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Studies on Thiazoline and Thiazolidine Derivatives. XI.[1] Synthesis of 3-N-Alkylthiocarbamoyl-2-alkyliminothiazolidines

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The compounds synthesized through the route (a) and the route (b) as shown in Chart 1 have been assigned by S. Gabriel in the past and by E. Cherbuliez, *et al.* recently to Type A, N-alkyl-N'-alkyl-N'-(2-thiazolin-2-yl)thiourea (**5**).

We had some doubt in the structure of the above compounds synthesized through the route (a) and (b), so they were hydrolyzed with 15% H_2SO_4 to give Type B, 3-N-alkylthiocarbamoyl-2-oxothiazolidine (**6**) which was assigned with infrared spectrum (IR), Mass Spectra and nuclear magnetic resonance (NMR) data and confirmed by synthesis of **6** through the route (c).

Thus, it was confirmed that the compounds obtained by our synthesis through the route (a) and (b) possessed the Type B structure; 3-N-alkylthiocarbamoyl-2-alkylimino-thiazolidine (**4**), instead of the Type A structure.

The data for ultraviolet spectrum (UV), IR, MS and NMR are shown in Table I, II and III.

3-N-Alkylthiocarbamoyl-2-iminothiazolidine (**4e, f**) exhibited a strong antiinflammatory activity, but showed an oral toxicity in rat.

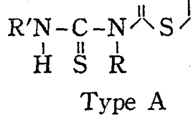
It was our intention to find a structure-activity relationship for a series of the title compounds (**4a, b, c, d**) in which an alkyl group replaced a hydrogen of 2-imino group of **4e, f.**

As we[1] reported before, **4e, f** was obtained by reacting 2-amino-2-thiazoline with R'N=C=S (**2**) in benzene at room temperature. A by-product (**5e, f**) was obtained at the same time. The reaction of 1-Alkyl-2,4-dithiobiuret with 1,2-dibromoethane in abs. ethanol also gave **4e, f.**

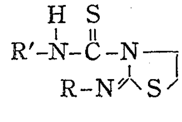
On the other hand, Gabriel[3] reported the reaction between 2-bromoethylamine (**1**) and methylisothiocyanate (**2a**) giving 2-methylamino-2-thiazoline (**3a**) together with a by-product remaining in benzene. The by-product (mp 70°, recryst. from petroleum-ether) gave analysis of $C_6H_{11}N_3S_2$. It was described in Beilstein[4] that the above by-product (mp 70°) was readily soluble in ether and chloroform, but difficulty soluble in petroleum-ether, having a structure N,N'-dimethyl-N-(2-thiazolin-2-yl)thiourea (**5a**).

E. Fromm, *et al.*[5] reported that 2-amino-2-thiazoline reacted with aromatic isothiocyanate under 50° to give a Type B compound, but a Type A compound at higher temperature.

D. Klayman, *et al.*[6] reported the experiment by E. Fromm, *et al.* thought that the Type A compounds were obtained regardless of temperature due to the lack of a proton signal for



Type A



Type B

1) Part X: Y. Yamamoto and R. Yoda, *Bull. Kyoritsu Pharm. College*, **18**, 53 (1973).
2) Location: *Shibakoen 1-Chome, Minato-ku, Tokyo.*
3) S. Gabriel, *Ber.*, **20**, 1150 (1889).
4) *Beilstein*, **27**, 361 (Dritte Band).
5) E. Fromm and Kapeller-Adler, *Ann. Chem.*, **467**, 259 (1928).
6) D. Klayman, J.J. Maul, and George W.A. Milne, *J. Hetero. Chem.* **5**, 520 (1968).

2-imino group around 5.0—6.5 ppm (DMSO-d_6) in the NMR data for a resulting mono-adduct. An influence to the 2-imino group of a thiocarbamoyl attached to a ring N was unknown, because NMR data for a model compound of the Type B which had an electron attracting group attached to a ring N were not studied. Therefore, Klayman prepared an isotopically labeled mono-adduct and concluded that it had the Type A structure from the Mass spectral and chemical data.

The reaction between 2-amino-2-thiazoline and alkylisothiocyanate (**2**), as reported by us,[1] gave mainly under 50° the Type B compounds which were isomerized thermaly to the Type A compounds.

