Research Laboratories, Eastman Kodak Company
and
Research Laboratories of Distillation Products Industries,
Division of Eastman Kodak Company

4-Thiazoline-2-thiones. III. The Thermodynamic Stability of Intermediate, Tautomeric Thiazolidines and Dithiocarbamates

R. W. Lamon (1), W. J. Humphlett (1) and W. P. Blum (2)

The intermediate products isolated from preparations of 3-substituted 4-thiazoline-2-thiones by the reaction of primary amines, carbon disulfide, and α-haloketones may be either 4-hydroxythiazolidine-2-thiones or dithiocarbamates. Tautomeric equilibrium of the two types of intermediates in solution is demonstrated, and the more thermodynamically stable form is determined. Steric and electronic effects of substitution on stability are described.

Intermediate dithiocarbamates previously have been reported (3) to be isolated in the syntheses of 4-thiazoline-2-thiones from ammonium dithiocarbamate and α-haloketones (Eq. a). Recent papers (4,5) have shown that the intermediates are 4-hydroxythiazolidine-2-thiones (Eq. b). *N,N*-Disubstituted dithiocarbamates are known (6) to be formed by the reaction of secondary amines, carbon disulfide, and α-haloketones (Eq. c). The latter products show C=O bands in their infrared absorption spectra and, in the absence of steric hindrance, yield carbonyl derivatives (4,7). Intermediate dithiocarbamates also have been reported (8) to be isolated in the preparations of 3-substituted 4-thiazoline-2-thiones by similar reaction with primary amines (Eq. d). Much of the work concerning 3-substituted 4-thiazoline-2-thiones has been related to the synthesis of Vitamin B_1. Yoshida, contributing in this field, first published the observation that the infrared spectra of the intermediates are not typical of dithiocarbamates (9) but are characteristic of 4-hydroxythiazolidine-2-thiones (10). Hirano reached a similar conclusion (6). Subsequent 4-hydroxythiazolidine-2-thiones have been isolated from reactions using methyl (4,6), ethyl (11), benzyl (12,7), and *o*-nitrobenzylamine (13), aniline (14), and 4-amino-5-aminomethyl-2-methylpyrimidine (15) (Eq. e). The isolation of intermediate dithiocarbamates in the preparation of 4-thiazoline-2-thiones generally has been refuted.

In the current work, syntheses of 3-substituted 4-thiazoline-2-thiones allowed isolation of the intermediate products listed in Chart I. Infrared absorption spectra of the expected intermediate 4-hydroxythiazolidine-2-thiones in the solid state show OH bands. However, certain sterically hindered intermediates proved to be dithiocarbamates. As an example, intermediate XVII shows NH and C=O bands and forms an oxime and a semicarbazone. Ultraviolet absorption spectra offer supporting evidence of structure. Many of the intermediates listed exhibit ring-chain tautomerism between the thiazolidine and dithiocarbamate forms in solution. Interconversions are demonstrable. After IV, X, or XI reached equilibrium in methylene chloride, dilution with hexane crystallized the cyclic forms. Both members of certain tautomeric pairs were isolated. After equilibration of the tautomers, XIII and XV, in methylene chloride, crystallization yielded the acyclic form. Recrystallization from methanol-water then yielded the cyclic form.

Effects of substitution on the formation of the cyclic and the acyclic intermediates may be expected. Alkyl and *gem.*-dimethyl substitution have been reported to facilitate ring formation (16). Steric hindrance may retard cyclization. Comparison of the stability of the intermediates

