[Chem. Pharm. Bull. 32(11)4292—4299(1984)]

Proton-Induced Ring Transformation of 2-Imino-3-thiocarbamoyl-4-thiazoline

YUICHI YAMAMOTO[1)] (deceased), REIKO YODA,* TOMOKO OKADA, and YOSHIKAZU MATSUSHIMA

Kyoritsu College of Pharmacy, Shibakoen 1-5-30, Minato-ku, Tokyo 105, Japan

(Received February 18, 1984)

The reaction of 4-methyl-2-methylaminothiazole (**1a**) and *N*, *N*-dimethylthiocarbamoyl chloride (**2a**) in a nonpolar solvent gave four products, 4-methyl-2-methylimino-3-(*N*, *N*-dimethylthiocarbamoyl)-4-thiazoline (**3a**), 1,1,3-trimethyl-3-(4-methyl-2-thiazolyl)thiourea (**4a**), 4-methyl-2-methylamino-5-(*N*, *N*-dimethylthiocarbamoyl)thiazole (**5a**), and 1,1-dimethyl-3-(3,4-dimethyl-2(3*H*)-thiazolylidene)thiourea (**6a**). The 2-phenylamino analog of **1a** (**1b**) gave the corresponding phenyl compounds (**3b**—**6b**) on reaction with **2a**. Compounds **3a** and **3b** were isomerized to **6a** and **6b**, respectively, in dioxane with a drop of hydrochloric acid. From studies with ^{15}N-labeled compounds, a mechanism is proposed involving a proton-induced ring transformation of **3**, *via* protonation of **3**, cleavage of the 3,4-bond, and bond formation between the imino nitrogen and 4-carbon atoms. A similar ring transformation took place with 3-*N*, *N*-dimethylcarbamoyl analogs of **3a** and **3b**, but not with a thiazolidine analog of **3b**.

Keywords——ring transformation; isomerization; 2-aminothiazole; 2-thiazolylthiourea; *N*, *N*-dimethylthiocarbamoylchloride; 2-imino-3-thiocarbamoyl-4-thiazoline

We previously found[2)] that 2-thiazolylthioureas are potentially useful chelating agents, which can be used for spectrophotometric determination of metal ions. We have reported several synthetic methods for the preparation of this series of compounds.[3)] One of the methods involves the reaction of 2-aminothiazole and thiocarbamoyl chloride. In an attempt to prepare 1,1,3-trimethyl-3-(4-methyl-2-thiazolyl)thiourea (**4a**) from 4-methyl-2-methylaminothiazole (**1a**) and *N*, *N*-dimethylthiocarbamoyl chloride (**2a**), four products including the expected one were obtained. Studies on the products as well as those of related reactions showed that the reaction involves ring transformation, which may be regarded as the exchange of substituents of the two nitrogen atoms in 2-imino-3-thiocarbamoyl-4-thiazoline. The present paper deals with the ring transformation and with the properties of thiazoles and thiazolines formed in the reactions.

Results and Discussion

4-Methyl-2-methylaminothiazole (**1a**) and *N*, *N*-dimethylthiocarbamoyl chloride (**2a**) were allowed to react at room temperature in a dry nonpolar solvent such as ether, benzene, or *n*-pentane. Products of the reaction were 4-methyl-2-methylimino-3-(*N*, *N*-dimethylthiocarbamoyl)-4-thiazoline (**3a**), 1,1,3-trimethyl-3-(4-methyl-2-thiazolyl)thiourea (**4a**), 4-methyl-2-methylamino-5-(*N*, *N*-dimethylthiocarbamoyl)thiazole (**5a**), and 1,1-dimethyl-3-(3,4-dimethyl-2(3*H*)thiazolylidene)thiourea (**6a**). The yields of the four products depended on the reaction conditions. From the reaction of 4-methyl-2-phenylaminothiazole (**1b**) and **2a**, the corresponding four phenyl compounds (**3b**—**6b**) were obtained (Chart 1).

