E. Campaigne and T. P. Selby

Chemistry Laboratories of Indiana University, Bloomington, Indiana 47405

Received May 14, 1980

Nitrosation of hydrazino substituted thiazole-4-acetates has been shown to occur on the ring, rather than the α-methylene carbon, as previously reported. Thus nitrosation of ethyl 2-isopropylidenehydrazono-, 2-benzylidenehydrazono-, 2-(2-benzoylhydrazino)-, and 2-(2-acetylhydrazino)thiazole-4-acetates yielded the corresponding 2-hydrazino-4-carbethoxymethylidene-4,5-dihydrothiazoline-5-oximes. Basic hydrolysis of the thiazoline-5-oxime esters, followed by decarboxylation gave tautomeric mixtures of the 2-hydrazino-4-methyl-2,5-dihydrothiazoline-5-oxime and 2-hydrazino-4-methyl-5-nitrosothiazol derivatives. These tautomeric mixtures were also prepared by nitrosating the 2-hydrazino-4-methylthiazoles.

The α,β-unsaturated acids, 2-isopropylidenehydrazono-, 2-benzylidenehydrazono-, and 2-(2-benzoylhydrazino)-4-carboxymethylidene-4,5-dihydrothiazoline, were isolated after basic hydrolysis of the corresponding 2-hydrazinothiazole-4-acetic esters. Dinitrosation of the 2-isopropylidenehydrazono-4-carboxymethylidene-4,5-dihydrothiazoline, followed by decarboxylation, generated 2-isopropylidenehydrazono-5-nitrosothiazole-4-formyloxime.

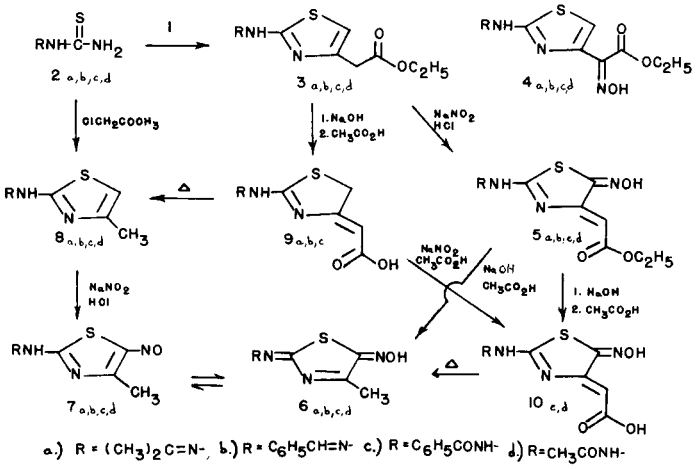
J. Heterocyclic Chem., **17**, 1249 (1980).

Previously, we reported that a number of thiazoleacetic esters were obtained in good yield by reacting ethyl 4-chloroacetoacetate (**1**) with thiosemicarbazones and acylthiosemicarbazides (3). Allowing ester **1** to react with acetonethiosemicarbazone (**2a**) and benzaldehydethiosemicarbazone (**2b**) yielded ethyl 2-isopropylidenehydrazonothiazole-4-acetate (**3a**) and ethyl 2-benzylidenehydrazonothiazole-4-acetate, (**3b**, Scheme 1), while cyclizing 1-benzoylthiosemicarbazide (**2c**) and 1-acetylthiosemicarbazide (**2d**) with ester **1** gave ethyl 2-(2-benzoylhydrazino)-thiazole-4-acetate (**3c**) and ethyl 2-(2-acetylhydrazino)-thiazole-4-acetate, (**3d**, Scheme 1).

Although nitrosation of these thiazole-4-acetic esters did occur, the exact site of nitrosation was uncertain since reaction could have taken place at the acetate methylene, on the thiazole ring, or on the hydrazino nitrogen. Nitrosation at the acetate methylene would generate α-oximo esters (*e.g.*, **4**) whereas oxime substituted thiazolines (*e.g.*, **5**) would arise from nitrosation at the C-5 thiazole ring position.

