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Under both weakly and strongly alkaline conditions, 1-alkyl-2,5-dithiobiureas (1-alkylthiocarbamoyl-3-thiosemicarbazides) form 4-alkyl-5-amino-1,2,4-triazoline-3-thiones and 4-alkyl-1,2,4-triazolidine-3,5-dithiones in varying proportions. 1-Alkoxythiocarbonyl-3-thiosemicarbazides expel hydrogen sulfide under weakly basic conditions to form the corresponding 5-alkoxy-1,2,4-triazoline-3-thiones. In a strongly alkaline environment, however, these alkoxythiocarbonyl thiosemicarbazides eliminate alcohol to form the appropriate 1,2,4-triazolidine-3,5-dithiones. 1-Alkoxycarbonyl-3-thiosemicarbazides eliminate alcohol in both weakly and strongly basic media to give 5-thiono-1,2,4-triazolidine-3-ones. Cyclization mechanisms of these thiosemicarbazides are postulated.

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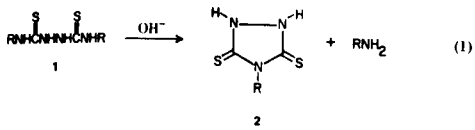
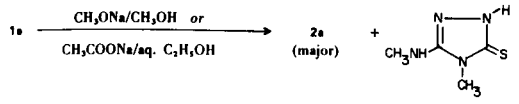
Symmetrical 2,5-dithiobiureas **1** eliminate ammonia or amine in the presence of alkali to form the corresponding 1,2,4-triazolidine-3,5-dithiones **2** (reaction 1) (1,2). We



(1)

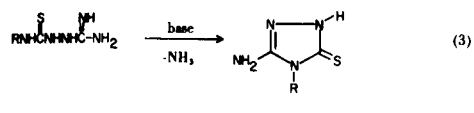
found that 1,6-dimethyl-2,5-dithiobiurea (**1a**, R = CH_3) cyclized under both strongly basic (sodium methoxide) and weakly basic (sodium acetate) reflux conditions to form **2a** as the principal product and a small amount of 4-methyl-5-methylamino-1,2,4-triazoline-3-thione **3** (reaction 2). These heterocycles arose respectively from the



(2)

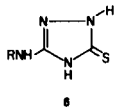
elimination of methylamine or hydrogen sulfide from **1a**. When three 1-alkyl-2,5-dithiobiureas **4** (Table I) were refluxed with sodium methoxide in methanol, however, the elimination of hydrogen sulfide occurred to some extent since the appropriate 4-alkyl-5-amino-1,2,4-triazoline-3-thiones **5** were usually isolated in moderate yields (Table II). Thus, the cyclization pathway of 1-alkyl-2,5-dithiobiureas appears to be dramatically altered from that of the symmetrical compounds in basic media (*vide infra*).

These 4-alkyl-5-amino-1,2,4-triazoline-3-thiones have been previously synthesized by the base-promoted cyclization of the appropriate *N*-substituted-*N'*-guanidinothioureas (reaction 3) (3,4).

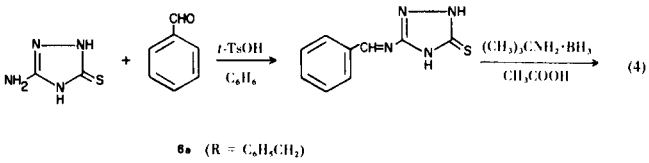


(3)

To obviate the possibility that **6** (isomeric with **5**) formed when **4** was refluxed in methanolic sodium methoxide, **6a** was prepared (reaction 4). The amino



proton of the benzylamino group of **6a** appeared as a triplet (due to coupling with the benzyl methylene protons) in the ^1H nmr spectrum. No such triplet was found in the ^1H nmr spectrum of **5a** and the melting point of **5a** was considerably lower than that of **6a**.



(4)

In connection with some other work, we prepared four 1-alkoxythiocarbonyl-3-thiosemicarbazides **7** (Table III) according to the procedure of Åkerblom and Skagius (5). We discovered that **7** expelled alcohol to form 1,2,4-triazolidine-3,5-dithiones **2** when refluxed with either aqueous ethanolic sodium hydroxide or with methanolic sodium methoxide (Table IV). These triazolidine-3,5-dithiones were identical with the heterocycles **2** obtained *via* reaction 1. However, when **7** was refluxed with a weak base (aqueous sodium acetate), hydrogen sulfide was eliminated to form the corresponding 4-alkyl-5-alkoxy-1,2,4-triazoline-3-thiones **8** (Table V). One of these

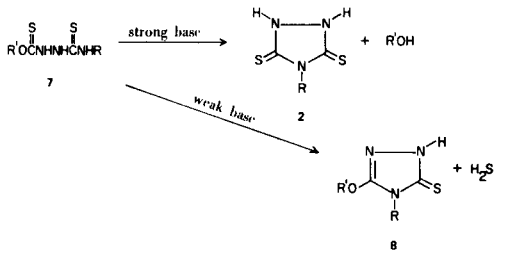
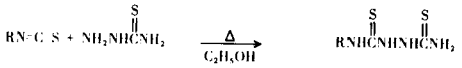