The formation of the unexpected products, **6a** and **6b**, led us to investigate the mechanism of this reaction. From studies on the interconversion of the four isomers (**3a**—**6a**),

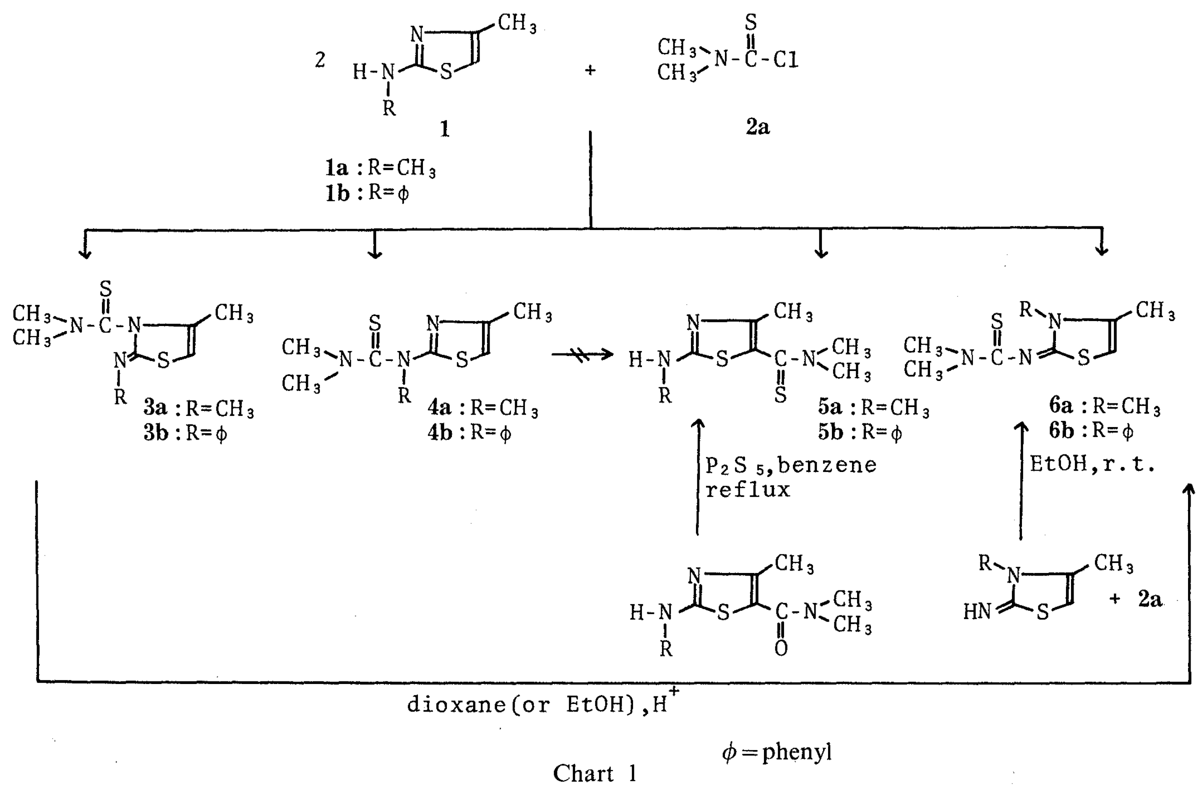


Chart 1

we found that **3a** was isomerized to **6a** at room temperature in dry dioxane with a drop of concentrated hydrochloric acid. Compound **3b** was isomerized to **6b** faster than **3a** to **6a** under similar conditions.

Isomerization of **4a** to **5a** or **6a** did not occur either in the presence or in the absence of acid. A thermal isomerization of 1,3-dimethyl-3-(4-methyl-2-thiazolyl)thiourea to 4-methyl-2-methylamino-5-(*N*-methylthiocarbamoyl)thiazole was reported in our previous paper.[4] These two compounds are *N*-monomethyl analogs of **4a** and **5a**.

To elucidate the mechanism of the isomerization of **3b** to **6b**, thiazolyl-3-^{15}N labeled **3b** (**3b***) was prepared and subjected to the isomerization reaction. The product (**6b***) was analyzed by means of mass spectroscopy. The mass spectra (MS) of **6b** and **6b*** are shown in Fig. 1 with assignments. The spectra were identical only in the region of *m/e* 175. Since the peaks in this region were assigned to a thiazoline fragment, the results indicate that ^{15}N was located at the thiourea moiety of **6b***. This conclusion is consistent with the results of high-resolution mass spectroscopy (Fig. 1).