Because the infrared and pmr spectra of these two types of products might not be significantly different, assigning the site of nitrosation solely on the basis of spectral data was questionable (4). We have therefore carried out chemical decomposition studies (ester hydrolysis and decarboxylation) which revealed that the oximothiazolines (**5**) were the correct structures, nitrosated on the ring, rather than the α-oximo acid formulas, initially assumed as the products (3). Basic hydrolysis and decarboxylation of the thiazole-4-acetic acid side chains yielded methyl substituted nitrosothiazoles, which could also be prepared by an alternative synthetic route, in which the starting thiosemicarbazone (**2a,b**) or thiosemicarbazide (**2c,d**) was cyclized with chloroacetone and the resulting 4-methyl-

SCHEME I



0022-152X/80/061249-05$02.25

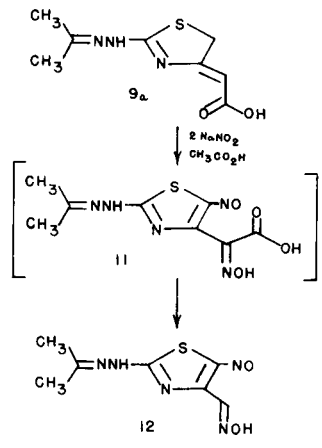
thiazoles nitrosated (Scheme 1).

Concerning the stability of thiazoleacetic acids, ease of decarboxylation depends largely on the substituent position (5). Thiazole-2-acetic acid is very unstable (6,7), decomposing on standing at room temperature, while the relative stability of the thiazole-4- and 5-acetic acids usually depended on the individual compound (8). With some thiazole-4-acetic acids (9,10), loss of carbon dioxide occurred readily and this property has been utilized in making 4-alkylthiazoles (11).

Following our previously published procedure (3), 2-isopropylidenehydrazono-4-carbethoxymethylidene-4,5-dihydrothiazoline-5-oxime (**5a**), and not α-oximo acid ester **4a** as originally characterized, was obtained after stirring ester **3a** with sodium nitrite in aqueous hydrochloric acid (Scheme 1). Ester hydrolysis of oxime **5a** in sodium hydroxide followed by acidification with acetic acid did not give an intermediate α,β-unsaturated acid oxime but directly yielded the decarboxylated adduct, 2-isopropylidenehydrazono-4-methyl-2,4-dihydrothiazoline-5-oxime (**6a**), along with its' nitroso tautomer, 2-isopropylidenehydrazono-4-methyl-5-nitrosothiazole (**7a**). A multiplet occurred at δ 2.70-2.90 in the pmr (trifluoroacetic acid), the methyl protons of **6a** and **7a** having slightly different chemical shifts, and a broad band (NOH, NH) appeared betweem 3300 and 2500 cm^{-1}. Presence of nitroso-oximo tautomerism was also indicated by earlier chemical studies in which the oxime oxygen was alkylated (13). Tautomers **6a** and **7a** were also prepared in good yield by nitrosating 2-isopropylidenehydrazono-4-methylthiazole (**8a**, Scheme 1).

Reacting ester **3b** with aqueous nitrous acid produced the α,β-unsaturated ester oxime, 2-benzylidenehydrazono-4-carbethoxymethylidene-4,5-dihydrothiazoline-5-oxime, **5b** (Scheme 1). Broad oxime hydrogen-oxygen stretching occurred at 3300-2600 cm^{-1} and the α,β-unsaturated carbonyl absorbed at 1680-1540 cm^{-1} in the ir potassium bromide while the conjugated vinylic proton resonated as a singlet at 6.00 δ in the pmr (trifluoroacetic acid).

SCHEME 2



No acid intermediate was isolated after hydrolyzing ester **5b** in sodium hydroxide. Instead, the methyl substituted tautomers: 2-benzylidenehydrazono-4-methyl-2,5-dihydrothiazoline-5-oxime (**6b**) and 2-benzylidenehydrazono-4-methyl-5-nitrosothiazole (**7b**) were isolated directly. The methyl protons of tautomers **6b** and **7b** exhibited different chemical shifts in the pmr (trifluoroacetic acid), showing singlets at 2.80 δ (1H) and 2.95 δ (2H). In the ir (potassium bromide) a broad band (NOH, NH) came