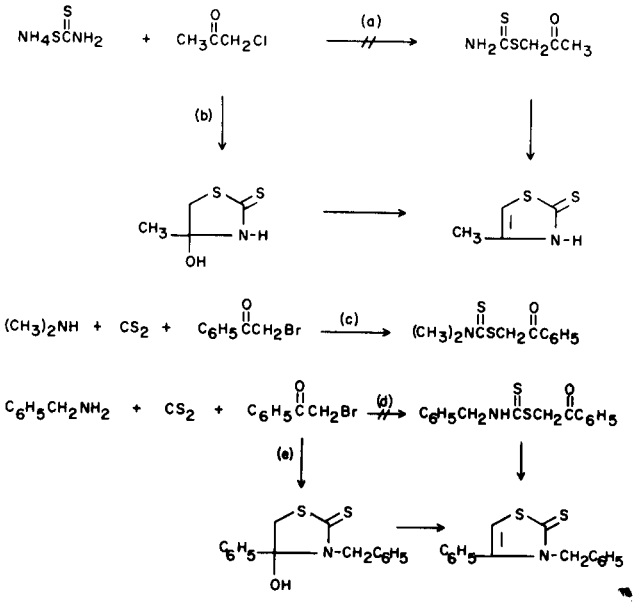
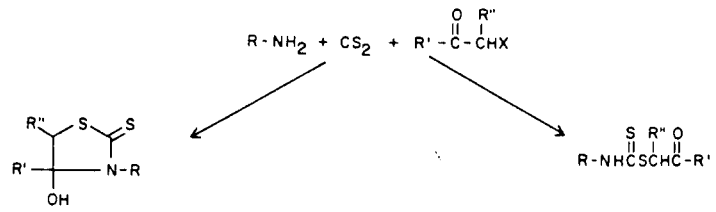


CHART I

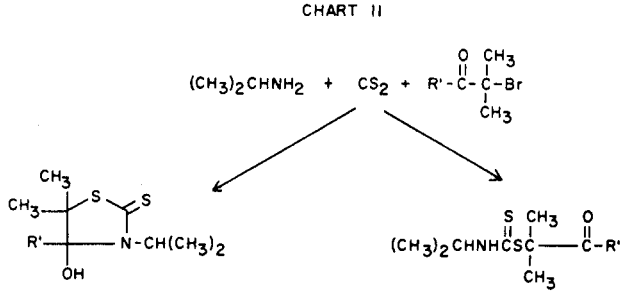


No.	R	R′	R″		No.	R	R′	R″
I	CH_3	C_2H_5	CH_3		XVI	$CH(CH_3)_2$	$C(CH_3)_3$	H
II	$CH_2CH{=}CH_2$	C_2H_5	CH_3		XVII	$CH(CH_3)_2$	C_6H_5	H
III	$CH_2C_6H_5$	CH_3	H		XVIII	$CH(CH_3)_2$	C_6H_5	C_6H_5
					XIX	$CH(CH_3)_2$	$C_6H_4OCH_3$-*p*	CH_3
IV	$CH(CH_3)_2$	C_6H_5	CH_3	90 / 10				
V	$CH(CH_3)_2$	C_6H_4Cl-*p*	CH_3	88 / 12	XIV			
VI	C_6H_5	$C_6H_4OCH_3$-*p*	CH_3	41 / 59				
VII	C_6H_5	C_6H_5	CH_3	15 / 85				
VIII	C_6H_5	C_6H_4Cl-*p*	CH_3	11 / 89				
IX	C_2H_5	C_6H_5	H	22 / 78		Acyclic in solution		
X	$CH(CH_3)_2$	CH_3	H	85 / 15				
XI	$CH(CH_3)_2$	C_2H_5	CH_3	94 / 6				
XII	CH_3	$C(CH_3)_3$	H	48 / 52				
XIII	C_6H_5	$C(CH_3)_3$	H	97 / 3	XV			

cannot be based on isolation, which depends on solubility. The isolated intermediates, IV, X, and XI, are, in fact, less stable forms. However, thermodynamic stability may be measured by the position of the equilibria of the cyclic and acyclic intermediates (16). The stable, unhindered thiazolidines, I–III, and hindered dithiocarbamates, XVI–XIX, show unaltered infrared spectra in solution. However, intermediates, IV–XV, show progressive changes of OH, NH, and C=O absorbances until equilibration. Solution of members of tautomeric pairs reached identical equilibrations.

Certain conclusions regarding the stability of the intermediates are based on the positions of the equilibria of