Compound **3b** was dissolved in dioxane containing a drop of hydrochloric acid and maintained at 55 °C. A portion of the solution was occasionally drawn off and subjected to spectral measurement. The results are shown in Fig. 2. The spectral change indicated a gradual transformation of **3b** to **6b**. No spectral change occurred in the absence of hydrochloric acid.

When **2a** was replaced by *N*, *N*-dimethylcarbamoyl chloride (**2b**) in the reactions with **1a** and **1b**, the corresponding 3-carbamoyl compounds, **3c** and **3d**, and urea derivatives, **6c** and **6d**, were formed. Compounds corresponding to **4** and **5** were not separated, probably due to low yields. They were prepared by other synthetic routes as shown in Chart 2 (details are described in Experimental). Compounds **3c** and **3d** underwent the isomerization to **6c** and **6d**, respectively, under acidic conditions, though that of **3d** was faster. The reaction of **1b** and *N*, *N*-diethylthiocarbamoyl chloride (**2c**) gave three *N*, *N*-diethyl compounds (**3e**, **5e** and **6e**). 1,1-Diethyl-3-(4-methyl-2-thiazolyl)-3-phenylthiourea (**4e**) was not obtained in any

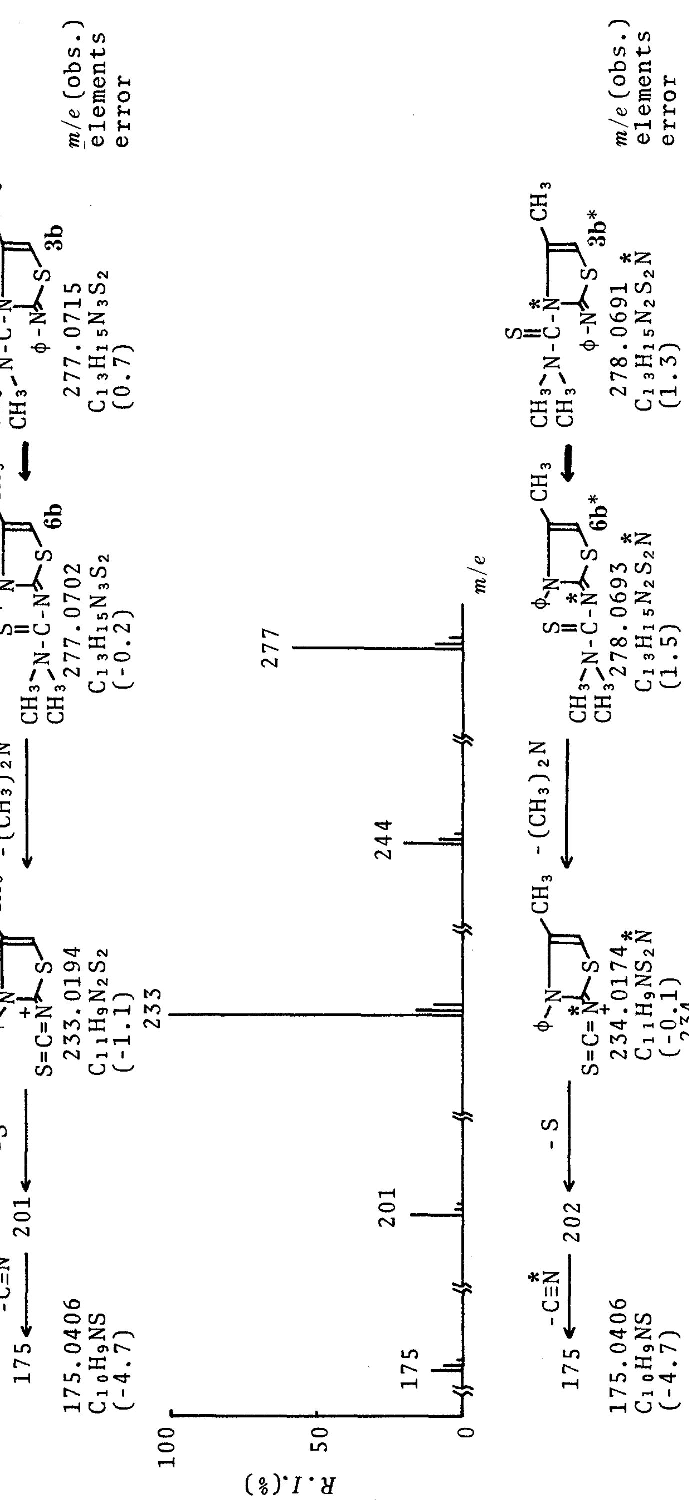


Fig. 1. Mass Spectra of **6b** and **6b***

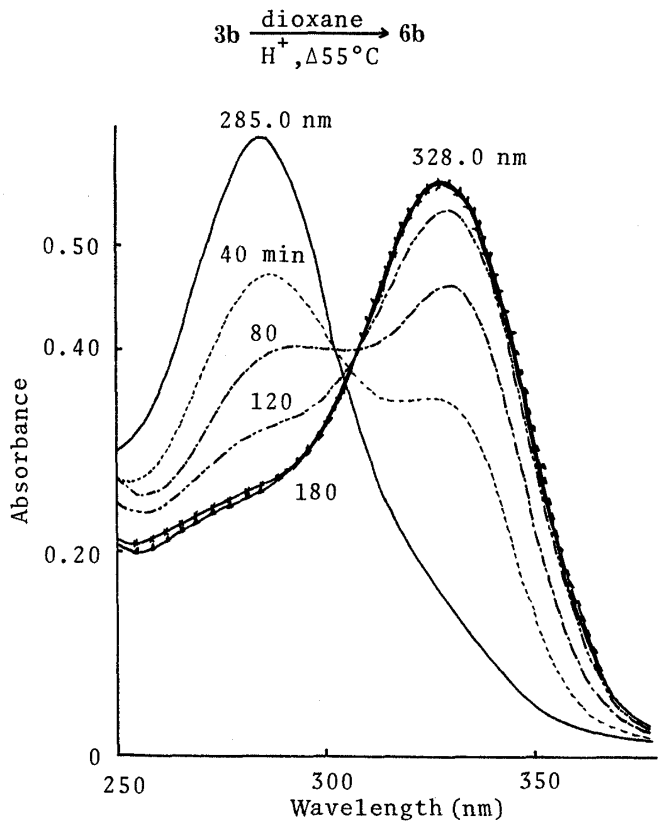


Fig. 2. Spectral Change Accompanying the Isomerization of **3b** to **6b**

——, **3b**: —×—×—, **6b**.