Table 1

Analytical Data of the Oximothiazoline (**6**) and Nitrosothiazole (**7**) Tautomeric Mixtures

Tautomers	Yield (Method A)	Yield (Method B)	M.p. dec.	Formula	m.w.	C	H	N	S	C	H	N	S	M⁺ (m/e)
						Calcd.				Found				
6a + **7a**	69%	38%	211°	$C_7H_{10}N_4OS$	198	42.42	5.10	28.28	16.28	42.26	5.33	28.01	16.34	198
6b + **7b**	71%	75%	213°	$C_{11}H_{10}N_4OS$ (a)	236									236
6c + **7c**	57%	46%	225°	$C_{11}H_{10}N_4O_3S$	262	50.38	3.85	21.37	12.21	49.91	3.78	21.64	12.26	262
6d + **7d**	83%	<4%	203°	$C_6H_8N_4O_2S$	200	36.00	4.04	28.00	16.00	35.95	4.26	27.88	16.13	200

(a) H. Beyer, W. Lassig, and U. Schultz, *Chem. Ber.*, **87**, 1401 (1954).

Table 2

Spectral Data for the Oximothiazoline (**6**) and Nitrosothiazole (**7**) Tautomeric Mixtures

Tautomers	Ir (potassium bromide) cm^{-1} (NH, NOH)	PMR (a) Chemical Shifts ppm δ
6a + **7a**	3300-2500	2.70-2.90 (m, 9H, $C(CH_3)_2$, CH_3)
6b + **7d**	3300-2600	2.80 (s, 1H, CH_3), 2.95 (s, 2H, CH_3), 8.10-7.40 (m, 6H, ArH and denzal hydrogen)
6c + **7c**	3300-2900	2.70 (broad s, 1H, CH_3), 2.90 (broad s. 2H, CH_3), 8.10-7.50 (m, 5H, ArH)
6d + **7d**	330, -2600	2.80-2.20 (m, 6H, $COCH_3$, CH_3)

(a) Absorptions from both tautomers (**6** and **7**) were recorded by the pmr (60 mHz) in trifluoroacetic acid.

between 3300 and 2600 cm^{-1}. Nitrosating 2-benzylidenehydrazono-4-methylthiazole (**8b**) (15) prepared from chloroacetone and **2b**, also gave the same mixture of **6b** and **7b** (Scheme 1).

Hydrolysis of esters **3a** and **3b** in sodium hydroxide followed by neutralization with acetic acid yielded the α,β-unsaturated acids: 2-isopropylidenehydrazono-4-carboxymethylidene-4,5-dihydrothiazoline (**9a**) and 2-benzylidenehydrazono-4-carboxymethylidene-4,5-dihydrothiazoline, **9b** (Scheme 1). Existence of the conjugated, exocyclic double bonds in **9a** and **9b** was revealed by the long wavelength carbonyl (α,β-unsaturated) absorptions at 1700-1500 cm^{-1} and 1690-1660 cm^{-1} in the ir (potassium bromide) for **9a** and **9b** respectively. The conjugated vinylic protons of both **9a** and **9b** resonated as singlets at δ 6.80 in trifluoroacetic acid.

Heated in alcohol, acids **9a** and **9b** decarboxylated to the corresponding methyl substituted thiazoles, **8a** and **8b** (Scheme 1). Neither the oximo acid **10a** nor its' decarboxylated adduct **6a** was isolated after nitrosating the α,β-unsaturated acid **9a**. Instead, the dinitrosated adduct, 2-isopropylidenehydrazono-5-nitrosothiazole-4-formyloxime, **12** (Scheme 2) was obtained. Some starting material (**9a**) was retrieved using one equivalent of nitrous acid (sodium nitrite and acetic acid). The nitrosation was carried out in dilute acetic acid at 0° in order to prevent decarboxylation prior to dinitrosation. Attempted nitrosation of **8a** to give **12** was unsuccessful.

