2-Acetylthio-4-(D-arabino-tetraacetoxybutyl)thiazole (5). — A solution of 1 (10.8 g, 0.046 mole) and potassium acetate (12 g) in acetic anhydride (120 ml) was kept for 1 h at 100°, and, after concentration *in vacuo*, the mixture was poured into water (3 liters) to yield 15 g (81%) of solid, m.p. 94–96°. Several recrystallizations from petroleum ether gave 7 g of 5, m.p. 97–98°.

Anal. Calc. for $C_{17}H_{21}NO_9S_2$: C, 45.7; H, 4.9; N, 3.2; S, 14.6. Found: C, 45.8; H, 4.6; N, 3.2; S, 14.3.

2,2'-Dithiobis[(4-D-arabino-tetrahydroxybutyl)thiazole] (6). — Oxidation of 1 (30 g, 0.127 mole) in boiling water (2.5 liters) by the iodine method¹⁸ gave 6, yield 27.7 g (82%), m.p. 218° (alone; but 203-205° if mixed with 1).

Anal. Calc. for C₁₄H₂₀N₂O₈S₄: C, 35.6; H, 4.3; N, 5.9; S, 27.1. Found: C, 35.8; H, 4.3; N, 6.2; S, 27.5.

2,2'Dithiobis[(4-D-arabino-2,3,4-trihydroxy-1-trityloxybutyl)thiazole] (7) — Tritylation of 6 (10.8 g, 0.023 mole) by the method just described gave 7 yield 12.9 g (59%), after repeated recrystallization from benzene-petroleum ether, m.p. (unsharp) at ca. 84°; $\lambda_{\text{max}}^{\text{MeOH}}$ 268 nm (ε 10,900); $[\alpha]_{D}^{25}$ -24 $\pm 2^{\circ}$ (c, 1 N,N-dimethylformamide).

Anal. Calc. for C₅₂H₄₈N₂O₈S₄: C, 65.2; H, 5.1; N, 2.9; S, 13.4. Found: C, 65.6; H, 5.4; N, 2.8; S, 13.2.

4-(D-arabino-*Tetrahydroxybutyl*)*thiazole* (8). — A mixture of 6 (40 g, 0.085 mole) sodium hydrogen carbonate (22 g), and water (1 liter) was boiled until a solution formed. The solution was cooled, and acidified with hydrochloric acid. Collection of 1 (in two crops) gave 32.7 g (82%). Concentration of the filtrate to dryness, and extraction with hot ethanol gave 8, yield 4.5 g (13%), m.p. 172–173°; recrystallized from ethanol it had λ_{max}^{MeOH} 242 nm (ε 3,300); $[\alpha]_D^{25}$ -35 ±1° (c 1, N,N-dimethylformamide).

Anal. Calc. for C₇H₁₁NO₄S: C, 41.0; H, 5.4; N, 6.8; S, 15.6. Found: C, 41.2; H, 5.3; N, 6.6; S, 15.2.

2,2'-Dithiobis(4-thiazolecarboxaldehyde) (9). — Oxidation of 1 (25 g, 0.11 mole) by the sodium metaperiodate method¹⁹ gave 9, yield 10.9 g (72%). Recrystallized from xylene, it had m.p. 193°, λ_{max}^{KBr} 5.96 (conjugated CHO), 6.2 μ m (C=C).

Anal. Calc. for C₈H₄N₂O₂S₄: C, 33.3; H, 1.4; N, 9.7; S, 44.5. Found: C, 33.5; H, 1.8; N, 9.9; S, 44.2.

Treatment of 6 by the same procedure gave similar results.

The thiosemicarbazone of 9 melted at 245° after recrystallization from pyridinewater.

Anal. Calc. for C₁₀H₁₀N₈S₆: N, 25.8. Found: N, 26.0.

4-Thiazoline-2-thione-4-carboxaldehyde (10). — Treatment of 9 (5.8 g, 0.02 mole) with sodium carbonate (3.5 g) and water (8 ml) gave 10; yield 2.8 g (48%). Twice

recrystallized from water, it had m.p. 173°, λ_{max}^{KBr} 5.98 (conjugated CHO), 6.2 μ m (C=C); λ_{max}^{MeOH} 313 nm (ε 14,700).

Anal. Calc. for C₄H₃NOS₂: C, 33.1; H, 2.1; N, 9.6; S, 44.2. Found: C, 33.2; H, 2.1; N, 9.4; S, 43.8.

Oxidation of 10 with iodine¹⁸ gave 9.

The oxime of 10 melted at 192° after recrystallization from methanol-water.

Anal. Calc. for C₄H₄N₂OS₂: N, 17.5. Found: N, 17.3.

4-(Hydroxymethyl)-4-thiazoline-2-thione (11). — A solution of 10 (3.2 g, 0.022 mole) in methanol (35 ml) was treated with a solution of potassium borohydride (1.2 g, 0.022 mole) in water (5 ml), and the solution was concentrated *in vacuo*. Treatment with excess hydrochloric acid gave 11, yield 1.6 g (50%). Twice recrystallized from water, it had m.p. 121°; $\lambda_{\text{max}}^{\text{KBr}}$ 2.95-3.6 (OH, NH, hydrogen bonding, CH), 6.23 μ m (C=C); $\lambda_{\text{max}}^{\text{MeOH}}$ 316 nm (ε 14,800).

Anal. Calc. for C₄H₅NOS₂: C, 32.6; H, 3.4; N, 9.5; S, 43.6. Found: C, 33.0; H, 3.6; N, 9.3; S, 44.0.