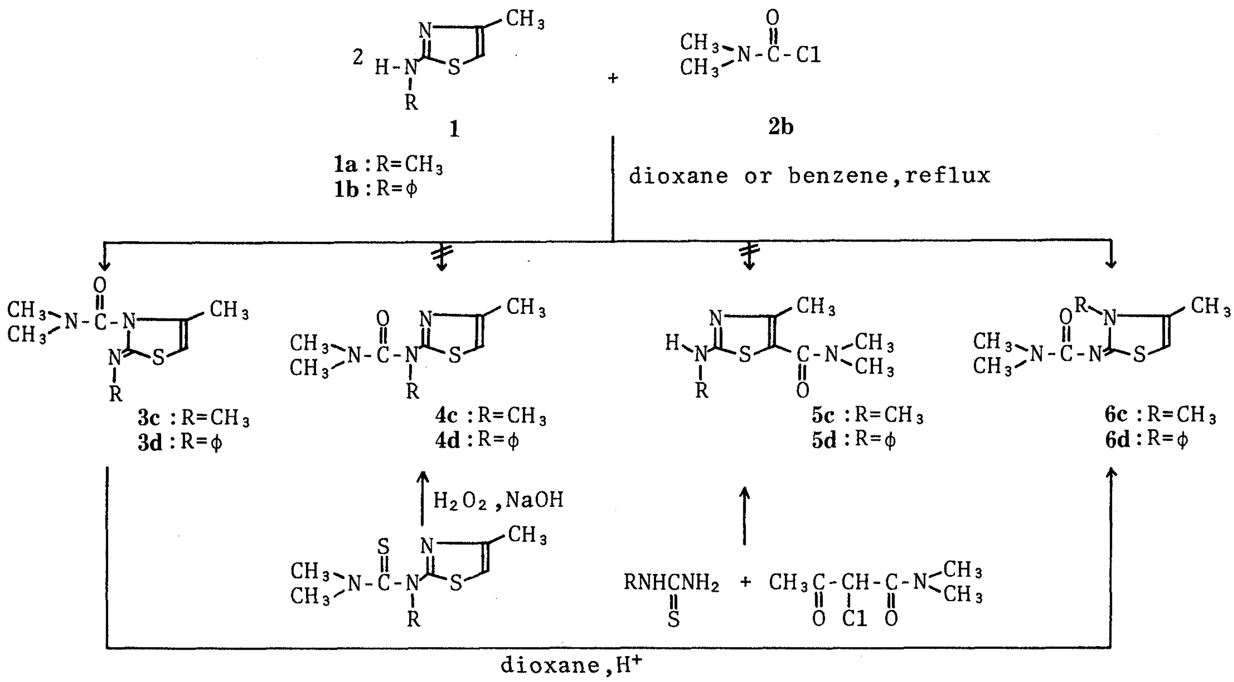


Chart 2

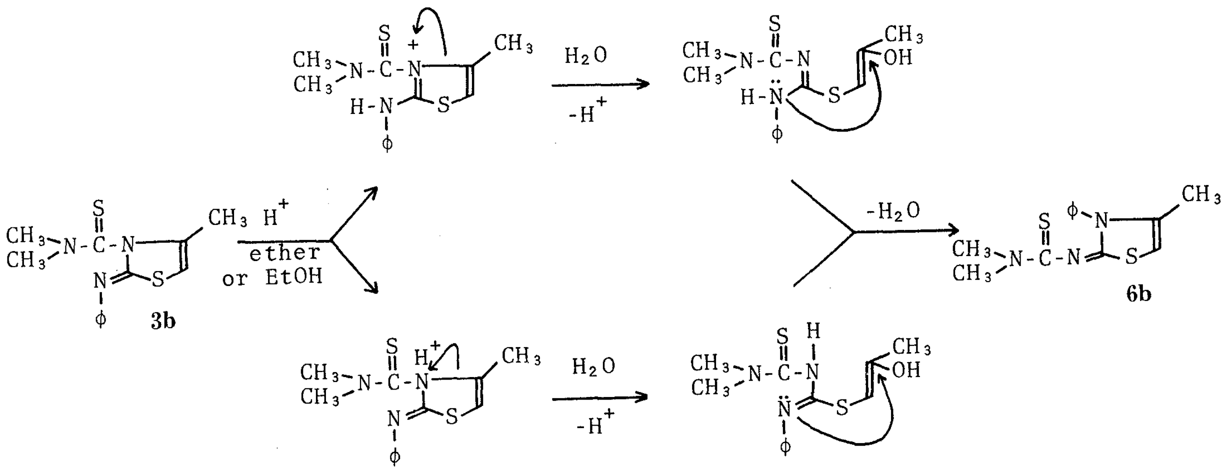


Chart 3

significant amount. Isomerization of **3e** to **6e** took place under the same conditions.

From the above results, it is clear that, in the reactions of 2-aminothiazoles (**1**) and thiocarbamoyl chlorides (**2**), 2-thiocarbamoylimino compounds (**6**) were derived by an acid-catalyzed ring transformation of 3-thiocarbamoyl compounds (**3**). Similarly, 2-carbamoylimino compounds were derived from 3-carbamoyl compounds. A mechanism of ring transformation consistent with the present results is shown in Chart 3. This involves protonation of either the 2-imino or thiazoline nitrogen atom followed by cleavage of the 3,4 bond. Compound **6** should be produced by bond formation between the imino nitrogen and 4-carbon atoms. That 4,5-unsaturation is required for the ring transformation is shown by the following finding: 3-(*N*, *N*-dimethylthiocarbamoyl)-2-phenyliminothiazolidine (**7a**), a 4,5-saturated analog of **3b**, did not form 1,1-dimethyl-3-(3-phenyl-2(3*H*)thiazolinylidene)-thiourea under the same conditions.

Physicochemical properties of the compounds prepared in the present study are listed in Table I.

Experimental

A JEOL JMS-D1000 mass spectrometer, a JEOL JMS-D300 high-resolution mass spectrometer, a JEOL JNM-NH 100 NMR spectrometer [100 MHz], a Shimadzu UV-200s double beam spectrometer and a Hitachi infrared spectrometer were used throughout the present study.