Contrary to our previous report (3), 2-(2-benzoylhydrazino)-4-carbethoxymethylidene-4,5-dihydrothiazoline-5-oxime (**5c**) and not the initially assigned α-oximo acid ester, **4c** was obtained by nitrosating ester **3c** in aqueous hydrochloric acid (Scheme 1). Basic hydrolysis of **5c** in sodium hydroxide followed by acidification with acetic acid gave crude 2-(2-benzoylhydrazino)-4-carboxymethylidene-4,5-dihydrothiazoline-5-oxime (**10c**) which decarboxylated to a tautomeric mixture of 2-(2-benzoylhydrazino)-4-methyl-2,5-dihydrothiazoline-5-oxime (**6c**) and 2-(2-benzoylhydrazino)-4-methyl-5-nitrosothiazole (**7c**) upon attempted recrystallization from alcohol. Tautomers **6c** and **7c** were also obtained from 2-(2-benzoylhydrazino)-4-methylthiazole (**8c**) (16) after reaction with sodium nitrite in hydrochloric acid. Good yields of the oximino acid **10c** were achieved by simply hydrolyzing ester **3c** in sodium hydroxide, acidifying with acetic acid, and then nitrosating directly without isolation of intermediate **9c**. Broad α,β-unsaturated carbonyl stretching appeared between 1680 and 1572 cm^{-1} in the ir (potassium bromide) of **10c** and a singlet δ 6.60 (trifluoroacetic acid) was recorded for the vinylic proton, while two distinct singlets at 2.70 δ and 2.90 δ were observed in the pmr for the methyl protons of tautomers **6c** and **7c**.

Heating ester **1** with **2d** in acetonitrile gave the hydrochloride of ester **3d** and subsequently nitrosation gave 2-(2-acetylhydrazino)-4-carbethoxymethylidene-4,5-dihydrothiazoline-5-oxime (**5d**) (Scheme 1). Oximino acid **10d** was obtained directly from ester **3d** by hydrolysis, acidification and nitrosation. Extremely long wavelength stretching at 1680-1577 cm^{-1} appeared in the vibrational spectrum of **10d** and the singlet at 6.60 δ in the pmr (trifluoroacetic acid) was assigned to the vinylic proton. Attempted recrystallization of **10d** from alcohol resulted in decarboxylation to a mixture of **6d** and **7d** (Scheme 1). By stirring 2-(2-acetylhydrazino)-4-methylthiazole, **8d** (17) (from chloroacetone and **2d**) in agueous nitrous acid, adducts **6d** and **7d** were also formed. A mutliplet between 2.80 and 2.20 δ was the sole absorption for **6d** and **7d** in trifluoroacetic acid.

Solution of ester **3c** in sodium hydroxide and careful acidification yielded a small amount of the α,β-unsaturated acid, 2-(2-benzoylhydrazino)-4-carboxymethylidene-4,5-dihydrothiazoline (**9c**). Attempted recrystallization of **9c** from alcohol readily brought about decarboxylation, to give **8c**. Presence of the conjugated carbonyl in **9c** was indicated by stretching between 1710 and 1625 cm^{-1} in the ir (potassium bromide). An acid intermediate (**9d**) was not isolated after hydrolysis of **3d** in base, but free base **8d** was extracted from the aqueous solution.

EXPERIMENTAL

(**CAUTION**: Some of the thiazoline-5-oximes may be strong skin allergens!)

Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137-B infrared spectrometer using potassium bromide pellets. With hexadeuteriodimethyl sulfoxide or trifluoroacetic acid as solvents, nuclear magnetic resonance spectra were determined on a Varian T-60 spectrometer. At 70 eV a Varian Mat CH-7 spectrometer recorded the mass spectra. Elemental analyses were performed at Midwest Micro Labs Inc., Indianapolis, Indiana. Usually based on the first crystallization, the present yields are not considered optimum. Thin-layer chromatography was performed on Kodal (13181) silica gel sheets with fluorescent indicator (No. 6060).

Compounds **3a**, **3b**, **3c**, **5a**, and **5c** were prepared as previously described (3).

Ethyl 2-(2-Acetylhydrazino)thiazole-4-acetate (**3d**) Hydrochloride.

