Research Laboratories, Eastman Kodak Company

4-Thiazoline-2-thiones. IV. Preparation from Amino Acids

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4-Thiazoline-2-thiones derived from amino acids have been obtained by an improved procedure. Depending on substitution, the type of intermediate product isolated may be a 4-hydroxythiazolidine-2-thione or a dithiocarbamate.

Few 4-thiazoline-2-thiones bearing a carboxyalkyl group in the 3-position have been synthesized by treating a dithiocarbamic acid derived from an amino acid and carbon disulfide with an α-halogenated ketone, according to equation 1, Chart I. Earlier work has reported the use of glycine, D L- or β-alanine, or 4-aminobutyric acid with chloroacetone, phenacyl bromide, or 3-chloro-2-butanone (1-3). In the present work, modification of the earlier procedure allowed a more general synthesis. The change of the solvent from water to methyl alcohol improved the solubility of the reactants. Higher yields resulted from the use of two equivalents of amino acid and carbon disulfide per equivalent of α-halo ketone. Table I includes 4-thiazoline-2-thiones obtained from D L-aspartic acid, taurine, D L-methione, 6-aminohexanoic acid, and *m*-aminobenzoic acid. Among the α-halo ketones employed were ethyl bromopyruvate (4), ethyl 2- and 4-chloroacetoacetate (5), 1-acetoxy-3-chloro-2-propanone (6), 1-butylsulfonyl-3-bromo-2-propanone (7), and 3-chloro-2,4-pentanedione (8).

CHART I

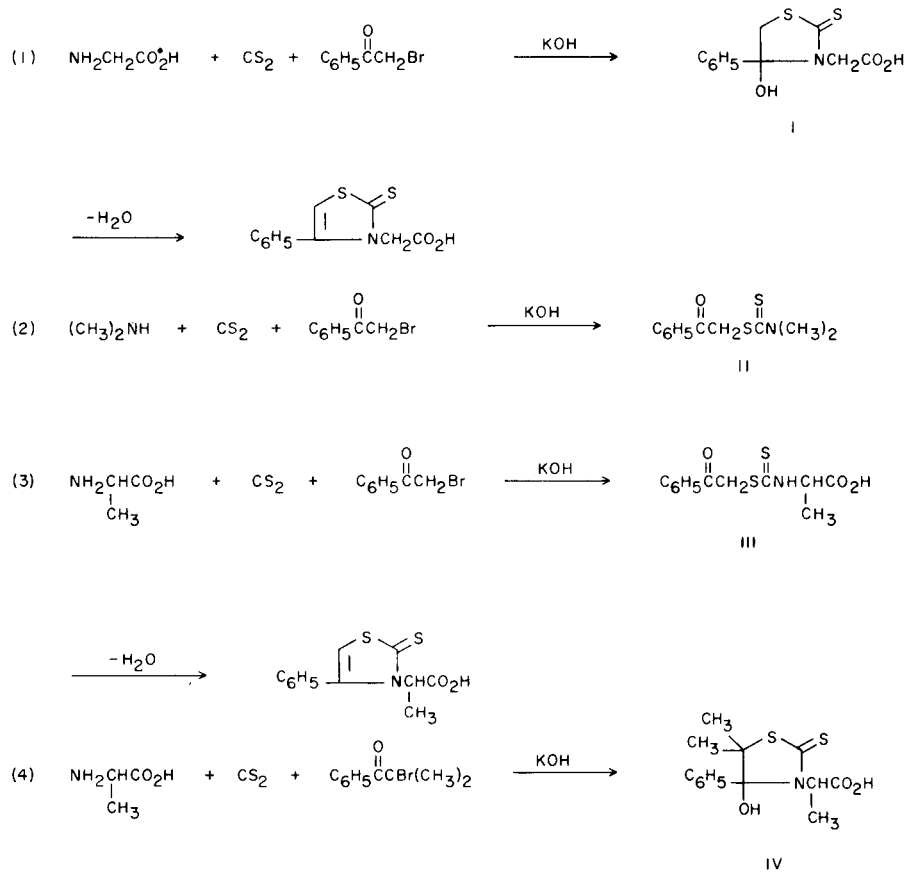
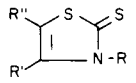