CHART II



XX R′ = CH_3

XXI R′ = C_6H_5

XXII R′ = $C(CH_3)_3$

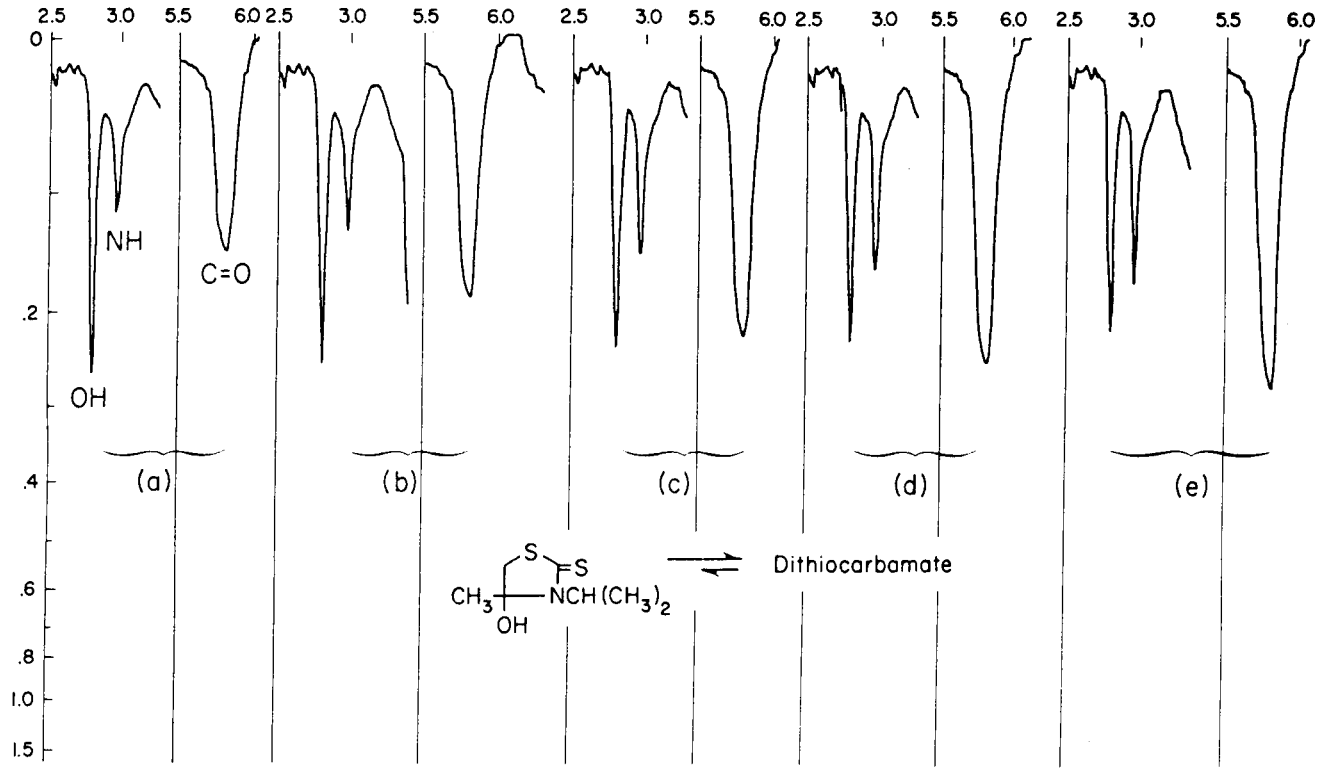


Fig. 1. 4-Thiazoline-2-thiones. III. The Thermodynamic Stability of Intermediate, Tautomeric Thiazolidines and Dithiocarbamates.

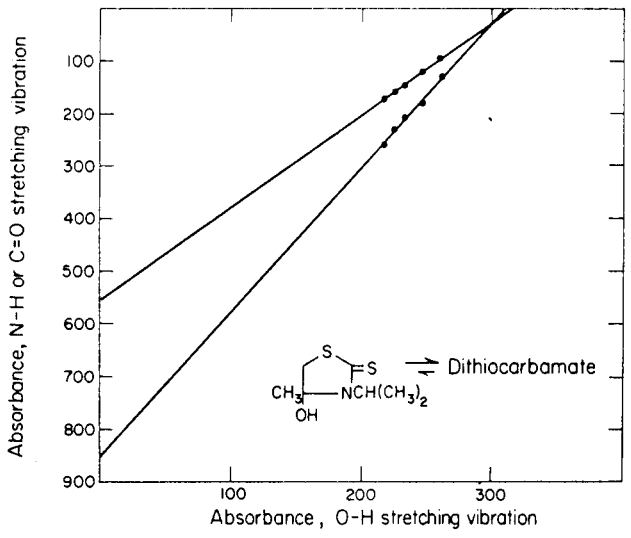


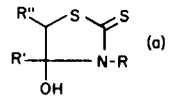
Fig. 2. 4-Thiazoline-2-thiones. III. The Thermodynamic Stability of Intermediate, Tautomeric Thiazolidines and Dithiocarbamates.

