4-Thiazoline-2-thiones. I. The Structure of Intermediate 4-Hydoxythiazolidine-2-thiones

W. J. HUMPHLETT AND R. W. LAMON

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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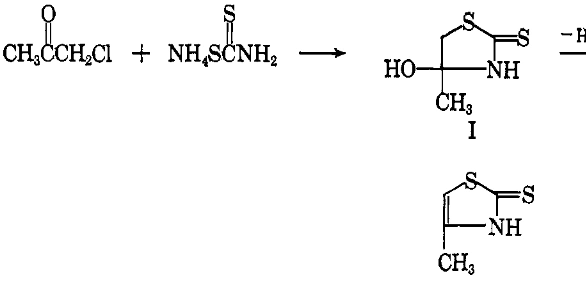
Intermediate products of the reaction of ammonium dithiocarbamate and α-halo aldehydes or ketones, formerly presumed to be substituted dithiocarbamates, have been determined to be 4-hydroxythiazolidine-2-thiones. They are compared with 4-hydroxy-3-methylthiazolidine-2-thiones obtained from reaction of α-halo ketones, carbon disulfide, and methylamine and with substituted dithiocarbamates obtained from the reaction of α-halo ketones, carbon disulfide, and dimethylamine.

A general method for preparing 4-thiazoline-2-thiones employs the reaction of ammonium dithiocarbamate and α-halo aldehydes or ketones. When the reaction is conducted for a short time with cooling, intermediate products can be isolated. These intermediates have been presumed to be acyclic.[1,2] They are referred to as substituted dithiocarbamates or dithiourethanes, which cyclize readily on standing or on being heated to form 4-thiazoline-2-thiones. Substituted dithiocarbamates have been described from the reactions of ammonium dithiocarbamate and chloroacetaldehyde,[3] chloroacetone,[4] ethyl α- and γ-chloroacetoacetate,[4-6] and phenacyl bromide.[4,5] Results of instrumental analyses and chemical evidence now reveal that these intermediates are actually 4-hydroxythiazolidine-2-thiones. The latter yield 4-thiazoline-2-thiones by dehydration.



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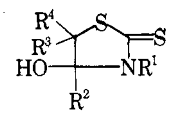
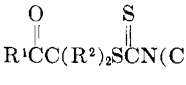
Determination of which of the two types of intermediates is isolated can be aided by comparison of the prepared series of 4-hydroxythiazolidine-2-thiones and substituted dithiocarbamates, I–VI.



I, $R^1 = R^3 = R^4 = H$; $R^2 = CH_3$
II, $R^1 = R^2 = CH_3$; $R^3 = R^4 = H$
IV, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$
V, $R^1 = R^2 = R^3 = R^4 = CH_3$
VII, $R^1 = R^3 = R^4 = H$; $R^2 = C_6H_5$
VIII, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = R^4 = H$
X, $R^1 = H$; $R^2 = C_6H_5$; $R^3 = R^4 = CH_3$
XI, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = R^4 = CH_3$
XIII, $R^1 = R^2 = R^3 = R^4 = H$
XIV, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = CO_2C_2H_5$
XV, $R^1 = R^3 = R^4 = H$; $R^2 = CH_2CO_2C_2H_5$



$$R^1\overset{\overset{O}{\|}}{C}C(R^2)_2S\overset{\overset{S}{\|}}{C}N(CH_3)_2$$