Suspended in 100 ml. of acetonitrile, 1-acetylthiosemicarbazide, **2d** (3.0 g., 0.0023 mole) was heated with 4.0 g. of ester **1** for 2.5 hours with stirring, as a clear yellow solution gradually formed. Upon cooling, white crystals of **3d** hydrochloride precipitated (5.2 g., 82%) and were filtered, washed with ether, dried, and recrystallized from 2-propanol, m.p. 183-185°; ir (potassium bromide): 3400-2700 (NH^+), 1725 (-O-C=O), 1700 (HNC=O), 1600, 1625, 1525-1540 (C=N), cm^{-1}; pmr (trifluoroacetic acid): δ 1.40 (t, 3H, $-CH_3$), 2.40 (s, 3H, $COCH_3$), 4.00 (s, 2H, CH_2CO), 4.40 (q, 2H, OCH_2), 6.90 (s, 1H, C-5 thiazole proton).

Anal. Calcd. for $C_9H_{14}ClN_3O_3S$: C, 38.63; H, 5.06; N, 15.02; S, 11.45. Found: C, 38.87; H, 4.99; N, 14.82; S, 11.28.

Benzylidenehydrazono-4-carbethoxymethylidene-4,5-dihydrothiazoline-5-oxime (**5b**).

To a stirred yellow suspension of **3b** (3.0 g., 0.01 mole), prepared as previously reported (3), in 30 ml. of water, 15 ml. of methanol, and 1 ml. of concentrated hydrochloric acid, sodium nitrite (0.69 g.) in 30 ml. of

water was added dropwise at 0°. The mixture was stirred overnight at room temperature. Dark yellow insoluble material was filtered, washed with water, dried, and recrystallized from aqueous acetone to yield 1.8 g. (56%) of yellow oxime (**5b**), decomposing at 208-211°; ir (potassium bromide): 3300-2600 (NH, NOH), 1680-1540 (C=O, C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 1.00 (t, 3H, $-CH_3$), 3.95 (q, 2H, OCH_2), 6.00 (s, 1H, conjugated vinylic proton), 7.60-7.00 (m, 5H, ArH), 8.00 (s, 1H, benzal hydrogen).

Anal. Calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.81; H, 4.45; N, 17.60; S, 10.06. Found: C, 52.54; H, 4.27; N, 17.36; S, 10.22.

2-(2-Acetylhydrazino)-4-carbethoxymethylidene-4,5-dihyrothiazoline-5-oxime (**5d**).

Sodium nitrite (0.25 g. in 15 ml. of water) was added dropwise, over a period of 45 minutes to a stirred aqueous solution (25 ml.) of **3d** hydrochloride (1.0 g., 0.0036 mole) at 0°. Room temperature was gradually attained after the final addition and the resulting yellow suspension stirred for several hours. It was filtered, washed with water, and dried to yield 0.9 g. (92%) of oxime **5d**. Recrystallized **5d** (acetone) decomposed in the range 212-215°; ir (potassium bromide): 3400-2700 (NH, NOH), 1680-1500 (C=O, HNC=O, C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 1.45 (t, 3H, $-CH_3$), 2.35 (s, 3H, $COCH_3$), 4.45 (q, 2H, OCH_2), 6.50 (s, 1H, conjugated vinylic proton).

Anal. Calcd. for $C_5H_{12}N_4O_4S$: C, 39.69; H, 4.45; N, 20.58; S, 11.76. Found: C, 39.72; H, 4.60; N, 20.40; S, 11.53.

2-Isopropylidenehydrazono-4-methyl-2,5-dihydrothiazoline-5-oxime (**6a**) and 2-Isopropylidenehydrazono-4-methyl-5-nitrosothiazole (**7a**).

Method A. Preparation from **8a** Hydrochloride.

Dissolved in 15 ml. of water, 0.5 g. of sodium nitrite was added dropwise to 1.5 g. (0.0073 mole) of **8a** hydrochloride (14) dissolved in 20 ml. of water at 0°. After warming slowly to room temperature, the resulting yellow suspension was stirred 1 hour, filtered, washed with water, and dried. Recrystallized (ethanol), the yellow material (**6a** and **7a**; 1.0 g., 69%) decomposed between 210° and 213°.

Method B. Preparation from Oxime **5a**.