Chart I. Steric hindrance at R appears to stabilize the acyclic form, *e.g.*, IV, R = $CH(CH_3)_2$ (90% acyclic) contrasts with VII, R = C_6H_5 (15% acyclic). In the comparison, R′ and R″ remain constant. A similar conclusion can be drawn regarding the effect of R = $CH(CH_3)_2$, on comparing V and VIII; XI and I; and XVII and IX. Steric hindrance at R′ also stabilizes the acyclic form evidenced by comparison of the position of equilibria of XII, R′ = $C(CH_3)_3$ (48% acyclic) and IX, R′ = C_6H_5 (22% acyclic). Increased stabilization of a cyclic intermediate by R″ = alkyl is suggested by comparison of the equilibrium of IV, R″ = CH_3 (10% cyclic) with XVII, R″ = H (stable, acyclic). A greater influence favoring cyclic forms is illustrated by a *gem.*-dimethyl effect, *e.g.*, on comparing XXI (stable, cyclic) of Chart II with IV, R″ = CH_3 (90% acyclic). Although the 5,5-dimethyl-4-hydroxythiazolidines, XX and XXI, were obtained despite R = $CH(CH_3)_2$ substitution, the *gem.*-dimethyl effect was insufficient to cyclize the more hindered XXII, R′ = $C(CH_3)_3$. Although XX, XXI, and XXII of Chart II cannot dehydrate to thiazolines, their spectra support the accompanying data.

Differences of basicity of the N atom, owing to substitution, appear to influence the stability of the intermediates. The positions of equilibria of XII (52% cyclic) *vs.* XIII (3% cyclic) suggest that nucleophilic ring closure of the dithiocarbamate is favored more when N is substituted

TABLE I

Thiazolidine-2-thiones

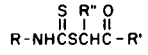


No.	Formula	Yield, %	M.p., °C (b)	λ max (EtOH), mμ	ε x 10^3	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
I	$C_7H_{13}NOS_2$	91	105–106	255, 273	9.6, 16.4	43.9	6.8	7.3	33.4	44.0	6.8	7.0	33.1
II	$C_9H_{15}NOS_2$	91	79–81 (c)	257s, 275	9.2, 15.4	49.7	7.0	6.5	29.5	49.9	7.0	6.1	29.1
III	$C_{11}H_{13}NOS_2$	78	102–103	252, 278	9.0, 13.5	55.2	5.5	5.9	26.8	55.0	5.8	5.6	26.5
IV	$C_{13}H_{17}NOS_2$	93	82–83	250, 277	12.6, 10.5	58.3	6.4	5.2	24.0	58.4	6.4	5.0	24.0
V	$C_{13}H_{16}ClNOS_2$	74	139–141 (d)	258, 275	10.9, 9.0	51.7	5.3	4.6	21.2	51.6	5.3	4.4	20.9
VI	$C_{17}H_{17}NO_2S_2$	53	137–138 (e)	270s, 278	19.7, 22.3	61.6	5.2	4.2	19.4	61.6	5.0	4.0	19.5
VII	$C_{16}H_{15}NOS_2$	96	124–125	268s, 278	13.6, 14.7	63.8	5.0	4.7	21.3	64.0	5.2	4.5	21.5
VIII	$C_{16}H_{14}ClNOS_2$	73	153–154	266, 277	15.4, 15.4	57.2	4.2	4.2	19.1	57.4	4.3	4.0	19.2
IX	$C_{11}H_{13}NOS_2$	78	118–119	255, 277	9.1, 15.3	55.2	5.5	5.9	26.2	55.4	5.6	5.8	26.6
X	$C_7H_{13}NOS_2$	38	86–87	253s, 275	9.0, 13.3	43.9	6.8	7.3	33.4	44.2	6.9	7.1	33.6
XI	$C_9H_{17}NOS_2$	89	68–70	252, 277	6.6, 7.8	49.3	7.8	6.4	29.2	49.7	7.8	6.1	29.4
XII	$C_8H_{15}NOS_2$	75	96–97	272	15.2	46.8	7.4	6.8	31.2	47.0	7.3	6.6	30.8
XIII	$C_{13}H_{17}NOS_2$	83	94–95 (d)	268, 278	10.5, 11.1	58.3	6.4	5.2	24.0	58.1	6.5	4.9	23.8
XX	$C_9H_{17}NOS_2$	92	114–115	278	14.5	49.3	7.8	6.4	29.2	49.4	7.7	6.2	29.6
XXI	$C_{14}H_{19}NOS_2$	95	142–143	279	15.5	59.7	6.8	5.0	22.8	59.6	6.7	4.8	23.0