2,2' Dithiobis[4-(hydroxymethyl)thiazole] (12).—Oxidation of 11 (30 g, 0.22 mole) by the ammonium persulfate method²⁰ gave 12; yield 19.5 g (61%), m.p. 115° after recrystallization from water; $\lambda_{max}^{KBr} 2.90 \ \mu m$ (OH); $\lambda_{max}^{MeOH} 266 \ nm$ (ε 9,400).

Anal. Calc. for C₈H₈N₂O₂S₄: C, 32.9; H, 2.8; N, 9.6; S, 43.9. Found: C, 32.6; H, 2.6; N, 9.5; S, 43.9.

Treatment of 12 by the method just given for the alkaline cleavage of disulfides gave 11.

4-(Hydroxymethyl)-3-(3-oxobutyl)-4-thiazoline-2-thione (13). — The conjugate addition²¹ of 11 (44.2 g, 0.3 mole) to 3-buten-2-one (51.6 g, 0.6 mole), catalyzed by sodium methoxide, gave 13, yield 24 g (52%); recrystallized from methanol, m.p. 114°; $\lambda_{\max}^{\text{KBr}}$ 3.02 (OH), 5.88 μ m (C=O); $\lambda_{\max}^{\text{MeCH}}$ 318 nm (ε 13,900).

Anal. Calc. for C₈H₁₁NO₂S₂: C, 44.2; H, 5.1; N, 6.4; S, 29.5. Found: C, 44.3; H, 5.2; N, 6.3; S, 29.2.

4-(Acetoxymethyl)-4-hydroxythiazolidine-2-thione (14). — Treatment of 1-acetoxy-3-chloro-2-propanone²² (120.5 g, 0.8 mole) plus ammonium dithiocarbamate (98 g, 0.89 mole) by the method¹¹ for preparing 4-hydroxythiazolidines gave 14, yield 152 g (91%), m.p. 114° after recrystallization from methanol; λ_{max}^{KBr} 3.05-3.08 (OH, NH), 5.75 μ m (OAc); λ_{max}^{MeOH} 242, 277 nm (ϵ 6,600; 14,600).

Anal. Calc. for C₆H₉NO₃S₂: C, 34.8; H, 4.4; N, 6.8; S, 30.9. Found: C, 35.0; H, 4.1; N, 6.7; S, 30.7.

4-(Acetoxymethyl)-4-thiazoline-2-thione (15). — Recrystallization of 14 from water containing a drop of hydrochloric acid gave 15 in 80% yield; m.p. 80°; λ_{max}^{MeOH} 317 nm (ε 14,800).

Anal. Calc. for C₆H₇NO₂S₂: C, 38.1; H, 3.7; N, 7.4; S, 33.4. Found: C, 37.7; H, 3.8; N, 7.4; S, 33.3.

Treatment of 15 (114 g, 0.6 mole) with potassium hydroxide (114 g) and water (570 ml) for 5 min at 100°, and subsequent acidification at 5°, gave 11, yield 71 g (80%).

4-Hydroxy-4-(D-arabino-tetraacetoxybutyl)thiazolidine-2-thione (16). - Treat-

ment of 3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-arabino-hexulose¹⁷ (14.7 g, 0.036 mole) with ammonium dithiocarbamate (4.4 g, 0.04 mole) by the method¹¹ for preparing 4-hydroxythiazolidines gave 16, yield 13.1 g (86%), m.p. 145°, unchanged on recrystallization from ether; λ_{max}^{MeOH} 242, 278 nm (ε 5,800; 12,200).

Anal. Calc. for C₁₅H₂₁NO₉S₂: C, 42.5; H, 5.0; N, 3.3; S, 15.1. Found: C, 42.8; H, 4.8; N, 3.2; S, 15.2.

Treatment of 16 (8.3 g, 0.02 mole) by the alkaline hydrolytic method gave 11; yield 4.2 g (90%).

4-(D-arabino-*Tetraacetoxybutyl*)-4-thiazoline-2-thione (17). — Recrystallization of 16 from water containing a drop of hydrochloric acid gave 17, yield 69%, m.p. 168° after recrystallization from ether (lit.³ m.p. 169–170°); $\lambda_{\text{max}}^{\text{KBr}} 3.2-3.6$ (NH, CH), 5.78 μ m (OAc); $\lambda_{\text{max}}^{\text{MeOH}} 316$ nm (ε 12,200); $[\alpha]_{D}^{24} - 79 \pm 1^{\circ}$ (c 2, chloroform) [lit.³ $[\alpha]_{D}^{20} - 37^{\circ}$ (c 1, N,N-dimethylformamide)].

Anal. Calc. for C₁₅H₁₉NO₈S₂: C, 44.4; H, 4.7; N, 3.5; S, 15.8. Found: C, 44.4; H, 4.3; N, 3.4; S, 15.6.

Alternatively, heating 16 to 195° gave 17 in quantitative yield.

Treatment of 17 (8.1 g, 0.02 mole) by the alkaline hydrolytic method gave 11, yield 3.7 g (78%).

2,2'-Dithiobis [(4-D-arabino-tetraacetoxybutyl)thiazole] (18). — Oxidation of 17 (3.9 g, 0.096 mole) by the iodine method¹⁸ gave 18, yield 3.4 g (88%), m.p. 145° (recrystallized from ether); λ_{\max}^{MeOH} 266 nm (ε 9,100); $[\alpha]_{D}^{24}$ -13° (c 4, chloroform).

Anal. Calc. for C₃₀H₃₆N₂O₁₆S₄: C, 44.5; H, 4.5; N, 3.5; S, 15.9. Found: C, 44.9; H, 4.8; N, 3.2; S, 15.5.

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