E. Cherbuliez, *et al.*[7] reported, that ω-aminoethanol sulfonicacid ester (**7**) in aq. dioxane at pH 9.4 at 40° for 6 hr gave N,N'-diethyl-N-(2-thiazolin-2-yl)thiourea (**5d**) in 64% yield through the route (b) as shown in Chart 1. E. Cherbuliez, *et al.* compared the NMR data of

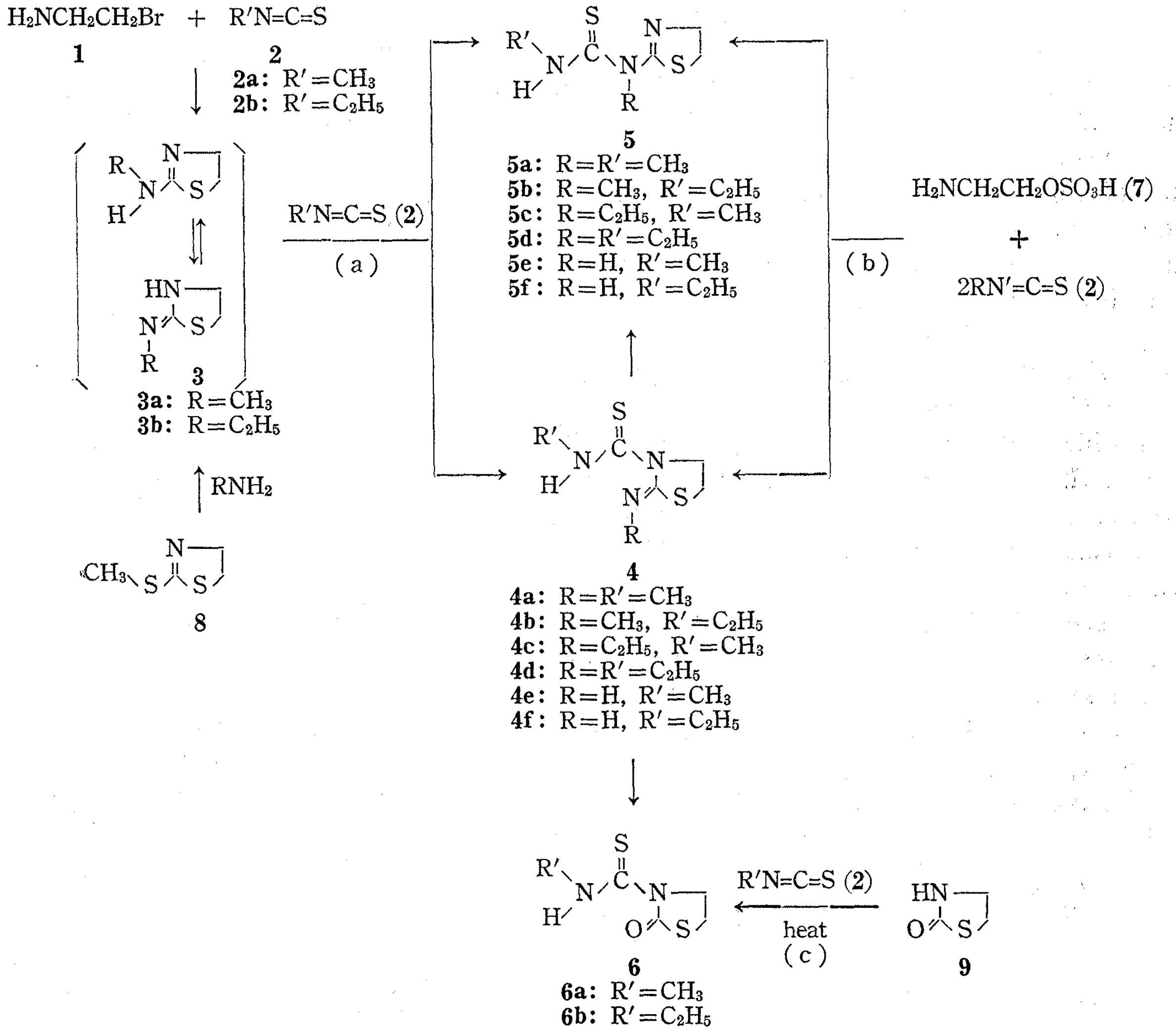


Chart 1

the compound at 4-methylene with a model compound; 2-phenylamino-2-thiazoline (Type A) and 2-phenylimino-3-methylthiazolidine (Type B) and decided that the compound had the structure of Type A. The NMR data of 2-phenylamino-2-thiazoline ($CDCl_3$) showed 3.95 ppm (triplet, J=7.0 Hz, 2H) for =N–$\underline{C}\underline{H}_2$–$CH_2$ and they agreed well with the data of the compound which gave 3.95 ppm (triplet, J=7.0 Hz, 2H). They are different from the data of 2-phenyl-