III, $R^1 = CH_3$; $R^2 = H$
VI, $R^1 = R^2 = CH_3$
IX, $R^1 = C_6H_5$; $R^2 = H$
XII, $R^1 = C_6H_5$; $R^2 = CH_3$

The infrared absorption spectrum of the intermediate isolated from reaction of ammonium dithiocarbamate and chloroacetone does not support a dithiocarbamate structure. Absorption bands expected in the 5.8- and 8-μ regions attributed to a ketone C═O group are missing. A band near 3.00 μ indicates the presence of the OH group, however, required by structure I. Disappearance of the C═O band of an intermediate dithiocarbamate was assumed earlier to be due to an enolized form or an overlapping with a C═N band, created in double enolization involving the methylene and amino groups. Hirano has suggested, based on infrared analysis, that intermediates formed from the reaction of α-halo ketones, primary amines, and carbon disulfide are 3-alkyl-4-hydroxythiazolidine-2-thiones rather than dithiocarbamates.[7] The intermediate isolated from reaction of chloroacetone, methylamine, and carbon disulfide fails to show C═O, NH stretching, and NHC═S out-of-plane deformation bands expected of a dithiocarbamate, but the OH band required by structure II is present. Use of dimethylamine in the reaction forms a dithiocarbamate (III) which cannot cyclize to a thiazolidine. Strong bands in the infrared spectrum of this substance attributed to a C═O group are apparent. The ultraviolet spectrum of the dithiocarbamate III has two major peaks at 246 and 274 mμ, contrasting with that of II or that of thiazolidine-2-thione which are similar and have one peak at 273 mμ. Results of examination of polarographic data, additionally, are consistent with the presence of a reducible C═O in compound III, and the absence of C═O in compound II. The dithiocarbamate III forms an oxime and a 2,4-dinitrophenylhydrazone, but compounds I and II do not. For further comparison, the series includes the corresponding reaction products, IV, V, and VI, derived from 3-bromo-3-methyl-2-butanone. Substitution of the methylene group of a dithiocarbamate by methyl groups would preclude cyclization *via* enolization.[2] The infrared spectra of 5,5-dimethylthiazolidines (IV and V) show OH absorption, but not C═O absorption which is shown by VI. The NH bands are apparent as required by IV. They are absent in V but would be required by a dithiocarbamate.

A related series of compounds bearing phenyl substitution is obtained by similar reactions of phenacyl bromide and α-bromoisobutyrophenone. From an

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[1] J. M. Sprague and A. H. Lane, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 8, p. 558.

[2] R. H. Wiley, *Org. Reactions*, **6**, 375 (1951).

[3] R. A. Mathes and A. J. Beber, *J. Am. Chem. Soc.*, **70**, 1451 (1948).

[4] T. G. Levi, *Gazz. chim. ital.*, **61**, 719 (1931).

[5] I. Ubaldini and A. Fiorenza, *ibid.*, **73**, 169 (1943).

[6] J. J. D'Amico and M. W. Harman, *J. Am. Chem. Soc.*, **77**, 476 (1955).

[7] H. Hirano, *J. Pharm. Soc. Japan*, **75**, 244 (1955); *Chem. Abstr.*, **50**, 1830^h (1956).

TABLE I

PREPARATIVE DATA OF 4-HYDROXYTHIAZOLIDINE-2-THIONES AND SUBSTITUTED DITHIOCARBAMATES

No.	Yield,[a] %	M.p., °C.[b]	Recrystn. solvent[c]	Formula	Calcd., %				Found, %			
					C	H	N	S	C	H	N	S
I	7	104 (80–82)[d]	Ether	$C_4H_7NOS_2$	32.2	4.7	9.4	43.0	32.0	4.6	9.2	43.1
II	84	83	Ether–ligroin	$C_5H_9NOS_2$	36.8	5.6	8.6	39.3	37.0	5.7	8.3	39.0
III	97	53	Methanol–water	$C_6H_{11}NOS_2$	40.6	6.3	7.9	36.2	40.3	6.1	7.7	36.4
III oxime		101–102	Methylene chloride–ligroin	$C_6H_{12}N_2OS_2$			14.6				14.2	
III 2,4-DNP		157.5	Ethanol	$C_{12}H_{15}N_5O_4S_2$			19.6				19.5	
IV	86	117	Benzene	$C_6H_{11}NOS_2$	40.6	6.3	7.9	36.2	40.7	6.1	7.8	35.9
V	96	64	Methanol–water	$C_7H_{13}NOS_2$	43.9	6.9	7.3	33.5	44.2	7.0	7.4	33.9
VI	97	63–64	Ethanol	$C_{11}H_{13}NOS_2$	55.2	5.5	5.9	26.8	54.8	5.7	5.6	27.0
VII	10	101–102.5 (100–103)[d]										
VIII	97	132–133	Methylene chloride–ligroin	$C_{10}H_{10}NOS_2$	53.5	4.5	6.3	28.6	53.3	4.9	5.9	28.8
IX	97	111–112	Ethanol	$C_{11}H_{13}NOS_2$	55.2	5.5	5.9	26.8	54.8	5.7	5.6	27.0
IX oxime		113–114	Methylene chloride–ligroin	$C_{11}H_{14}N_2OS_2$			11.0				10.7	
IX 2,4-DNP		199–200	Ethyl acetate	$C_{17}H_{17}N_5O_4S_2$			16.7				16.4	
X	97	154	Methanol	$C_{11}H_{13}NOS_2$	55.2	5.5	5.9	26.8	55.5	5.5	5.7	26.9
XI	75[e]	184	Methanol	$C_{12}H_{15}NOS_2$	56.9	6.0	5.5	25.4	56.9	6.2	5.4	25.6
XII	91	114	Ether	$C_{13}H_{17}NOS_2$	58.4	6.4	5.2	24.0	58.3	6.4	5.1	23.7
XIII	20	112 (110)[f]										
XIV[g]	83	128	Ether	$C_7H_{11}NO_3S_2$	38.0	5.0	6.3	29.0	37.9	4.8	6.2	28.8
XV	80	90 (74–75)[h]	Ether	$C_7H_{11}NO_3S_2$	38.0	5.0	6.3	29.0	37.7	4.8	6.1	28.7