A solution of 0.5 g. (2.0 mmoles) of oxime **5a** in 12 ml. of 0.5*N* sodium hydroxide and 2 ml. of ethanol, was heated on a steam bath for 15 minutes forming a black solution. In an ice bath, the basic solution was acidified to *p*H 5 with 20% acetic acid and the resulting suspension allowed to set 30 minutes before filtering the dark yellow precipitate (**6a** and **7a**), which was washed with water, and dried (0.15 g., 38%).

Analytical and spectral data for tautomers **6a,b,c,d** and **7a,b,c,d** are given in Tables 1 and 2.

2-Isopropylidenehydrazono-4-methylthiazole (**8a**) Hydrochloride.

The hydrochloride of **8a** was prepared from **2a** and chloroacetone by the method of Fodor (14). However, better yields of **8a** hydrochloride (53%) were obtained in acetone, as opposed to alcohol. Recrystallized (ethanol), **8a** hydrochloride melted between 166° and 168°, in agreement with the reported m.p. 165° (14).

2-Isopropylidenehydrazono-4-methylthiazole (**8a**).

Procedure I. Preparation from **8a** Hydrochloride.

The hydrochloride of **8a** (2.0 g., 0.01 mole) was dissolved in 25 ml. of water by warming on a steam bath and the resulting yellow solution neutralized with 10% sodium bicarbonate at room temperature with stirring. Yellow solid separated immediately and was filtered, washed with water, and dried (1.2 g., 71%). After recrystallizing from ethyl ether/petroleum ether, yellow free base **8a** melted at 117-120°, the reported melting point being 122° (14).

Procedure II. Preparation from Acid **9a**.

Free base **8a** was also formed after heating 0.3 g. (0.0014 mole) of acid **9a** *(vide infra)* in a mixture of 15 ml. of ethanol and 5 ml. of water on a steam bath. After heating to near dryness, the oily residue was dissolved in 30 ml. of ethyl ether, washed with water, dried (magnesium sulfate) and filtered. The oily residue (0.1 g., 42%), which was obtained after evaporating the solvent, was identified as free base **8a** by a thin-layer chromatographic (acetone) comparison with an authentic sample of the free base, obtained from **8a** hydrochloride.

The hydrochlorides and free bases of **8b, 8c,** and **8d** were prepared in a similar manner to the hydrochloride and free base of **8a**.

2-Benzylidenehydrazono-4-methylthiazole (**8b**).

Hydrochloride **8b** was prepared by the method of Fodor (15), in which benzaldehydethiosemicarbazone (18) (**2b**) was reacted with chloroacetone in alcohol (85%) and decomposed in the range 188-192° as compared to the reported melting point of 193° (15).

Free base **8b** melted at 190-192° (lit. m.p. 190°) (15) after recrystallizing from ethyl ether/petroleum ether and was prepared from both the hydrochloride (85%, Procedure I) and the acid **9b** (24%, Procedure II).

2-(2-Benzoylhydrazino)-4-methylthiazole (**8c**).

Hydrochloride **8c** was prepared as previously reported (16), in which chloroacetone was reacted with 1-benzoylthiosemicarbazide (**2c**) (19) in ethanol (85%). Recrystallized (ethanol) **8c** hydrochloride decomposed in the range 236-240° which differed drastically from the reported melting point, 190° (16). However, the hydrochloride was neutralized to the free base which did analyze correctly for structure **8c**.

Free base **8c** was obtained in 86% yield from the hydrochloride (Procedure I). Decarboxylation of acid **9c** in hot ethanol (Procedure II) also gave **8c**, as evidenced by thin-layer chromatography (acetone/methylene chloride; 2:1); m.p. 203-206° (isopropanol); ir (potassium bromide): 3300-2600 (NH), 1650 (HNC=O), 1575, 1520, 1450 (C=N); pmr (hexadeuterioacetone): δ 2.90 (broad s, 3H, CH_3), 6.35 (s, 1H, thiazole ring proton), 7.70-7.45 (m, 3H, ArH), 8.10-7.90 (m, 2H, ArH).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 54.48; H, 5.00; N, 18.91. Found: C, 54.36; H, 5.00; N, 19.14.

2-(2-Acetylhydrazino)-4-methylthiazole (**8d**).