7) E. Cherbuliez, Br. Baehler, S. Jaccard, H. Jindra, G. Wyss, and J. Rabinowitz, *Helv. Chim. Acta.*, **49**, 807, 2408 (1966); *idem, ibid.*, **52**, 255 (1969).

imino-3-methyl-thiazolidine ($CDCl_3$) which gave 3.43 ppm (triplet, $J=7.0$ Hz, 3H) for CH_3–N–$C\underline{H}_2$–CH_2.

We repeated the method of Gabriel by adding **2a** to a benzene solution of **1** with cooling by ice and then the mixture was refluxed for 2.5 hr. After cooling the solution was extracted with water to remove hydrochloride of **3a** and then evaporated to dryness to leave a crude solid which was recrystallized from ligroin giving colorless crystals of mp 67°. This product of mp 67° was identical (mixed mp and IR spectra) with a product obtained from **2a** and **3a**, which was obtained from 2-methylthio-2-thiazoline (**8**) and methylamine according to the method of Klayman.[8] We also repeated the method of E. Cherbuliez through the route (b) by reacting **7** and **2a** in dioxane at pH 9.4 and the resulting crystals of mp 67° was identical (mixed mp and IR spectra) with the above product.

On the other hand, the NMR data for our compounds synthesized through the route (a, b) and (c) are shown in Table IIa and IIIb. The chemical shift of neighboring N–CH_2 next to endo N-atom showed triplets at 4.65—4.78 ppm ($CDCl_3$) indicating the similarity to 3-N-Alkylthiocarbamoyl-2-iminothiazolidine (**4e, f**) and showed the shift a lower field by 0.52—0.74 ppm from the chemical shift of 2-N-Alkylthioureido-2-thiazoline (**5e, f**) would give chemical shift of methylene at 4.65—4.87 ppm ($CDCl_3$) and is clearly different from the shift of 4.06—4.13 ppm of **5e, f** which belong to the Type A structure. The NMR data for the compound in DMSO-d_6 are listed in the Table IIb. A chemical shift of 4-methylene for the Type B compounds appeared 0.94—0.85 ppm in a lower field than those of the Type A compounds. This deshielding effect should be due to the substitution of thiocarbamoyl group.

On the other hand, L. Toldy, *et al.*[9] and S. Akaboshi, *et al.*[10] reported that a chemical shift of a methylene group at the position 4 varies extensively due to a different type of substituent when thiazoline derivatives of the Type B structure was substituted at the position.

It is considered that E. Cherbuliez *et al.* had a wrong selection for model compound when they determine the structure of **4d** by NMR data. We proved chemically that **4a, b, c, d** belonged to the Type A compounds.

Our compounds synthesized through the route (a) in Chart 1 were hydrolyzed at 100° (5 hr) with 15% H_2SO_4 to give 3-N-Alkylthiocarbamoyl-2-oxothiazolidine (**6**). The hydrolyzed products

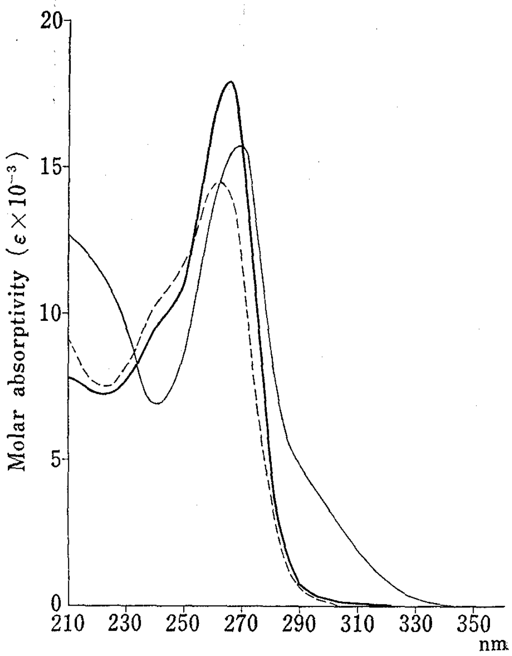
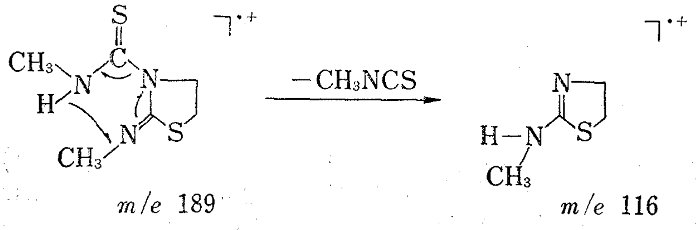