Table I

1-Alkyl-2,5-dithiobiureas



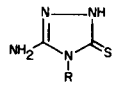
4

Compound	R	Yield, %	M.p. °C	*Anal.* Calcd: Found: C	H	N
4a	$C_6H_5CH_2$	82 (a)	202-204	45.0	5.0	23.3
				44.9	5.1	23.7
4b	CH_3	90 (b)	183-185	21.9	4.9	34.1
				21.9	5.2	34.0
4c	n-C_4H_9	93 (b)	190-191 dec.	34.9	6.8	27.2
				34.7	7.1	27.2

(a) The white powder was isolated from the chilled alcohol solution and washed with ethyl acetate. (b) The white powder was collected from the chilled alcohol solution. The analytical sample was crystallized from 95% ethanol.

Table II

4-Alkyl-5-amino-1,2,4-triazoline-3-thiones

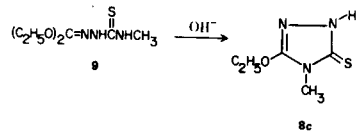


5

Compound	R	Yield, %	M.p. °C	*Anal.* Calcd: Found: C	H	N
5a	$C_6H_5CH_2$	46 (a)	205-207 (b)	52.4	4.9	27.2
				52.3	5.0	27.6
5b	CH_3	56 (c)	273-275 (d)	27.7	4.6	43.0
				27.6	4.8	43.0
5c	n-C_4H_9	(e)	153-155 (f)	41.8	7.0	32.5
				42.0	6.8	32.8

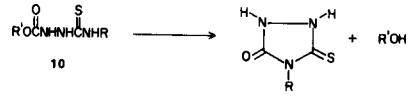
(a) Crystallized from ethyl acetate-ethanol to give a white powder. The analytical sample was crystallized once more from ethyl acetate-ethanol. (b) Lit. (3) 206-208°. (c) An off-white solid was obtained from the acidified (glacial acetic acid) product mixture. The analytical sample was crystallized from 50% aqueous ethanol to give pale yellow needles. (d) Lit. (4) 267-269°. (e) The white powder (26.0 g.) was shown by tlc to contain both **4c** and **5c**. The analytical sample of **5c** was obtained after six crystallizations from ethyl acetate. (f) Lit. (4) 151-153°.

compounds **8c** had been synthesized previously by interacting tetraethoxymethane with 4-methyl-3-thiosemicarbazide followed by the base-promoted cyclization of the intermediate 1-diethoxymethylene-4-methyl-3-thiosemicarbazide **9** to **8c** (reaction 5) (6).



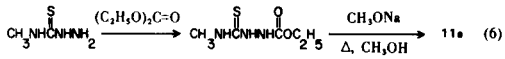
9 8c (5)

We then investigated the cyclization behavior under alkaline conditions of three 1-alkoxycarbonyl-3-thiosemicarbazides **10** that were prepared by treating the corresponding alkyl chloroformate with one equivalent of a thiosemicarbazide in chloroform in the presence of triethylamine (Table VI). As expected, **10** eliminated



10 11

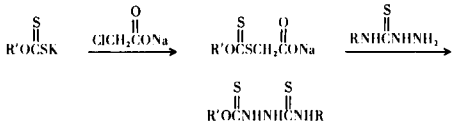
alcohol when treated with either aqueous ethanolic sodium hydroxide or with methanolic sodium methoxide to form the appropriate 5-thiono-1,2,4-triazolidine-3-ones **11** (Table VII). A somewhat similar synthesis of **11a** has



11a (6)

Table III

1-Alkoxythiocarbonyl-3-thiosemicarbazides

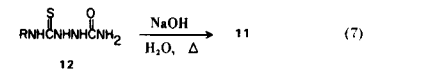


7

Compound	R	R′	Yield, % (a)	M.p. °C	*Anal.* Calcd: Found: C	H	N
7a	CH_3	CH_3	16 (b)	133-134	26.8	5.0	23.4
					27.1	5.4	23.4
7b	C_2H_5	CH_3	15 (c)	119-120	31.1	5.7	21.7
					31.1	5.7	21.9
7c	CH_3	C_2H_5	26 (d)	156-157	31.1	5.7	21.7
					31.1	6.1	22.0
7d	CH_3	i-C_3H_7	24 (b)	158-160	34.8	6.3	20.3
					34.5	6.5	20.5