TABLE I

4-Thiazoline-2-thiones Derived from Amino Acids

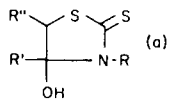


R	R′	R″	Formula	M.p., °C (a)	Yield, %	Analyses % Calcd. C	H	N	S	Found C	H	N	S	MeOH λ max mμ	ε x 10^3
CH_2CO_2H	$CH_2CO_2C_2H_5$	H	$C_9H_{11}NO_4S_2$	142-143	62	41.4	4.2	5.4	24.5	41.2	4.1	5.3	24.8	317	14.6
CH_2CO_2H	CH_2CO_2H	H	$C_7H_7NO_4S_2$	175-176	100	36.0	3.0	6.0	27.5	36.2	3.0	5.8	27.2	318	14.8
CH_2CO_2H	CH_2OCOCH_3	H	$C_8H_9NO_4S_2$	162-163	44	38.9	3.7	5.7	25.9	38.9	3.6	5.5	25.6	262, 315	2.2, 14.5
CH_2CO_2H	CH_3	$CO_2C_2H_5$	$C_9H_{11}NO_4S_2$	159-160	83	41.4	4.2	5.4	24.5	41.3	4.1	5.1	24.8	285, 337	3.1, 20.2
CH_2CO_2H	CH_3	CO_2H	$C_7H_7NO_4S_2$	224-225	100	36.0	3.0	6.0	27.5	35.9	2.7	5.8	27.2	284, 334	2.8, 19.4
CH_2CO_2H	CH_3	$COCH_3$	$C_8H_9NO_3S_2$	184-185	83	41.5	3.9	6.1	27.7	41.6	4.1	6.0	27.7	295, 349	4.0, 17.2
$(CH_2)_2CO_2H$	H	H	$C_6H_7NO_2S_2 \cdot H_2O$	58-60	71	34.8	4.4	6.7	30.9	34.7	4.2	6.4	31.2	315	14.3
$(CH_2)_2CO_2H$	CH_3	H	$C_7H_9NO_2S_2$	132-134	95	41.4	4.4	6.9	31.5	41.6	4.3	6.8	31.9	318	13.6
$(CH_2)_2CO_2H$	CH_2OCOCH_3	H	$C_9H_{11}NO_4S_2$	153	85	41.4	4.2	5.4	24.5	41.5	4.3	5.2	24.6	315	14.1
$(CH_2)_2CO_2H$	CH_2OH	H	$C_7H_9NO_3S_2$	141	84	38.3	4.1	6.4	29.2	38.1	4.1	6.1	29.6	315	14.4
$(CH_2)_2CO_2H$	$CH_2SO_2C_4H_9$	H	$C_{11}H_{17}NO_4S_3$	137-138	74	40.8	5.3	4.6	29.7	40.7	5.5	4.3	30.0	271, 318	3.5, 13.9
$(CH_2)_2CO_2H$	C_6H_5	H	$C_{12}H_{11}NO_2S_2$	136-137 (b)	100	54.3	4.2	5.3	24.2	53.9	4.3	4.9	23.9	319	14.9
$(CH_2)_2CO_2H$	CH_3	$COCH_3$	$C_9H_{11}NO_3S_2$	142-143	92	44.1	4.5	5.7	26.1	44.1	4.6	5.5	25.8	295, 351	3.9, 17.7
$(CH_2)_2CO_2H$	CH_3	$CO_2C_2H_5$	$C_{10}H_{13}NO_4S_2$	145-146	48	43.6	4.8	5.1	23.3	43.8	4.7	5.0	23.3	285, 339	2.8, 18.6
$(CH_2)_2CO_2H$	CH_3	CO_2H	$C_8H_9NO_4S_2$	206-207	83	38.9	3.7	5.7	25.9	38.6	3.7	5.5	25.8	281, 335	2.9, 19.5
$CH(CH_3)CO_2H$	H	H	$C_6H_7NO_2S_2$	146-148	38	38.1	3.7	7.4	33.9	37.9	3.7	7.1	34.2	315	14.7
$CH(CH_3)CO_2H$	$CO_2C_2H_5$	H	$C_9H_{11}NO_4S_2$	194	73	41.4	4.2	5.4	24.5	41.3	4.2	5.2	24.3	307	14.9
$CH(CH_3)CO_2H$	CO_2H	H	$C_7H_7NO_4S_2$	212	88	36.0	3.0	6.0	27.5	35.8	3.1	5.8	27.8	307	14.3
$CH(CH_3)CO_2H$	$CH_2CO_2C_2H_5$	H	$C_{10}H_{14}NO_4S_2$	60-61	42	43.6	4.8	5.1	23.3	43.2	4.8	4.9	23.7	320	13.8
$CH(CH_3)CO_2H$	CH_2CO_2K	H	$C_8H_8KNO_4S_2$	232	56	33.7	2.8	4.9	22.5	33.7	2.9	4.8	22.7	320	13.6
$CH(CH_3)CO_2H$	CH_3	$COCH_3$	$C_9H_{11}NO_3S_2$	136-137	91	44.1	4.5	5.7	26.1	43.8	4.4	5.6	25.9	297, 352	4.1, 17.5
$(CH_2)_3CO_2H$	$CH_2CO_2C_2H_5$	H	$C_{11}H_{15}NO_4S_2$	100-101	79	45.7	5.2	4.8	22.2	45.7	5.2	4.6	21.9	319	14.1
$(CH_2)_3CO_2H$	CH_2CO_2H	H	$C_9H_{11}NO_4S_2$	147-148	100	41.4	4.2	5.4	24.5	41.5	4.2	5.2	24.2	318	14.7
$(CH_2)_3CO_2H$	$CH_2SO_2C_4H_9$	H	$C_{12}H_{19}NO_4S_3$	145-146	60	42.6	5.7	4.2	28.5	42.5	5.5	4.4	28.9	271, 318	3.1, 12.0
$(CH_2)_3CO_2H$	C_6H_5	H	$C_{13}H_{13}NO_2S_2$	137-138	52	55.9	4.7	5.0	22.9	55.5	4.5	5.0	22.6	320	14.4
$(CH_2)_3CO_2H$	CH_3	$CO_2C_2H_5$	$C_{11}H_{15}NO_4S_2$	122-123	71	45.7	5.2	4.8	22.9	45.9	5.0	4.8	22.3	285, 340	3.0, 19.6
$(CH_2)_3CO_2H$	CH_3	CO_2H	$C_9H_{11}NO_4S_2$	203	89	41.4	4.2	5.4	24.5	41.2	4.1	5.1	24.3	281, 334	2.4, 15.9
$(CH_2)_5CO_2H$	CH_3	H	$C_{10}H_{15}NO_2S_2$	86-87	70	48.9	6.2	5.7	26.1	49.3	6.1	5.4	25.8	318	13.5
$CHCO_2H$ | CH_2CO_2H	CH_3	H	$C_8H_9NO_4S_2$	217-218	26	38.9	3.7	5.7	25.9	39.3	4.0	5.4	25.8	323	13.9
$CH_2CH_2SO_3K$	CH_3	H	$C_6H_8NO_3S_3K$	362 (c)	20	26.0	2.9	5.1	34.7	25.7	2.9	4.8	34.8	319	12.3
$CH_3S(CH_2)_2CHCO_2H$	CH_3	H	$C_9H_{13}NO_2S_3$	130	80	41.0	5.0	5.3	36.5	41.0	4.9	5.0	36.9	321	13.4
$C_6H_4CO_2H$-*m*	CH_3	H	$C_{11}H_9NO_2S_2$	191-193 (b)	66	52.6	3.6	5.6	25.5	52.4	3.5	5.3	25.2	324	12.4