(a) The structure bears 5-hydrogen in addition to R'', except for XX and XXI, where R'' = $(CH_3)_2$. (b) Recrystallized from methylene chloride-hexane, unless otherwise noted. (c) From ether-hexane. Reported in Ref. 18 as a dithiocarbamate. (d) From methanol-water. (e) From acetone-hexane.

TABLE II

Dithiocarbamates

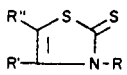


No.	Formula	Yield, %	M.p., °C (a)	λ max (MeOH), mμ	ε x 10^3	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
XIV	$C_{13}H_{16}ClNOS_2$	74	89–90	257, 275	11.1, 9.3	51.7	5.3	4.6	21.2	51.6	5.2	4.4	20.9
XV	$C_{13}H_{17}NOS_2$	83	84–85	268, 277	12.0, 12.3	58.3	6.4	5.2	24.0	58.4	6.4	5.1	23.8
XVI	$C_{10}H_{19}NOS_2$	75	96–97	251, 271	7.6, 6.6	51.5	8.2	6.0	27.5	51.7	8.0	5.9	27.6
XVII	$C_{12}H_{15}NOS_2$	71	94–95	248, 270s	17.1, 9.6	56.9	6.0	5.5	24.3	56.9	6.4	5.3	24.6
Oxime	$C_{12}H_{15}N_2OS_2$	72 (b)	148–149	250	17.6	53.7	6.0	10.4	23.9	53.6	6.0	10.0	23.5
Semi-carbazone	$C_{13}H_{18}N_4OS_2$	95 (c)	179–180	268	12.7	50.3	5.9	18.0	20.7	50.2	5.9	17.9	20.5
XVIII	$C_{18}H_{19}NOS_2$	56	138–139	251, 275s	18.5, 10.5	65.5	5.8	4.3	19.5	65.5	5.9	4.1	19.2
XIX	$C_{14}H_{19}NO_2S_2$	74	95–96	220, 276	17.0, 18.1	56.5	6.4	4.7	21.6	56.3	6.3	4.6	21.9
XXII (d)	$C_{12}H_{23}NOS_2$	47	71–72 (e)	254, 280s	4.8, 3.4	55.1	8.8	5.3	24.5	55.3	8.6	4.9	24.2

(a) Recrystallized from methylene chloride-hexane, unless otherwise indicated. (b) From chloroform. (c) From methanol. (d) XXII bears R'' = $(CH_3)_2$ and no α-H. (e) From hexane.

TABLE III

4-Thiazoline-2-thiones



Subst'd. as in No.	Formula	Yield, %	M.p., °C(a)	λ max (EtOH), mμ	ε x 10^3	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
I	$C_7H_{11}NS_2$	91	59–60 (b)	321	15.0	48.5	6.4	8.1	37.0	48.7	6.3	7.9	36.8
II	$C_9H_{13}NS_2$	77	(c)	323	14.6	----	---	---	----	----	---	---	----
III	$C_{11}H_{11}NS_2$	96	86–87	320	14.6	59.7	5.7	6.3	29.0	59.5	4.8	6.1	28.6
IV	$C_{13}H_{15}NS_2$	92	158–159 (d)	325	15.4	62.6	6.1	5.6	25.7	62.5	6.0	5.3	25.6
V	$C_{13}H_{14}ClNS_2$	87	112–113	221, 326	18.5, 15.7	55.0	5.0	4.9	22.6	54.8	5.0	4.7	22.2
VI	$C_{17}H_{15}NOS_2$	87	151–152	236, 330	18.5, 16.1	65.1	4.8	4.5	20.5	65.3	4.7	4.4	20.2
VII	$C_{16}H_{13}NS_2$	91	201–202 (e)	238, 334	11.2, 14.8	67.8	4.6	4.9	22.6	67.7	4.7	4.8	22.6
VIII	$C_{16}H_{12}ClNS_2$	88	201–202 (e)	333	15.2	60.5	3.8	4.4	20.6	60.6	3.6	4.2	20.1
IX	$C_{11}H_{11}NS_2$	99	84–85 (f)	319	22.0	----	---	---	----	----	---	---	----
X	$C_7H_{11}NS_2$	85	67–68 (g)	321	13.7	----	---	---	----	----	---	---	----
XI	$C_9H_{15}NS_2$	83	(h)	327	14.4	53.7	7.5	7.0	31.8	53.5	7.2	6.8	31.5
XII	$C_8H_{13}NS_2$	99	116–117	313	14.7	51.3	7.0	7.5	34.2	51.5	7.3	7.4	34.4
XIII	$C_{13}H_{15}NS_2$	72	173–174 (i)	321	14.3	----	---	---	----	----	---	---	----
XVI	$C_{10}H_{17}NS_2$	90	89–90 (j)	323	13.8	55.8	8.0	6.5	29.8	56.2	8.1	6.2	29.4
XVII	$C_{12}H_{13}NS_2$	97	145–146 (d)	323	14.7	61.2	5.6	6.0	27.2	61.3	5.9	5.7	26.9
XVIII	$C_{18}H_{17}NS_2$	42	213–214 (k)	338	18.2	69.4	5.5	4.5	20.6	69.6	5.7	4.2	20.2
XIX	$C_{14}H_{17}NOS_2$	82	117–118	240, 326	16.0, 15.3	60.2	6.1	5.0	23.0	60.1	6.1	4.7	23.0