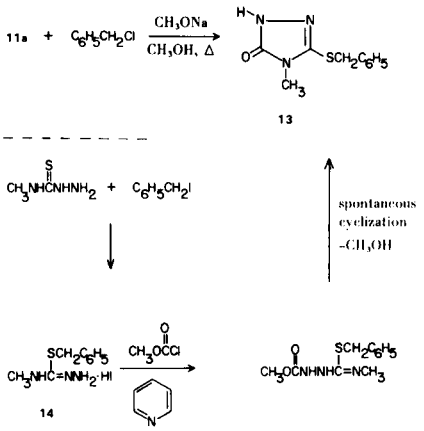
(a) Based on the potassium hydroxide. (b) Crystallized from ethyl acetate. (c) The pale yellow crystalline solid that was initially obtained was suspended in hot ethanol, and undissolved solid was removed by filtration. The filtrate was evaporated to dryness, and the resulting white solid was triturated with ethyl ether. (d) Crystallized from ethanol.

already been reported (reaction 6) (7,8). These heterocycles have also been prepared by cyclizing the appropriate 1-substituted-2-thiobiureas **12** with aqueous sodium hydroxide (reaction 7) (9). The *S*-benzyl derivative of **11a** was identical in all respects with 4-methyl-5-benzylthio-1,2,4-triazoline-3-one **13** that was prepared by a modification of a reported synthesis (10) (Scheme I).



12 11 (7)

Scheme I

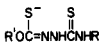


When refluxed with aqueous sodium acetate, **10** again cyclized with the loss of alcohol to form **11** (Table VII) instead of **8** that would result from the loss of water.

Discussion.

Arndt's generalization states that thiosemicarbazide derivatives cyclize to 1,2,4-triazoline-3-thiones in alkaline media and to 2-amino-1,3,4-thiadiazoles under acidic conditions (11). We have demonstrated that the cyclization pathway of certain thiosemicarbazides can be altered by the choice of suitable basic conditions to give different triazoles. The behavior of 1,6-dialkyl-2,5-dithiobiureas under alkaline conditions also changes when one of the alkyl groups is replaced by hydrogen.

The cyclization of the 1-alkoxythiocarbonyl-3-thiosemicarbazides **7** can be rationalized through stabilization of the alkoxythiocarbonyl moiety by alkali salt formation in strong base (12a,b). Alcohol rather than hydrogen sulfide is eliminated from the resulting mercaptide **15** to form the triazolidines **2**. Under more weakly basic conditions (sodium acetate), however, **7** apparently does not

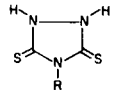


15

appreciably ionize to form a mercaptide, and hydrogen sulfide is eliminated to give the triazolines **8**. Depending on the alkaline conditions, the cyclization of **7** occurs cleanly to form either **2** or **8**. When **7b** or **7d** was cyclized with sodium acetate, no mass spectral evidence for **2b** or **2a**, respectively, was found in the crude product. When **7c** was treated with aqueous sodium hydroxide, only *ca.* 1% of **8c** by mass spectral evidence was found in the crude

Table IV

4-Alkyl-1,2,4-triazolidine-3,5-dithiones



2

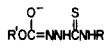
Precursor	Product	R	Yield, %
7a	**2a**	CH_3	68 (a) (b) (c)
7a	**2a**	CH_3	33 (d) (e)
7b	**2b**	C_2H_5	21 (a) (f) (g)
7c	**2a**	CH_3	97 (a) (b)
7c	**2a**	CH_3	80 (d) (e)
7d	**2a**	CH_3	68 (a) (b)
7d	**2a**	CH_3	81 (d) (e)

(a) Cyclized with sodium hydroxide in refluxing 25% aqueous ethanol. (b) Separated from the acidified (hydrochloric acid) aqueous solution. (c) M.p. 228-229°, lit. (1) 230°, *Anal.* Calcd. for $C_3H_5N_3S_2$: C, 24.4; H, 3.4; N, 28.5. Found: C, 24.4; H, 3.5; N, 28.5. (d) Cyclized with sodium methoxide in refluxing methanol. (e) Crystallized from ethanol. (f) Crystallized from ethyl ether-pentane. (g) M.p. 153-155°, lit. (1) 171°, see Experimental.

product. The latter result may indicate that not all of **7c** ionizes under these strongly basic conditions. The role that sodium acetate plays during the cyclization of **7** is not understood at present. When **7c** was refluxed by itself in aqueous solution, little, if any, cyclization occurred since **7c** was recovered unchanged.

In some instances, *spontaneous* cyclization to form **8** occurred during the preparation of **7** (Table III). Although we have not investigated this anomaly in any detail, the *p*H of the reaction medium may be an important factor.

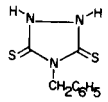
Thiosemicarbazides **10** appear to have a pK_a less than that of acetic acid, since under both strongly and weakly (sodium acetate) basic conditions these derivatives expel alcohol to form **11** from the probable intermediate alkoxide **16**.



16

The behavior of the 1-alkyl-2,5-dithiobiureas **4** under basic conditions is less readily explainable. Dithiobiurea **1a** eliminates methylamine under strongly alkaline conditions to form **2a** (1), and we have confirmed that **2a** is indeed the major product (reaction 2). Even with sodium acetate, **2a** was again the major product. This dithiobiurea appears to form stable mercaptide salts under these conditions, and the amine is liberated.