(a) Recrystallized from water unless otherwise indicated. (b) From 50% ethanol. (c) From methanol.

TABLE II

4-Hydroxythiazolidine-2-thiones Derived from Amino Acids



(a)

R	R′	R″	Formula	M.p., °C	Yield, %	Analyses % Calcd. C	H	N	S	Found C	H	N	S	MeOH λ max mμ	ε x 10^3
CH_2CO_2H	C_6H_5	H	$C_{11}H_{11}NO_3S_2$	103 (d)	87	49.1	4.1	5.2	23.8	48.9	3.9	4.9	23.6	255, 278	9.6, 16.1
$(CH_2)_2CO_2H$	C_6H_5	H	$C_{12}H_{13}NO_3S_2$	132 (e)	80	50.9	4.6	4.9	22.6	50.9	4.6	4.8	22.4	254, 277	10.0, 16.1
$(CH_2)_2CO_2H$	CH_3	$(CH_3)_2$	$C_9H_{15}NO_3S_2$	94-95 (f)	75	43.4	6.1	5.6	25.7	43.0	5.9	5.6	25.3	259, 277	9.5, 15.6
$CH(CH_3)CO_2H$	$CH_2CO_2C_2H_5$	H	$C_{10}H_{15}NO_5S_2$	102-103 (e)	77	40.9	5.2	4.8	21.9	40.8	5.0	4.5	21.7	258, 277	7.8, 12.6
$CH(CH_3)CO_2H$	CH_3	$(CH_3)_2$	$C_9H_{15}NO_3S_2$	123-124 (g)	85	43.4	6.1	5.6	25.7	43.4	6.2	5.5	25.7	260, 278	8.7, 14.7
$CH(CH_3)CO_2H$ (b)	C_6H_5	$(CH_3)_2$	$C_{14}H_{17}NO_3S_2$	125 (h)	94	54.0	5.5	4.5	20.7	53.7	5.3	4.4	21.0	260, 280	8.8, 15.4
$CH(CH_3)CO_2H$ (c)	C_6H_5	$(CH_3)_2$	$C_{14}H_{17}NO_3S_2$	136-137 (h)	52	54.0	5.5	4.5	20.7	54.0	5.4	4.2	20.6	260, 280	8.6, 15.4
$(CH_2)_3CO_2H$	C_6H_5	H	$C_{13}H_{15}NO_3S_2$	131-132 (e)	71	52.5	5.1	4.7	21.6	52.8	5.3	4.4	21.8	266, 277	9.5, 14.8
$(CH_2)_3CO_2H$	$CH_2CO_2C_2H_5$	H	$C_{11}H_{17}NO_5S_2$	96 (d)	94	43.0	5.6	4.6	20.9	43.2	5.4	4.4	20.7	255, 277	8.8, 14.9