Fig. 1. UV Absorption Spectra of **4a**, **4e**, **5e** in 2-Propanol for Spectroscopy (MERCK)

reference: dist. H_2O
—— : 4a
········ : 4e
—— : 5e



8) D.L. Klayman and P.T. McIntyre, *J. Org. Chem.*, 33, 884 (1968).
9) L. Toldy, P. Sohár, and K. Faragó, *Tetrahedron Letters*, **25**, 2183 (1970).
10) T. Hino, K. Tana-ami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1201 (1966).

from **4** were identical with the known **6a** and **6b**[1] through mixed mp determinations. The structure **6** was confirmed by the synthesis from 2-oxothiazolidine (**9**)[11] and **2** by heating in pyridine.

The TLC, IR, UV, High Resolution Mass spectra data are summarized in Table I and III. Low Mass spectra data were given in the experimental part. The fragmentation of **4a** having the structure are shown below.

The Mass spectrum of **4a** gave *m/e* 189 (84%) M^+ and a base for 2-methylamino-2-thiazoline (*m/e* 116) which was derived from M^+ a possible splitting of CH_3NCS. m* at 71.5 was confirmed by $m^* = (116)^2/189 = 71.20$ (theoretical value). A strong 88% peak was observed at *m/e* 115 which was obtained by removed of H•.

The Type A (**5e, f**), as shown in Fig. 1 showed UV absorption at 225 nm for 2-thiazoline and 267 nm for thioureido group. On the other hand, the Type B (**4e, f**) showed absorption shoulders around 240 nm and at 265 nm for this thiocarbamoyl group. Since **4a** and **4e** gave same absorption curves, **4a** was assigned to the Type B structure.

TABLE I. Physical Properties of **4**

Compd.	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4a	67 (Ligroin)	$C_6H_{11}N_3S_2$	38.07	5.86	20.20	38.23	5.84	20.20
4b	34—35 (EtOH–H_2O)	$C_7H_{13}N_3S_2$	41.35	6.44	20.66	41.25	6.43	20.54
4c	76—77 (EtOH–H_2O)	$C_7H_{13}N_3S_2$	41.35	6.44	20.66	41.11	5.96	20.52
4d	84 (EtOH–H_2O)	$C_8H_{15}N_3S_2$	44.20	6.96	19.33	44.25	6.69	19.32

Compd.	TLC (*Rf* value) Solvent $CHCl_3$	$(CH_3)_2CO$	C_6H_{12} EtOAc	IR (KBr disk) cm^{-1} —3000	1700—1500	—1300	—1200	UV λ_{max}^{IPA} nm (ε)
4a	0.45	0.75	0.63	3425 3228 3140	1634 1572 1566	1382 1346	1295 1257	239.0(sh.) 266.0(18025)
4b	0.49	0.75	0.66	3412 3225 3130	1629 1570	1387 1354 1337	1295 1250	241.0(sh.) 268.0(16932)
4c	0.47	0.77	0.66	3415 3200 3150	1614 1584	1374 1350	1286 1252	239.5(sh.) 266.0(18813)
4d	0.50	0.78	0.56	3390 3250 3150	1620 1565 1550	1380 1335	1290 1250	241.0(sh.) 267.0(19487)

UV: sh. (shoulder), IPA (2-propanol)
TLC: (used by MERCK pre-coated Silica gel spot film, layer thickness 0.25 mm; detected by I_2 vapor.)