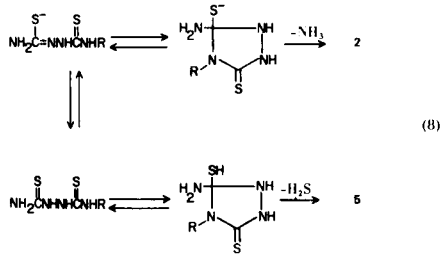
The 1-alkyl-2,5-dithiobiureas are likely stronger acids than the corresponding 1,6-dialkyl-2,5-dithiobiureas because electron-donating alkyl groups are absent from one of the terminal nitrogens. The former derivatives probably form stable salts with the three bases used in these studies and the elimination of ammonia to form **2** would be predicted. The 5-amino-1,2,4-triazoline-3-thiones **5** were isolated, however, after the corresponding dithiobiureas **4** were cyclized with sodium methoxide in methanol. Careful examination (mass spectrum and tlc) of the crude product of the sodium methoxide (two equivalents)/methanol (three-day reflux) cyclization of **4a** revealed approximately equal amounts of **5a** and **2c** arising respectively by the elimination of hydrogen sulfide



2c

and ammonia from **4a**. Under the same conditions, **4b** gave 85-90% of **5b** and only 10-15% of **2a**. Both **4a** and **4b** were totally consumed under these conditions. When **4a** was refluxed with 50% aqueous ethanolic sodium acetate (five equivalents) for either one or five days, approximately equal amounts of **5a** and **2c** were found in the crude product, and no evidence for the precursor **4a** was seen in either case. When **4b** was refluxed for three days under the same conditions, both **2a** and **5b** were formed with the latter compound slightly predominating. We found **5a** to be the principal product along with 2-3% of **2c** and some elemental sulfur (S_8) when **4a** was refluxed with two equivalents of sodium hydroxide in aqueous solution for 24 hours. Furthermore, **4b** gave >99% of **5b** (<1% of **2a**) when refluxed with aqueous sodium hydroxide (five equivalents) for three days.

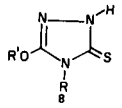
Factors in addition to the pK_a of thiosemicarbazide derivatives appear to influence their cyclization in basic media. The existence of 1-alkyl-2,5-dithiobiureas as their un-ionized form in aqueous sodium hydroxide is difficult to rationalize since **1a** appears to ionize under the same conditions (**2a** is the principal cyclization product). The pK_a of thiosemicarbazides probably influences their cyclization behavior if kinetic control is important. The behavior of **4** in alkaline media indicates that the thermodynamic stability of the cyclization products may also determine their relative formation. If so, the equilibria indicated by reaction 8 may exist under alkaline conditions. The different ratio of triazoles **2** and **5** that is observed when the base is changed indicates that the base



(8)

Table V

4-Alkyl-5-alkoxy-1,2,4-triazoline-3-thiones

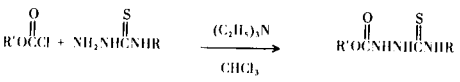


Compound	R	R′	Yield, %	M.p. °C	*Anal.* Calcd: Found: C	H	N
8a	CH_3	CH_3	10 (a)	161-162	33.1	4.8	28.9
					33.0	4.9	28.5
8b	C_2H_5	CH_3	20 (b)	93-95	37.7	5.7	26.4
					37.8	5.6	26.7
8c	CH_3	C_2H_5	60 (c)	167-168.5 (d)	37.7	5.7	26.4
					37.9	6.0	26.8
8d	CH_3	$i\text{-}C_3H_7$	66 (e)	195-196	41.6	6.4	24.3
					41.5	6.7	24.3

(a) Crystallized three times from ethyl acetate to colorless prisms. (b) Colorless flakes from ethyl acetate. (c) Colorless prisms from ethyl acetate. (d) Lit. (6) 172°. (e) Colorless microcrystals from ethanol.

Table VI

1-Alkoxycarbonyl-3-thiosemicarbazides



Compound	R	R′	Yield, %	M.p. °C	*Anal.* Calcd: Found: C	H	N
10a	CH_3	CH_3	51 (a)	187-188	29.4	5.5	25.8
					29.6	5.8	26.0
10b	C_2H_5	CH_3	32 (b)	136-137	33.9	6.2	23.7
					34.1	6.1	23.4
10c	CH_3	C_2H_5	(c)				

(a) Recrystallized from ethyl acetate-ethanol. (b) Separated from methylene chloride solution. (c) Was not isolated, but converted to **11a**. See Table VII.

strength influences the relative contribution of kinetic and thermodynamic factors to the cyclization behavior of **4**. Our results also suggest that **5** is thermodynamically more stable than **2**. The formation of **5**, rather than **6**, signifies that the alkylated terminal nitrogen of **4** is more nucleophilic, as expected, than the unsubstituted terminal amino group. Clearly, detailed kinetic studies on more examples of **4** should result in a better understanding of their cyclization pathways under basic conditions.