(a) The structure bears 5-hydrogen in addition to R″, unless otherwise indicated. (b) From DL-alanine; product, $[\alpha]^{25}$ 0° (c 3, chloroform). (c) From L-alanine; product, $[\alpha]^{25}$ −24.0° (c 3, chloroform). (d) Recrystallized from ethyl acetate-pentane. (e) From acetone-pentane. (f) From water. (g) From ethanol-water. (h) From chloroform-pentane.

Depending upon the conditions, the method can yield an intermediate product. Our previous papers have shown that the reaction of ammonium dithiocarbamate and α-halo ketones yields intermediate 4-hydroxythiazolidine-2-thiones (9,10). Recent work has indicated that a similar reaction of primary amines, carbon disulfide, and α-halo ketones yields either intermediate 4-hydroxythiazolidine-2-thiones or dithiocarbamates (11). Dehydration or cyclodehydration of the latter compounds produces 3-substituted 4-thiazoline-2-thiones. In the present study of the reaction with amino acids, certain of the intermediates were isolated. Determination of their structure supports recent conclusions regarding the influence of substitution on the type of intermediate isolated.

The reaction of phenacyl bromide and glycine (equation 1) has been assumed to yield an intermediate dithiocarbamate. The intermediate, however, has failed to yield a phenylhydrazone or semicarbazone (12). Related dithiocarbamates, *e.g.*, II, known to be formed from secondary amines (equation 2), have yielded carbonyl derivatives (10,13). A dithiocarbamate similarly derived from a primary amine has given carbonyl derivatives (11). The infrared spectrum of intermediate I fails to show ketone C=O absorption required by a dithiocarbamate, but shows an OH band; II shows C=O absorption. The ultraviolet spectrum of intermediate I, λ max 255, 278 mμ (ε, 9,600; 16,100), is unlike that of II, but is similar to that of the previously reported 3-ethyl-4-hydroxy-4-phenylthiazolidine-2-thione, λ max 255, 277 mμ (ε, 9,100; 15,300) (11). On this basis, the intermediate is assigned the cyclic structure, I.

The type of intermediate isolated from preparations of 3-substituted 4-thiazoline-2-thiones has been reported to depend on the nature and degree of substitution (11). Substitution by sterically hindering groups at positions 3 or 4 has favored isolation of dithiocarbamates, whereas alkyl substitution at position 5 has favored 4-hydroxythiazolidines. A "*gem*-dimethyl effect" on facilitating cyclization of common rings is well documented (14). The influence of substitution on the type of intermediate obtained from amino acids parallels these effects. An acyclic intermediate, III, bearing a sterically hindering group on the nitrogen atom, was isolated according to equation 3. The product, IV, equation 4, bearing *gem*-dimethyl substitution has a cyclic structure. In certain cases of steric hindrance, tautomeric equilibrium of the cyclic and acyclic intermediates in solution has been demonstrated (11). No evidence of equilibrium of the present examples was observed.