(a) Recrystallized from methanol, unless otherwise indicated. (b) From ether-hexane. (c) B.p. 65°/3 μ, n_D^{25} 1.6185. Reported in Ref. 18. (d) From ethanol. (e) From chloroform-ethanol. (f) Reported m.p. 84° in Ref. 11. (g) Reported m.p. 68–69° in Ref. 19. (h) B.p. 70°/3 μ, n_D^{25} 1.6039. (i) Reported m.p. 167–168° in Ref. 20. (j) From hexane. (k) From methylene chloride-methanol.

by R = CH_3 than by R = C_6H_5. The inductive effect of R′ = C_6H_5Cl-*p*, opposed by a strong resonance effect, shows little additional activation of the C=O of the dithiocarbamate towards cyclization when compared to R′ = C_6H_5. This is indicated by the similar equilibria of V and IV and of VIII and VII. An electronic effect appears to decrease the stability of cyclic intermediates when R′ = $C_6H_4OCH_3$-*p* compared to R′ = C_6H_5 indicated by comparison of different equilibria of VI and VII and of XIX and IV. The electron-repelling $C_6H_4OCH_3$-*p* group, which is expected to deactivate the dithiocarbamate C=O, appears to suppress cyclization.

Few quantitative data have been reported previously for equilibrated ring-chain systems. Analysis of infrared absorption spectra appears suited for the determination of the composition at equilibrium. Such a method requires standard bands for comparison. However, even the stable intermediates show variable OH, NH, and C=O absorbances, depending upon substitution. Earlier workers, unable to measure precisely cyclic-acyclic ratios in solution in the absence of pure cyclic or acyclic forms, have made estimates (17). An analytical method based on infrared spectra provided the data of Chart I with improved precision. The method is demonstrated by the following example: In Fig. 1, the OH, NH, and C=O bands are shown periodically by segments of the spectra, a–e, resulting when a 1% solution of the thiazolidine indicated stands for 2 hours. The approach to equilibrium causes progressive decreases of OH and increases of NH and C=O absorbances. In Fig. 2, graphs of these functions are linear. The upper line results from plotting OH *vs.* NH absorbances. Extrapolation gives OH and NH absorbances of pure cyclic and acyclic intermediates which can serve as standards for comparison. The lower line results from plotting OH *vs.* C=O absorbances, and upon extrapolation provides standard OH and C=O absorbances. The composition of the system at equilibrium was determined based on comparison of the OH, NH, and C=O absorbances at equilibrium with the absorbances of the standards. New standards were determined for each equilibrated system.

Physical properties of intermediate thiazolidines and dithiocarbamates are recorded in Tables I and II, respectively. Thiazolines prepared from the intermediates are characterized in Table III.

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected; boiling points are uncorrected. Infrared spectra, in μ, were recorded on a Perkin-Elmer Infrared Model 21 Spectrophotometer with sodium chloride optics, and 1% solutions of samples in methylene chloride in a 1-mm. cell. Major characteristic stretching bands: Thiazolidines show OH at 2.84; dithiocarbamates have NH at 3.00 and C=O at 5.84 (R′ = aliphatic), 5.90 (R′ = $C_6H_4OCH_3$-*p*).