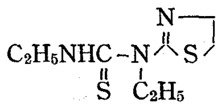
Experimental

Infrared spectra were obtained with a Hitachi EPI-G3 spectrometer, ultraviolet spectra with a Hitachi EPS-3T automatic recording spectrophotometer, nuclear magnetic resonance spectra with a Nihon Denshi JNM-NH100 (100 MHz), mass spectra with a Nihon Denshi TMS-OSG (70 eV) and high mass resolution spectra with a Hitachi RMV-7M HI-resolution mass spectrometer.

3-N-Alkylthiocarbamoyl-2-alkyliminothiazoline (4) by the Route (a)——To a solution of 2-alkylamino-2-thiazoline (3) (0.01 mole) in toluene or benzene (20 ml), alkylisothiocyanate (2) (0.01 mole) was added.

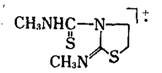
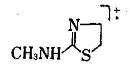
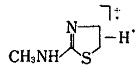
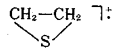
11) J.C. Crawhall, *J. Chem. Soc.*, **1952**, 3094.

TABLE II. NMR Spectral Data by JNM-NH 100 (100 MHz)

Compd.	NCH_2	CH_2S	$=N-CH_3$	$=N-\underline{CH_2}CH_3$	$=N-CH_2\underline{CH_3}$	$-N\begin{smallmatrix}H\\ \underline{CH_3}\end{smallmatrix}$	$-N\begin{smallmatrix}H\\ \underline{CH_2}CH_3\end{smallmatrix}$	$-N\begin{smallmatrix}H\\ CH_2\underline{CH_3}\end{smallmatrix}$	NH (=NH)
4a	4.65 t, J=7.0	3.30 —	2.96 m 8H						12.80 b
4b	4.73 t, J=7.0	3.13 t, J=7.0	3.10 s				3.65 oct.	1.25 t, J=7.0	12.48—12.0
4c	4.76 t, J=7.0	3.40 —	3.08 m 7H		1.24 t, J=7.0				12.49 b
4d	4.78 t, J=7.0	3.17 t, J=7.0		3.32 q	*1.24—1.23 t, J=7.0 6H		3.70 oct.	*1.24—1.23 t, J=7.0 6H	12.72 b
4e	4.87 t, J=7.0	3.19 t, J=7.0				3.16 d, J=5.0			12.43 (8.07) b s
4f	4.87 t, J=7.0	3.20 t, J=7.0					3.70 oct.	1.26 t, J=7.0	12.46 (8.04) b s
5e	4.13 t, J=7.0	3.36 t, J=7.0				3.18 d, J=5.0			9.0 —10.40
5f	4.06 t, J=7.0	3.29 t, J=7.0					3.68 oct.	1.25 t, J=7.0	9.60—10.40
 60 MHz E. Cherbuliez	4.72 t, J=7.0	3.12 t, J=7.0		$>N-\underline{CH_2}CH_3$ 3.08—3.42	*1.20 t, J=7.0 6H		3.50—3.75	*1.20 t, J=7.0 6H	
4a	4.58 t, J=7.0	3.26 t, J=7.0	3.07 s			3.04 s			12.20 b
4b	4.57 t, J=7.0	3.18 t, J=7.0	3.08 s				3.58 oct.	1.22 t, J=7.0	12.16 s
4c	4.66 t, J=7.0	3.43 —	3.05 m 7H		1.23 t, J=7.0				12.43 b
4d	4.62 t, J=7.0	3.22 t, J=7.0		3.24 q, J=7.0	1.22 t, J=7.0		3.58 oct.	1.20 t, J=7.0	12.52 b
4e	4.58 t, J=7.0	3.20 t, J=7.0				3.07 d, J=5.0			12.48 (9.75) b b
5e	3.72 t, J=7.0	3.40—3.20 m 2H				2.94 d, J=5.0			8.20—9.40

The NMR spectra were measured at room temperature in $CDCl_3$.
Chemical shifts are expressed in δ (ppm) with tetramethyl silane (TMS) as internal standard.
The coupling constant (J) is expressed in Hz; s: singlet, d: doublet, q: quartet, oct.: octet, m: multiplet, b: broad.