[a] Based on crude product. [b] Determined after recrystallization. [c] The ligroin used is a hydrocarbon solvent, b.p. 35–60°. [d] Ref. 4. [e] Recrystallized. [f] Ref. 3. [g] Reported in ref. 5 without properties. [h] Ref. 6.

examination of properties, the products of these reactions can be concluded to have corresponding structures, VII–XII.

Intermediate products isolated from reaction of chloroacetaldehyde, ethyl α-chloroacetoacetate, or ethyl γ-chloroacetoacetate and ammonium dithiocarbamate are found upon similar examination to be the 4-hydroxythiazolidines XIII–XV, respectively. Preparative and comparative analytical data related to the thiazolidines and dithiocarbamates (I–XV) are summarized in Tables I and II.

The reactivity of 4-hydroxythiazolidine-2-thiones towards dehydration varies depending on substitution. Storage at room temperature for a few hours results in conversion of intermediates I and VII to corresponding 4-thiazoline-2-thiones. Analyses must be made immediately after preparation. However, intermediates XIII and XV may be kept for several days without change. Dehydration generally occurs in boiling water over 1–2 hr. For this reason recrystallization of the intermediates from water as reported earlier is not recommended. Dehydration is complete in a few minutes in boiling dilute hydrochloric acid. Progress of this reaction can be observed conveniently by ultraviolet spectra analyses since the thiazolidine-2-thiones studied are characterized by λ_{max} 273–279 mμ, and the 4-thiazoline-2-thiones formed, by λ_{max} 315–340 mμ. 5-Carbethoxy-4-methyl-4-thiazoline-2-thione absorbs at the higher wave length. Substitution at the 5-position appears to result in this shift. 5-Acetyl-4-methyl-4-thiazoline-2-thione[8] and the oxime have λ_{max} 353 mμ (ε 19,000) and 339 mμ (ε 19,800). In contrast, 4-carbethoxy- and 4-carboxy-4-thiazoline-2-thione[8] are characterized by λ_{max} 302 mμ (ε 12,800) and 305 mμ (ε 12,800).

TABLE II

No.	Major characteristic infrared wave lengths, λ_{max}, μ[a],[b]	Ultraviolet absorption spectra[c]			
		λ_{max}^{MeOH}, mμ	ε	λ_{max}^{MeOH}, mμ	ε
4-Hydroxythiazolidine-2-thiones					
I	3.03, 3.16, 14.00	245	7150	276	16500
II	3.07	252 sh	9150	272	15600
IV	3.00, 3.20, 13.85	248	6470	274	17400
V	2.92	255 sh	9300	274	16600
VII	3.05, 3.27, 13.78	245	14400	273	7600
VIII	3.02	253 sh	10100	275	16100
X	2.90, 3.07, 13.73	247	7560	279	17900
XI	3.00	250 sh	8600	274	17700
XIII	3.07, 3.15, 14.08	244	6600	277	15500
XIV	2.92, 3.17, 5.80, 8.60, 13.77	244	5530	277	13900
XV	2.90, 3.19, 5.82, 8.56	244	6830	277	15700
Substituted Dithiocarbamates					
III	5.80, 7.97	246	9020	274	10100
VI	5.85, 8.00	248	9150	278	9370
IX	5.90, 8.03	245	21700	272	10800
XII	6.00, 8.00	246	16700	277	10400

[a] Recorded on a Baird-Atomic Model NK-1 spectrophotometer with sodium chloride optics. [b] Assignment: 2.90–3.07, stretching OH; 3.07–3.27, stretching NH; 5.80–6.00, stretching C═O; 7.97–8.03, aliphatic ketone; 8.56–8.60, stretching ester O—C═O; 13.77–14.08, out-of-plane deformation NHC═S. [c] Recorded on a Cary Model 11MS spectrophotometer.