EXPERIMENTAL

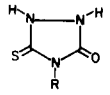
All commercial compounds were *Eastman* Organic Chemicals except for 2-chloro-3-nitropyridine and 5-amino-1,2,4-triazoline-3-thione which were from the Aldrich Chemical Company. Mass spectra were measured with a Hitachi-Perkin-Elmer RMS-4 mass spectrometer. Infrared spectra were determined in potassium bromide discs with a Beckman IR-20A spectrophotometer. The ^1H nmr spectra were measured with a Varian Associates A60 or a Perkin-Elmer R-32 (90 MHz) nmr spectrometer. The ^{13}C nmr spectra were determined with a Brücker Model HX-90 (22.63 MHz) nmr spectrometer. The solvent DMSO-d_6 (unless noted otherwise) was used for all of the nmr spectra with TMS as the internal standard. All of the compounds in this report exhibited satisfactory mass and ^1H nmr spectra.

Cyclization of **1a** with Sodium Acetate.

A stirred 50% aqueous ethanol solution (200 ml.) of **1a** (13) (7.3 g., 0.041 mole) and sodium acetate (16.4 g., 0.2 mole) was refluxed for 18 hours. Concentrated hydrochloric acid was added to the cooled solution, and the resulting separated crystalline solid was chilled for 18 hours, yield, 6.0 g. (>99%) of **2a**, m.p. 225-226° (lit. (1) 230°). The mass spectrum showed the parent peak at m/e 147 (Calcd. 147). The filtrate was evaporated to

Table VII

4-Alkyl-5-thiono-1,2,4-triazolidine-3-ones



11

Precursor	Product	R	Yield, %
10a	**11a**	CH_3	39 (a) (b) (c)
10a	**11a**	CH_3	12 (d) (e)
10a	**11a**	CH_3	67 (e) (f)
10b	**11b**	C_2H_5	49 (a) (g) (h)
10c	**11a**	CH_3	44 (a) (i)
10c	**11a**	CH_3	70 (f) (i)

(a) Refluxing aqueous sodium acetate. (b) Colorless microcrystals from aqueous solution. (c) M.p. 209-211°, lit. (8) 217°, *Anal.* Calcd. for $C_3H_5N_3OS$: C, 27.5; H, 3.8; N, 32.0. Found: C, 27.7; H, 3.8; N, 32.0. (d) Refluxing methanolic sodium methoxide. (e) White flakes from ethanol. (f) Sodium hydroxide in refluxing 25% aqueous ethanol. (g) Crystallized from ethyl acetate. (h) M.p. 180-181°, lit. (9) 184-184.5°, see Experimental. (i) Crystallized from ethanol-ethyl acetate.

dryness under reduced pressure. The residual white solid was suspended in hot ethanol, and undissolved solid was removed by filtration. The filtrate was evaporated to dryness, and tlc analysis (silica gel/acetonitrile) of the residue showed two spots. One ($R_f \sim 0.2$) corresponded with **2a**. This colorless residue was then suspended in hot ethyl acetate that contained a small amount of ethanol. Undissolved solid was removed by filtration and the filtrate was chilled. A colorless solid (1.2 g.) separated that was shown to be methylamine hydrochloride (the methylamine was undoubtedly produced during the formation of **2a**). The filtrate was evaporated to dryness and the residual oil was crystallized from a minimal amount of ethyl acetate to give a colorless crystalline solid **3**, yield, 0.4 g., m.p. 212-213° (lit. (14) 268°), ^{1}H nmr: δ (ppm) 2.71 (d, 3H, NHCH_3) (the doublet coalesced to a singlet when the nmr spectrum was measured in deuterium oxide) and 3.26 (s, 3H, NCH_3). The mass spectrum showed the parent peak at m/e 144 (Calcd. 144).

Anal. Calcd. for $C_4H_8N_4S$: C, 33.3; H, 5.6; N, 38.9; S, 22.3. Found: C, 33.4; H, 5.9; N, 39.3; S, 22.1.

Cyclization of **1a** with Sodium Methoxide.

A stirred methanol (500 ml.) solution of sodium methoxide (30.2 g., 0.56 mole) and **1a** (50.0 g., 0.28 mole) was refluxed overnight. The solvent was removed under reduced pressure, the residue was dissolved in distilled water, and the solution was acidified with concentrated hydrochloric acid. Filtration afforded 5 g. of a white powder that was identified as **2a** (*vide supra*). The aqueous filtrate was evaporated to dryness and the residue was extracted three times with boiling ethyl acetate. The combined extracts were dried with magnesium sulfate and passed through 50 g. of Florisil. Evaporation of the eluted solvent to dryness gave 5 g. of a pale yellow solid that consisted of **1a**, **2a**, and a third component. This mixture was absorbed onto a silica gel dry column (2 x 20-in.), and ethyl acetate was the developing solvent. The product band ($R_f \sim 0.3$) was excised and then extracted with ethanol. After removal of the solvent, 2 g. of an off-white powder remained. Recrystallization from ethyl acetate-ethanol afforded **3** as pale yellow needles, m.p. 211-213° (*vide supra*).