Table III. Results of High Resolution Mass of 4a

Elements	m/e (Calcd.)	m/e (Obs.)	Assign	E.R. Mass unit
$C_6H_{11}N_3S_2$	189.0393	189.0365		−2.8
$C_4H_8N_2S$	116.0407	116.0405		−0.2
$C_4H_7N_2S$	115.0329	115.0326		−0.3
C_2H_4NS	74.0064	74.0038	$CH_3NH=C=S$]$^+$	−2.6
C_2H_4S	60.0033	60.0037		0.4

The mixture was heated under reflux for 3 hr. After standing at room temperature for several hours the solvent was evaporated *in vacuo*, and the remaining residue was recrystallized from ligroin or EtOH–H_2O.

Mass Spectrum m/e (relative intensity) **4a**: M^+189 (84), M^+-CH_3NCS 116 (base), 115 (88), 74 (53), 73 (18), 60 (38). **4b**: M^+203 (base), M^+-C_2H_5NCS 116 (57), 115 (39), 88 (9), 87 (14), 60 (37). **4c**: M^+203 (base), M^+-CH_3NCS 130 (56), 129 (31), 102 (69), 74 (28), 73 (23), 60 (28). **4d**: M^+217 (base), M^+-C_2H_5NCS 130 (58), 129 (54), 102 (88), 88 (25), 87 (25), 60 (59).

3-N-Methylthiocarbamoyl-2-methyliminothiazolidine (4a) by the Route (b)——The mixture of ω-aminoethyl hydrogen sulfate (7) (0.03 mole) in H_2O (100 ml) and dioxane (30 ml) was adjusted to pH 9.4 by the addition of 1N NaOH soln. A solution of methylisothiocyanate (**2a**) (0.06 mole) in dioxane (15 ml) was added slowly with stirring to the above solution. After stirring for 4.5 hr at 40° and further for 14 hr at 20°, 1N NaOH (11 ml) was added to the reaction mixture. Then the crude product was collected on a filter and recrystallized from petroleum ether or EtOH–H_2O, mp 67°, which showed no depression of the melting point on admixture with the above sample. **4a**: M^+189 (56), M^+-CH_3NCS 116 (base), 115 (67), 74 (59), 73 (22), 60 (43). **4a** HCl salt: **4a** (0.0005 mole) was dissolved in ethanolic HCl (2 ml). The solution was evaporated *in vacuo* to dryness after standing for several minutes. The crude product was recrystallized from 2-propanol, mp 137—139°. *Anal.* Calcd. for $C_6H_{12}N_3S_2Cl$: C, 31.92; H, 5.36; N, 18.61. Found: C, 32.20; H, 5.36; N, 18.59. UV λ_{max}^{IPA} nm (ε), 239 (sh.), 266.5 (16860).

2-Alkylamino-2-thiazoline (3) and 3-N-Alkylthiocarbamoyl-2-alkyliminothiazolidine (4) by S. Gabriel Method——To the benzene layer of free 2-bromoethylamine (1), liberated from its HBr salt (0.122 mole), 33% KOH soln. (80 ml) and benzene (80 ml), alkylisothiocyanate (2) (0.2 mole) was added with ice cooling. The mixture was refluxed for 2.5 hr. After standing room temperature the reaction mixture was extracted three times with water (60 ml). Extracted aqueous layer was adjusted to pH 12 by the addition of 40% NaOH soln. Then after extracting with benzene the solvent was evaporated *in vacuo* to give **3**.

On the other hand, the residue of evaporated benzene layer was dissolved in 5% H_2SO_4 soln. and treated with 10% NH_3 soln. to give **4**.

Acid Hydrolysis of (4)——**4a** (1 g) in 15% H_2SO_4 soln. (27 ml) was heated on a steam bath for 5.5 hr. After cooling the crystallized precipitates were filtered and washed with water. Recrystallization from EtOH gave **6a**, mp 140°. M^+176 (56), 116 (48), 74 (base), 60 (35). UV λ_{max}^{IPA} nm (ε) 252 (14542), 271 (13316).

3-N-Alkylthiocarbamoyl-2-oxothiazolidine (6)——To a solution of 2-oxothiazolidine (9) (0.001 mole) in pyridine (5 ml), alkylisothiocyanate (2) (0.01 mole) was added. After heating 8.5 hr at 150—160°, the reaction mixture was kept at room temperature overnight. The solvent was evaporated *in vacuo*. The residue was recrystallized from EtOH or EtOH–H_2O.

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