Hydrochloride **8d** was prepared from chloroacetone and **2d** by the procedure of Beyer (17). However, better yields (48%) were obtained with acetonitrile as the reaction solvent as opposed to alcohol; m.p. 208-211° dec. (2-propanol) (lit. m.p. 210°) (17).

Free base **8d** was obtained in 60% yield from the hydrochloride (Procedure I). Preparation of **8d** by Procedure II was not possible since acid **9d** was not isolated. Colorless crystals of **8d** melted between 209-214° with decomposition; (lit. m.p. 207-210° dec.) (17).

2-Isopropylidenehydrazono-4-carboxymethylidene-4,5-dihydrothiazoline (**9a**).

Free base **3a** (3.0 g., 0.0125 mole) was dissolved in 50 ml. of 1.0 *N* sodium hydroxide and 5 ml. of ethanol by warming on a steam bath for 20 minutes with occasional stirring. Within a few minutes of heating, the initial dark yellow suspension turned black. The yellow precipitate (**9a**), which was obtained by neutralizing the chilled basic solution with 20% acetic acid, was filtered, washed with water, and then washed with methylene chloride to remove decarboxylated material, and dried (2.0 g., 75%). Recrystallized from ethanol/2-propanol, acid **9a** decomposed between 143° and 147°. Some decarboxylation to **8a** did occur during recrystallization, however **8a** remained in the solvent; ir (potassium bromide): 3200-2300 (NH, CO_2H), 1700-1500 (C=O, C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 2.30 (d, 6H, $C(CH_3)_2$, J = 4 Hz), 4.05 (s, 2H, CH_2CO), 6.80 (s, 1H, conjugated vinylic proton).

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.21; N, 19.71; m.w. 213. Found: C, 45.44; H, 5.46; N, 19.38; M^+ = m/e 213.

Crude acids **9b** and **9c** were prepared in a similar manner to acid **9a**.

2-Benzylidenehydrazono-4-carboxymethylidene-4,5-dihydrothiazoline (**9b**).

Following the procedure above, for **9a, 3b** gave a 45% yield of crude **9b**. Decarboxylation to **8b** occurred readily when recrystallization was attempted in alcohol. Crude acid **8b** decomposed in the range 150-154°;

ir (potassium bromide): 3500-2700 (NH, CO_2H), 1690-1660 (C=O), 1575-1474 (C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 4.00 (s, 2H, CH_2CO), 6.80 (s, 1H, conjugated vinylic proton), 7.90-7.30 (m, 5H, ArH), 8.15 (s, 1H, benzal hydrogen).

2-(2-Benzoylhydrazino)-4-carboxymethylidene-4,5-dihydrothiazoline (**9c**).

Using the same procedure, **3c** gave a 24% yield of crude **9c**. Due to the instability of acid **9c**, it readily decarboxylated to **8c** during recrystallization in alcohol. Crude **9c** decomposed in the broad range, 73-80°; ir (potassium bromide): 3500-2600 (NH, CO_2H), 1710-1625 (C=O), 1575-1475 (C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 4.05 (s, 2H, SCH_2), 8.05-7.55 (m, 6H, ArH and conjugated vinylic proton).

2-(2-Benzoylhydrazino)-4-carboxymethylidene-4,5-dihydrothiazoline-5-oxime (**10c**).

The hydrochloride of **3c** (1.0 g., 0.003 mole) was dissolved in a solution of 5.0 *N* sodium hydroxide (3 ml.), ethanol (3 ml.), and 10 ml. of distilled water and warmed on a steam bath for 5 minutes forming a dark purple solution. After acidifying to *p*H 6 with 20% acetic acid at 0°, sodium nitrite (0.21 g.) in 10 ml. of water was added dropwise with stirring and yellow solid (**10c**), which precipitated almost immediately, was filtered, washed with water, and dried (0.6 g., 65%). Attempted recrystallization from alcohol caused decarboxylation to a mixture of **6c** and **7c**. Crude **10c** decomposed at 213-216°; ir (potassium bromide): 3300-2500 (NH, CO_2H, NOH), 1680-1577, 1550-1450 (C=O, HNC=O, C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 6.60 (s, 1H, conjugated vinylic proton), 8.10-7.60 (m, 5H, ArH).