1-*n*-Butyl-2,5-dithiobiurea (**4c**).

A stirred suspension of thiosemicarbazide (50.0 g., 0.55 mole) and *n*-butyl isothiocyanate (63.5 g., 0.55 mole) in ethyl acetate (500 ml.) was refluxed for 18 hours. The reaction mixture was cooled and filtered to yield 106.0 g. (93%) of a white powder. A small sample was crystallized from 95% ethanol, m.p. 190-191° dec.; ^{1}H nmr: δ (ppm) 7.7 (t, 1H, N*H*CH$_2$). The mass spectrum showed the parent peak at m/e 206 (Calcd. 206).

Anal. Calcd. for $C_6H_{14}N_4S_2$: C, 34.9; H, 6.8; N, 27.2. Found: C, 34.7; H, 7.1; N, 27.2.

Other examples are presented in Table I.

4-*n*-Butyl-5-amino-1,2,4-triazoline-3-thione (**5c**).

A stirred methanol solution (400 ml.) of **4c** (41.2 g., 0.2 mole) and sodium methoxide (21.6 g., 0.4 mole) was refluxed for three days. The solvent was removed under reduced pressure, and the residue was dissolved in distilled water and acidified with concentrated hydrochloric acid. The resulting precipitate was collected by filtration and washed with distilled water to give 26.0 g. of a white powder that consisted of the desired **5c** and the starting material **4c**. A pure sample of this triazole was obtained after six crystallizations from ethyl acetate, m.p. 153-155°; ^{1}H nmr (deuteriochloroform): δ (ppm) 3.86 (t, 2H, NCH_2) and 4.9 (s, 2H, NH_2). The mass spectrum showed the parent peak at m/e 172 (Calcd. 172).

Anal. Calcd. for $C_6H_{12}N_4S$: C, 41.8; H, 7.0; N, 32.5. Found: C, 42.0; H, 6.8; N, 32.8.

For other examples, see Table II.

5-Benzylamino-1,2,4-triazoline-3-thione (**6a**).

A stirred suspension of 5-amino-1,2,4-triazoline-3-thione (20.0 g., 0.17 mole), benzaldehyde (18.0 g., 0.17 mole), and a trace of *p*-toluenesulfonic acid in benzene (500 ml.) was refluxed for seven days. During this time, the water that formed was removed azeotropically with a Dean Stark trap. The resulting bright yellow reaction mixture was evaporated to dryness, and the solid residue was slurried with glacial acetic acid (250 ml.) and cooled in an ice bath. A solution of *t*-butylamine borane (18.3 g., 0.21 mole) in glacial acetic acid (100 ml.) was added dropwise to the stirred suspension over a 30-minute period. The resulting stirred mixture was kept at ambient temperature for four days. Filtration of the white suspension gave 16.0 g. of 5-amino-1,2,4-triazoline-3-thione. The filtrate was evaporated to dryness, and the residue was dissolved in ethyl acetate, washed with distilled water, and dried with magnesium sulfate. After filtration through 75 g. of Florisil, the solution was evaporated to dryness. The residual cloudy yellow oil deposited a precipitate after several days. Crystallization from ethyl acetate afforded 0.8 g. of a pale yellow powder, m.p. 240-242°; ^{1}H nmr: δ (ppm) 4.28 (d, 2H, CH_2NH), 6.7 (t, 1H, CH$_2$N*H*), and 7.3 (m, 5*H*, C$_6H_5$). The mass spectrum showed the parent peak at m/e 206 (Calcd. 206).

1-Isopropoxythiocarbonyl-4-methyl-3-thiosemicarbazide (**7d**).

Carbon disulfide (68.4 g., 0.9 mole) was added slowly to a stirred isopropyl alcohol (500 ml.) solution of potassium hydroxide (44.8 g., 0.8 mole). An aqueous solution (200 ml.) of sodium chloroacetate [prepared *in situ* with chloroacetic acid (75.6 g., 0.8 mole) and sodium hydroxide (32.0 g., 0.8 mole)] was added to the stirred alcohol mixture. This stirred mixture was kept at ambient temperature for 18 hours. 4-Methyl-3-thiosemicarbazide (84.0 g., 0.8 mole) was added, and the stirred mixture was refluxed for five hours. After chilling this mixture in an ice bath, the colorless precipitate was collected, washed with copious amounts of distilled water, and then recrystallized from ethyl acetate to yield 40.0 g., (24%) of a white powder, m.p. 158-160°; ^{1}H nmr:

δ (ppm) 1.29 (d, 6*H*, $(CH_3)_2CH$), 2.87 (d, 3H, CH_3N), and 5.42 (m, 1*H*, $(CH_3)_2CH$). The mass spectrum showed the parent peak at m/e (207 (Calcd. 207).