The ultraviolet spectrum of the acyclic intermediate, III, has λ max 250, 277 mμ (ε, 16,100; 11,400), compared with that of the earlier reported benzoylmethyl isopropyldithiocarbamate, λ max 248, 270 mμ (ε, 17,100; 9,600) (11). The infrared spectrum of III shows NH at 3.02 μ, benzoyl C=O at 5.97 μ, and carboxy C=O at 5.85 μ. The ultraviolet spectrum of the cyclic intermediate, IV,, λ max 280 mμ (ε, 15,000), is similar to that of the reported 4-hydroxy-3-isopropyl-4-phenyl-5,5-dimethylthiazolidine-2-thione, which has λ max 279 mμ (ε, 15,000) (11). The infrared spectra of the cyclic intermediates, I and IV, show bands, respectively, for OH at 3.15 μ and 2.95 μ (the latter due to steric hindrance), and carboxy C=O at 5.85 μ. The dithiocarbamate structure of III appears to be correct, as previously proposed in the literature (2). Analysis of other intermediates derived from D L-alanine suggests, in the crude state, the presence of a dithiocarbamate.

The 4-hydroxythiazolidine-2-thiones isolated are characterized in Table II. A bathochromic shift of the ultraviolet spectra occurs among the thiazolines bearing 5-acetyl, carbethoxy, or carboxy substitution (Table I).

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected. Infrared spectra were recorded on a Baird-Atomic Model NK-1 Spectrophotometer with sodium chloride optics. 3-Bromo-3-methyl-2-butanone was prepared as reported (15); other α-halo ketones were obtained commercially unless otherwise indicated in the discussion.

General Procedure.

4-Thiazoline-2-thiones (Table I).

These substances were obtained (a) directly from the reaction mixture or (b) by dehydration of the isolated intermediates, according to the following examples.

(a) 4-Acetoxymethyl-3-(2-carboxyethyl)-4-thiazoline-2-thione.

A mixture of 55.2 g. (0.62 mole) of D L-alanine and 36.8 g. (0.56 mole) of potassium hydroxide in 150 ml. of methanol was made, with warming and stirring. The small amount of D L-alanine in excess failed to dissolve. To the stirred mixture, cooled in an ice bath, was added 34 ml. (0.56 mole) of carbon disulfide over 20 minutes, forming a gummy, white solid. After the cooled mixture had been stirred for 1 hour, a solution of 42 g. (0.28 mole) of 1-acetoxy-3-chloro-2-propanone in an equal volume of methanol was added, with cooling and stirring, over 20 minutes. The reaction mixture was stirred for 1 hour, with cooling. The reactions were exothermic. Sufficient water, about 200 ml., to form a solution was added, and the solution was stirred 15 minutes longer. Methanol was removed *in vacuo*, leaving a yellow solution. Acidification with excess concentrated hydrochloric acid caused an oil to separate which solidified on standing overnight. Filtration yielded 66 g. of crude product, m.p. 144°. Pure product was obtained after two recrystallizations, amounting to 46 g. of light tan needles.

(b) 3-(2-Carboxyethyl)-4-phenyl-4-thiazoline-2-thione.

A solution of 10 g. (0.035 mole) of 3-(2-carboxyethyl)-4-hydroxy-4-phenylthiazolidine-2-thione in 50 ml. of glacial acetic acid was refluxed for 0.5 hour. On cooling, crystals formed as prisms. Water (100 ml.) was added, and the crystals were collected, giving 7 g. of the thiazoline, m.p. 134-136°. A second crop gave 2.5 g.

In general, 1 hour of refluxing of solutions of 4-hydroxythiazolidines in large volumes of water also afforded thiazolines.

4-Hydroxythiazolidine-2-thiones (Table II).

The preparation of 4-carbethoxymethyl-3-(3-carboxypropyl)-4-hydroxythiazolidine-2-thione is typical of the procedure used to obtain these intermediates. To a stirred solution of 41.7 g. (0.41 mole) of 4-aminobutyric acid and 26.2 g. (0.4 mole) of potassium hydroxide in 250 ml. of methanol was added 24.1 ml. (0.4 mole) of carbon disulfide, with cooling in an ice-brine bath. After the cold mixture had been stirred for 2 hours, a solution of 32.9 g. (0.2 mole) of ethyl 4-chloroacetoacetate in an equal volume of methanol was added over 20 minutes. The reaction mixture was stirred for 2.5 hours, 220 ml. of water was added, and the methanol removed *in vacuo*. To the rapidly stirred, resulting solution, cooled in an ice bath, concentrated hydrochloric acid was added dropwise until the mixture was acidic. Fine, white crystals gradually formed. The product was collected, rinsed with cold water, and dried *in vacuo* at room temperature to constant weight, 57.4 g., m.p. 96°. The melting point was unchanged on recrystallization.

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