Experimental

Melting points were determined in open, soft-glass capillary tubes; melting points below 200° are corrected.

Materials.—Chloroacetone, phenacyl bromide, and ethyl α-chloroacetoacetate were used as obtained commercially (Eastman Kodak Co.); α-bromoisobutyrophenone (Aldrich Chemical Co.) was redistilled, b.p. 126° (13 mm.), $n^{25}D$ 1.5543. 3-Bromo-3-methyl-2-butanone was obtained by bromination,[9] b.p. 59° (40

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(8) J. J. D'Amico, *J. Am. Chem. Soc.*, **75**, 102 (1953).

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mm.), n^{25}_D 1.4562. Solid ammonium dithiocarbamate[10] was used without purification.

4-Hydroxythiazolidine-2-thiones (I, VII, and XIII).—These substances were found to be the intermediate products isolated from the reactions of ammonium dithiocarbamate with chloroacetone, phenacyl bromide, and chloroacetaldehyde, respectively, under the conditions of procedures previously described.[3,4]

4-Hydroxythiazolidine-2-thiones (IV, X, XIV, and XV).—In a typical preparation, 27.9 g. (0.253 mole, 10% excess) of freshly prepared ammonium dithiocarbamate was suspended in 250 ml. of acetone in a 1-l. suction flask and stirred, with cooling, in an ice-brine bath. A solution of 37.9 g. (0.23 mole) of ethyl γ-chloroacetoacetate in 100 ml. of acetone was added dropwise over a 30-min. period, the temperature of the reaction mixture being kept below 10°. After the solution had been stirred for 45 min. longer, the minimum volume of water to cause solution was added and the cold solution was stirred for 15 min. longer. Removal of acetone *in vacuo* without letting the reaction mixture become warm resulted in separation of a colorless oil. Crystallization was induced by stirring a small portion of the oil in a little ether. Crude 4-carbethoxymethyl-4-hydroxythiazolidine-2-thione (XV) amounted to 45.0 g. and melted at 90°.

4-Hydroxy-3-methylthiazolidine-2-thiones (II, V, VIII, and XI).—An example of the general procedure used to prepare these compounds is the synthesis of 4-hydroxy-3,4,5,5-tetramethylthiazolidine-2-thione (V). Potassium acetate (43.2 g., 0.44 mole) was dissolved in 250 ml. of methanol. The solution was cooled in an ice–brine bath, and 34.2 g. (0.44 mole) of 40% methylamine was added. The temperature was maintained below 10° throughout the remainder of the reaction. To the stirred solution was added dropwise 26.5 ml. (0.44 mole) of carbon disulfide mixed with an equal volume of methanol during 15 min. The resulting solution stood for 2.5 hr. A solution of 36.3 g. (0.22 mole) of 3-bromo-3-methyl-2-butanone in 50 ml. of methanol was added over 15 min., with stirring. After standing for 3 hr., 150 ml. of water was added. To isolate the product, methanol was removed *in vacuo*, the reaction mixture being kept cold. Crude product separated as a white solid weighing 27.3 g., m.p. 96°.

Substituted Dithiocarbamates (III, VI, IX, and XII).—In a typical synthesis employing largely the method just described, a solution of 20.2 g. (0.206 mole) of potassium acetate, 37.1 g. (0.206 mole) of 25% dimethylamine and 12.4 ml. (0.206 mole) of carbon disulfide in 175 ml. of methanol was treated with 23.4 g. (0.103 mole) of α-bromoisobutyrophenone in 50 ml. of methanol. Standing overnight at room temperature afforded glistening, white crystals. After the solids had been collected by filtration and washed with cold water to separate a little potassium chloride, the crude α-(N,N-dimethylthiocarbamoylthio)isobutyrophenone (XII) amounted to 25 g., m.p. 113–114°.

An oxime and 2,4-dinitrophenylhydrazone of III and IX were made (see Table I). The hindered ketones VI and XII failed to form these carbonyl derivatives under similar conditions.