Anal. Calcd. for $C_6H_{13}N_3OS_2$: C, 34.8; H, 6.3; N, 20.3; S, 30.9. Found: C, 34.5; H, 6.5; N, 20.5; S, 30.8.

Physical characteristics of other 1-alkoxythiocarbonyl-3-thiosemicarbazides are found in Table III.

4-Ethyl-1,2,4-triazolidine-3,5-dithione (**2b**).

A stirred solution (40 ml. of ethanol and 10 ml. of distilled water) of **7b** (1.6 g., 0.008 mole) and sodium hydroxide (1.6 g., 0.04 mole) was refluxed for 18 hours. After acidifying the solution with concentrated hydrochloric acid, the solvents were removed under reduced pressure. The residual solid was suspended in hot ethanol and undissolved solid was removed by filtration. The ethanolic filtrate was evaporated to dryness, and the residual pale yellow solid was crystallized from ethyl ether-pentane to give 0.3 g. (21%) of a pale yellow microcrystalline solid, m.p. 153-155°. The mass spectrum showed the parent peak at m/e 161 (Calcd. 161).

Anal. Calcd. for $C_4H_7N_3S_2$: C, 29.8; H, 4.3; N, 26.0; S, 39.8. Found: C, 30.1; H, 4.7; N, 25.7; S, 40.0.

The filtrate, after evaporating to dryness under reduced pressure, was shown by mass spectrometry to contain only **2b**.

Other examples may be found in Table IV.

4-Methyl-5-isopropoxy-1,2,4-triazoline-3-thione (**8d**).

A stirred solution (150 ml. of distilled water and 100 ml. of ethanol) of **7d** (12.0 g., 0.058 mole) and sodium acetate (23.8 g., 0.29 mole) was refluxed for 18 hours. This solution was then strongly acidified with concentrated hydrochloric acid, and the solvents were removed under reduced pressure. Residual traces of water were removed by azeotropic distillation with benzene. The solid was suspended in hot ethanol, and undissolved solid (presumably sodium chloride) was removed by filtration. A colorless microcrystalline solid separated from the ethanol filtrate, and after 18 hours at ambient temperature the crystalline solid was collected and dried, yield, 6.6 g. (66%), m.p. 195-196°; ^{1}H nmr: δ (ppm) 1.35 (d, 6*H*, $(CH_3)_2CH$), 3.22 (s, 3H, NCH_3), and 4.91 (septet, 1H, $(CH_3)_2CH$). The mass spectrum showed the parent peak at m/e 173 (Calcd. 173).

Anal. Calcd. for $C_6H_{11}N_3OS$: C, 41.6; H, 6.4; N, 24.3; S, 18.5. Found: C, 41.5; H, 6.7; N, 24.3; S, 18.9.

The ethanol filtrate from the above solid was evaporated to dryness. The mass spectrum of the residue revealed only **8d**.

Other examples are presented in Table V.

1-Methoxycarbonyl-4-methyl-3-thiosemicarbazide (**10a**).

To a stirred chloroform (200 ml.) mixture of 4-methyl-3-thiosemicarbazide (21.0 g., 0.2 mole) and methyl chloroformate (18.9 g., 0.2 mole) at the ice-bath temperature was slowly added triethylamine (40.5 g., 0.4 mole). The resulting stirred colorless suspension was kept at ambient temperature for 18 hours, and the solid was collected, washed with chloroform, then dried. This solid (20.3 g.) was crystallized from ethyl acetate-ethanol to give a snow-white powder, yield, 16.7 g. (51%), m.p. 187-188°. The mass spectrum showed the parent peak at m/e 163 (Calcd. 163).

Anal. Calcd. for $C_4H_9N_3O_2S$: C, 29.4; H, 5.5; N, 25.8; S, 19.7. Found: C, 29.6; H, 5.8; N, 26.0; S, 19.6.

Physical properties of other 1-alkoxycarbonyl-3-thiosemicarbazides are found in Table VI.

4-Ethyl-5-thiono-1,2,4-triazolidine-3-one (**11b**).

A stirred aqueous solution (75 ml.) of **10b** (6.0 g., 0.034 mole) and sodium acetate (13.9 g., 0.17 mole) was refluxed for 18 hours. This solution was then acidified with concentrated hydrochloric acid and the solution was evaporated to dryness. The residual colorless solid was suspended in hot ethanol and undissolved solid was removed by filtration. The filtrate was evaporated to dryness, and the slowly solidifying oil was crystallized from ethyl acetate, yield, 2.4 g. (49%), m.p. 180-181°. The mass spectrum showed the parent peak at m/e 145 (Calcd. 145).

Anal. Calcd. for $C_4H_7N_3OS$: C, 33.1; H, 4.8; N, 28.9. Found: C, 33.0; H, 5.0; N, 28.4.