2-(2-Acetylhydrazino)-4-carboxymethylidene-4,5-dihydrothiazoline-5-oxime (**10d**).

Crude **10d** was prepared from **3d** in a similar manner. Decomposition of crude **10d** occurred between 170 and 174°. Decarboxylation to a mixture of **6d** and **7d** took place during attempted recrystallization from alcohol; ir (potassium bromide): 3400-2600 (NH, CO_2H, NOH), 1675-1575, 1520 (C=O, HNC=O, C=N) cm^{-1}; pmr (trifluoroacetic acid): δ 2.45 (broad s, 3H, $COCH_3$), 6.55 (s, 1H, conjugated vinylic proton).

2-Isopropylidenehydrazono-5-nitrosothiazole-4-formyloxime (**12**).

To an aqueous mixture (30 ml.) of acid **9a** (0.7 g., 0.0033 mole) and sodium nitrite (0.47 g., 0.0068 mole), 15 ml. of 5% acetic acid was slowly added at 0° with stirring. A yellow suspension which formed was stirred overnight. After adding 50 ml. of water, the yellow precipitate was filtered, washed with water, and dried. Recrystallizing from 2-propanol/ether yielded 0.4 g. (54%) of brown powdery **12**, which decomposed between 218° and 220°; ir (potassium bromide): 3400-2600 (NH, NOH), 1625, 1515, 1425, (C=N, N=O) cm^{-1}; pmr (trifluoroacetic acid): δ 2.90 (s, 6H, $C(CH_3)_2$), 8.60 (s, 1H, formyl-oxime hydrogen).

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 36.99; H, 4.00; N, 30.82; S, 14.09; m.w. 227. Found: C, 36.76; H, 4.11; N, 30.56; S, 14.36; M^+ = m/e 227.

REFERENCES AND NOTES

(1) Contribution No. 3524.

(2) Taken in part from a thesis submitted by T. P. S. in partial fulfillment of the requirements for the Ph.D. degree at Indiana University, May, 1979.

(3) E. Campaigne and T. P. Selby, *J. Heterocyclic Chem.*, **15**, 401 (1978).

(4) We are indebted to Dr. Gary Koppel, Eli Lilly Research Laboratories, Indianapolis, for calling our attention to this point.

(5) R. C. Elderfield, "Heterocyclic Compounds", Vol. 5, John Wiley and Sons, Inc., New York, London, 1957, p. 629.

(6) W. R. Boon, *J. Chem. Soc.*, 601 (1945).

(7) R. Mory and H. Schenkel, *Helv. Chim. Acta*, **33**, 16, 405 (1950).

(8) J. M. Sprague, R. M. Lincoln, and C. Ziegler, *J. Am. Chem. Soc.*, **68**, 266 (1946).

(9) E. R. H. Jones, F. A. Robinson, and M. N. Strachan, *J. Chem. Soc.*, 87 (1946).

(10) H. Erlenmeyer and C. J. Morel, *Helv. Chim. Acta*, **28**, 362 (1945).

(11) C. Ziegler, *J. Am. Chem. Soc.*, **63**, 2946 (1941); **66**, 744 (1944).

(12) Trifluoroacetic acid was utilized as the standard pmr solvent due to the ease of decarboxylation of these thiazole-4-acetic acids in neutral solvents.

(13) H. Beyer, W. Lassig, and U. Schultz, *Chem. Ber.*, **87**, 1401 (1954).

(14) G. Fodor and G. Wilheim, *Acta. Chim., Acad. Sci. Hung.*, **2**, 189 (1952).

(15) G. Fodor, *Acta. Univ. Szeged Chem.*, **2**, 167 (1949); CA. 6414c (1949).

(16) M. Lora-Tamayo, G. A. Cortiguera, and R. Madronero, *Bull. Soc. Chim. France*, 1020 (1962).

(17) H. Beyer, H. Hohn, and W. Lassig, *Chem. Ber.*, **85**, 1122 (1952).

(18) P. P. Sah and T. C. Daniels, *Rev. Trav. Chim.*, **69**, 1545 (1950).

(19) E. Hoggarth, *J. Chem. Soc.*, 1167 (1949).