Halo Ketones.

Commercial sources provided 3-chloro-2-propanone, 2-bromoacetophenone, 2-bromo-2-phenylacetophenone (Eastman Kodak Co.); α-bromoisobutyrophenone (Aldrich Chemical Co.); and 2-bromopropiophenone (K and K Laboratories, Inc.). 3-Bromo-3-methyl-2-butanone (21), 1-bromo-3,3-dimethyl-2-butanone (22), 2-bromo-2,4,4-trimethyl-2-pentanone (23), and *p*-chloro- and *p*-methoxy-2-bromopropiophenone (24) were prepared as previously described.

General Procedures.

Intermediate products were isolated when the following procedures were effected; the use of heat or acid was avoided to prevent dehydration.

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

(a) To a stirred solution of 53.6 g. (0.5 mole) of benzylamine and 49.1 g. (0.5 mole) of potassium acetate in 300 ml. of methanol, which was cooled in an ice bath, was added 33 ml. (0.55 mole) of carbon disulfide over 10 minutes. The cold mixture was stirred for 2.5 hours. A solution of 27.8 g. (0.3 mole) of 3-chloro-2-propanone in an equal volume of methanol was added over 15 minutes to the stirred mixture at *ca.* 10°. After 3 hours, 300 ml. of water was added to the cold mixture, and stirring was continued for 0.5 hour. The solution was concentrated *in vacuo* to remove methanol. The resulting solids were separated by suction filtration and dried *in vacuo* at room temperature. One recrystallization, effected by dissolving the solids in methylene chloride and adding hexane, gave 56.1 g. of white product, m.p. 94–96°. Further recrystallization yielded pure 3-benzyl-4-hydroxy-4-methylthiazolidine-2-thione, III.

(b) After 4-*t*-butyl-4-hydroxy-3-phenylthiazolidine-2-thione, XIII, had been prepared by the foregoing method, the preparation could not be duplicated. A more dependable route was afforded on slowly evaporating *in vacuo* a solution of the tautomeric, acyclic form (XV, Table II) in methanol-water. Under these conditions, the desired cyclic isomer separated. The cyclic isomer could be converted to its acyclic form by recrystallization from methylene chloride-hexane by concentration *in vacuo*.

Dithiocarbamates (Table II).

An example of a general procedure is the synthesis of 3,3-dimethyl-2-oxobutyl phenyldithiocarbamate, XV. To a cooled, stirred solution of 14.0 g. (0.15 mole) of aniline and 14.6 g. (0.15 mole) of potassium acetate in 120 ml. of methanol was added 11 ml. (0.18 mole) of carbon disulfide over 10 minutes. The cold mixture was stirred for 1.5 hours, and 17.9 g. (0.10 mole) of 1-bromo-3,3-dimethyl-2-butanone in an equal volume of methanol was added over 15 minutes. After the mixture had been stirred for 3 hours at *ca.* 10°, 100 ml. of water was added, dropwise, over 15 minutes, and the methanol was removed *in vacuo*. The solids precipitated were collected and dried at room temperature *in vacuo*, amounting to 22.3 g., m.p. 75–77°. The crude material was dissolved in 500 ml. of methylene chloride, and 2 l. of hexane was added. Concentration *in vacuo* gave 15.3 g. of pure product, as white needles.

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

(a) As an example of a general method, 20 g. (0.082 mole) of 3-benzyl-4-hydroxy-4-methylthiazolidine-2-thione (III, Table I) was dissolved in 250 ml. of warm 50% ethanol and 1 ml. of concentrated hydrochloric acid was added. On refluxing the reaction mixture for 0.5 hour, an oil separated which solidified on cooling. Collection of the crystals yielded 18.6 g. of crude product, m.p. 85–86°. Two recrystallizations yielded pure 3-benzyl-4-methyl-4-thiazoline-2-thione.

(b) A similar procedure produced cyclodehydration of the dithiocarbamates of Chart I, giving the corresponding 4-thiazoline-2-thiones. The sterically hindered dithiocarbamate, XVI, was refluxed for 6 hours to complete the dehydration.

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Received March 25, 1967 Rochester, New York 14650