4-Thiazoline-2-thiones.—The 4-hydroxythiazolidine-2-thiones were dehydrated readily either by boiling in water for 1–2 hr. or in 0.5% hydrochloric acid for a few minutes. Methanol can be added to aid solution and then boiled off. In this way there was obtained the known derivative, 4-thiazoline-2-thione, λ_{max} 313 mμ (ε 12,500), m.p. 79–80°, lit.[3] m.p. 79–80°. Also afforded were the 4-methyl, λ_{max} mμ 318 (ε 15,700), m.p. 87.5–88.5°, lit.[4] m.p. 87°; 3,4-dimethyl, 315 mμ (ε 15,000), m.p. 117°, lit.[11] m.p. 119°; 4-phenyl, 236 and 318 mμ (ε 16,800 and 14,300), m.p. 173–174°, lit.[12] m.p. 173–174°; and 5-carbethoxy-4-methyl, 340 mμ (ε 21,800), m.p. 144–145°, lit.[8] m.p. 143–144°, homologs.

3-Methyl-4-phenyl-4-thiazoline-2-thione.—This substance was obtained essentially quantitatively, m.p. 131–132°, by boiling 4-hydroxy-3-methyl-4-phenylthiazolidine-2-thione (VIII) in a solution of methanol and 0.5% hydrochloric acid. Recrystallization from ethanol gave white plates, m.p. 131–132°, λ_{max} 316 mμ (ε 15,600).

Anal. Calcd. for $C_{10}H_9NS_2$: C, 57.9; H, 4.4; N, 6.8; S, 30.9. Found: C, 57.7; H, 4.3; N, 6.9; S, 30.6.

2,2′-Dithiobis(4-phenylthiazole).—Oxidation of 4-phenyl-4-thiazoline-2-thione by the method using iodine[13] yielded the new disulfide in approximately quantitative yield, m.p. 158–159°. Recrystallization from chloroform–ethanol gave fine, white needles, m.p. 159.5–160.5°, λ_{max} 235 and 258 mμ (ε 33,800 and 30,700).

Anal. Calcd. for $C_{18}H_{12}N_2S_4$: C, 56.2; H, 3.2; N, 7.3; S, 33.3. Found: C, 55.9; H, 3.0; N, 6.9; S, 33.3.

5-Acetyl-4-methyl-4-thiazoline-2-thione Oxime.—Recrystallized from 80% ethanol, this derivative gave pale yellow needles, m.p. 215° dec.

Anal. Calcd. for $C_6H_8N_2OS_2$: C, 38.3; H, 4.3; N, 14.9. Found: C, 38.1; H, 4.5; N, 14.8.

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4-Thiazoline-2-thiones. II. Preparation of 4-Alkylsulfonylmethyl Derivatives

W. J. HUMPHLETT AND R. W. LAMON

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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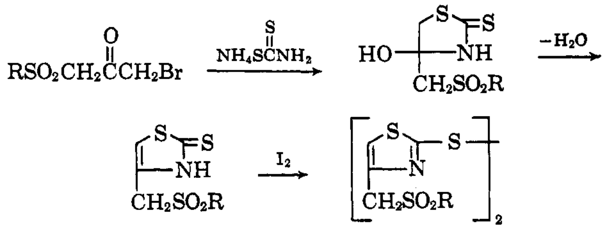
Syntheses and properties are described of the homologous series of 4-alkylsulfonylmethyl-4-thiazoline-2-thiones and disulfide derivatives obtained through intermediate 1-alkylsulfonyl-2-propanones, 1-alkylsulfonyl-3-bromo-2-propanones, and 4-alkylsulfonylmethyl-4-hydroxythiazolidine-2-thiones.

A series of 4-alkylsulfonylmethyl derivatives of 4-thiazoline-2-thiones has been obtained by reaction of ammonium dithiocarbamate and 1-alkylsulfonyl-3-bromo-2-propanones. This type of synthesis proceeds through an intermediate product which can be isolated and has been shown to be a substituted 4-hydroxythiazolidine-2-thione.[1] In a subsequent step, dehydration forms a 4-thiazoline ring. Required 1-alkylsulfonyl-3-bromo-2-propanones were obtained by reactions in the over-all scheme of synthesis, at the left. Use of these methods afforded the 1-alkylsulfonyl-2-propanones described in Table I. These ketones are characterized by 2,4-dinitrophenylhydrazones. Bromination of 1-butylsulfonyl-2-propanone in acetic acid has been reported to occur at C-3, and the site of reaction has been determined by unequivocal synthesis.[2]



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