See Table VII for other examples.

4-Methyl-5-benzylthio-1,2,4-triazoline-3-one (**13**).

Benzyl chloride (1.0 g.) was added to a stirred methanol (25 ml.) solution of the sodium mercaptide of **11a** [prepared *in situ* from **11a** (1.0 g.) and sodium methoxide (0.5 g.)]. The resulting stirred mixture was refluxed for 18 hours, and the methanol was removed under reduced pressure. The residue was suspended in hot ethyl acetate, and undissolved solid was removed by filtration. The filtrate was evaporated to dryness, and the clear colorless oil was crystallized from ethyl acetate-ethyl ether to give 0.6 g. of a colorless powder. This solid was crystallized from ethyl acetate, yield 0.2 g. of colorless prisms, m.p. 97-98°; ^{1}H nmr: δ (ppm) 2.92 (s, 3H, CH_3N), 4.20 (s, 2*H*, SCH_2), and 7.29 (m, 5*H*, C_6H_5); ^{13}C nmr: δ (ppm) 26.885 (CH_2S), 36.236 (CH_3N), 142.189 (-*C*-S-) and 154.897 (-*C*=O). The mass spectrum showed the parent peak at m/e 221 (Calcd. 221).

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.3; H, 5.0; N, 19.0; S, 14.5. Found: C, 53.8; H, 5.3; N, 19.2; S, 14.6.

4-Methyl-3-benzylthiosemicarbazide Hydriodide (**14**).

A stirred 95% ethanol (500 ml.) solution of 4-methyl-3-thiosemicarbazide (48.3 g., 0.46 mole) and benzyl iodide (100.0 g., 0.46 mole) was refluxed overnight. The resulting yellow solution was evaporated to dryness under reduced pressure, and the residue was slurried with ethyl acetate and filtered to yield 106.0 g. (71%) of an off-white powder. A small sample was crystallized from ethanol, m.p. 131-133°. The mass spectrum showed the parent peak of the free-base at m/e 195 (Calcd. 195).

Anal. Calcd. for $C_9H_{14}IN_3S$: C, 33.4; H, 4.4; N, 13.0; S, 9.9. Found: C, 33.7; H, 4.5; N, 13.2; S. 10.0.

4-Methyl-5-benzylthio-1,2,4-triazoline-3-one (**13**).

A pyridine (1 l.) solution of **14** (75.0 g., 0.23 mole) was cooled to -10° in an ice-methanol bath. Methyl chloroformate (21.7 g., 0.23 mole) was added dropwise over a period of about 20 minutes so that the temperature remained below -5°. When addition was complete, the stirred solution was kept for 18 hours at ambient temperature. The solvent was removed under reduced pressure, and the residue was dissolved in distilled water and extracted three times with ethyl acetate. The combined extracts were dried with magnesium sulfate and treated with charcoal. After evaporation to dryness, the residue was crystallized from ethyl acetate to yield 12.0 g. (24%) of an off-white powder. The product was crystallized twice more from ethyl acetate, m.p. 95-97°; ir (potassium bromide): 1720 cm^{-1} (C=O). The mass spectrum showed the parent peak at m/e 221 (Calcd. 221). This product was identical with **13** prepared by the benzylation of **11a** (*vide supra*).

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REFERENCES AND NOTES

(1) B. R. D. Whitear and D. J. Fry, British Patent 1,049,053, November 23, 1966.

(2) The triazoles will be represented as their -one or -thione tautomers. The infrared spectra of **11a** and **13**, for example, revealed an intense band at 1720 cm^{-1}.

(3) D. J. Fry and A. J. Lambie, British Patent 741,228, November 30, 1955.

(4) L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.*, 5137 (1961).

(5) E. Åkerblom and K. Skagius, *Acta. Chem. Scand.*, **18**, 174 (1964).

(6) R. Clarkson and J. K. Landquist, *J. Chem. Soc. (C)*, 2700 (1967).

(7) S. A. Greenfield, M. C. Seidel, and W. C. Von Meyer, German Offen. 1,943,915, March 12, 1970.

(8) H. Hoffman and I. Hammann, U. S. Patent 3,862,125, January 21, 1975.

(9) C. K. Bradsher, F. C. Brown, and S. T. Webster, *J. Org. Chem.*, **23**, 618 (1958).

(10) E. Fromm and E. Nehring, *Ber.*, **56B**, 1370 (1923).

(11) F. Arndt and E. Milde, *ibid.*, **54**, 2089 (1921).

(12a) F. Kurzer, *J. Chem. Soc.*, 1617 (1961); (b) K. M. Doyle and F. Kurzer, *Tetrahedron*, **32**, 1031 (1976).

(13) M. Busch and H. Lotz, *J. Prakt. Chem.*, **90**, 257 (1914).

(14) Y. R. Rao, *Indian J. Chem.*, **6**, 287 (1968).