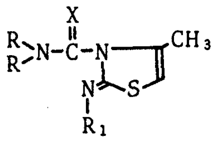
Reaction of 1a and 2a——Compound **2a** was mixed with a 2-fold molar excess of **1a** in a dry solvent and allowed to react at room temperature. An equimolar amount of **1a** was separated as the hydrochloride. The filtrate was evaporated *in vacuo* and the residue was subjected to chromatography on a silica gel column with acetone–$CHCl_3$ (1:9) as an eluent. Four products were separated, and recrystallized. They were identified as **3a**—**6a** by physicochemical data. Compounds **5a** and **6a** were identified by comparison with samples which were obtained by different synthetic routes as described below. The yields of the products are given in Table II.

Reactions of other aminothiazoles and carbamoyl chlorides were carried out similarly. Ether, dioxane, and *n*-pentane were used as solvents. Heating accelerated the reactions. In the reaction of 2-phenylamino-2-thiazoline and **2a**, 3-(*N*, *N*-dimethylthiocarbamoyl)-2-phenyliminothiazolidine (**7a**) was the sole product.

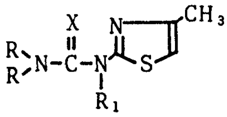
Isomerization of 3a to 6a——Compound **3a** was dissolved in dioxane (20 mg/20 ml) and a drop of conc. HCl was added. The solution was kept at 80 °C for 10 h. White crystals that separated were identified as **6a**. Yield, 15%.

4-Methyl-2-methylamino-5-(*N*, *N*-dimethylthiocarbamoyl)thiazole (5a)——2-Chloro-*N*, *N*-dimethylacetoacetamide (8.18 g) was added dropwise to a suspension of methylthiourea in abs. EtOH (4.51 g/30 ml). The reaction proceeded exothermically. After the reaction had ceased, the mixture was refluxed for an additional 2 h and then evaporated to dryness. The residue was dissolved in H_2O and the solution was made alkaline with 10% NaOH. 4-Methyl-2-methylamino-5-(*N*, *N*-dimethylcarbamoyl)thiazole (**5c**) was obtained as a white precipitate and recrystallized from cyclohexane. Yield, 4.1 g. Compound **5c** was dissolved in dry benzene (1.99 g/100 ml) and an

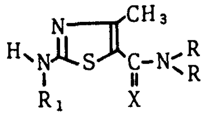
TABLE I. Physicochemical Properties of **3**, **4**, **5**, **6** and **7** Derivatives



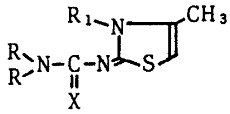
3



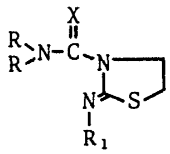
4



5



6



7

Compd. No.[a]			R	R_1	mp (°C)	Recryst. from	UV $\lambda_{max}^{2\text{-PrOH}}$ nm	ε ($\times 10^3$)	MS m/e (R.I.%) main peak M^+	M^+-R_2N	$R_2\overset{+}{N}CX$
3	X=S	**3a**	CH_3	CH_3	105	Ⓗ	277 325sh	18.9 1.3	215 (26)	171 (0)	88 (base)
		3b	CH_3	Ph	144	Ⓗ	280 328sh	18.2 3.1	277 (19)	233 (0)	88 (base)
	X=O	**3c**	CH_3	CH_3	105	Ⓗ	253 288sh	7.9 1.6	199 (60)	155 (2)	72 (base)
		3d	CH_3	Ph	110	Ligroin	254 297	6.3 7.8	261 (15)	217 (5)	72 (base)
	X=S	**3e**	C_2H_5	Ph	77	Ⓗ	284 332sh	21.0 3.8	305 (12)	233 (0)	116 (base)
4	X=S	**4a**	CH_3	CH_3	30—39	[b]	277	14.9	215 (55)	171 (2)	88 (base)
		4b	CH_3	Ph	Oil	[b]	279	14.3	277 (24)	233 (0)	88 83 (68) (base)
	X=O	**4c**	CH_3	CH_3	33	[b]	268	4.8	199 (65)	155 (4)	72 (base)
5	X=S	**5a**	CH_3	CH_3	173—175	Ligroin	283 333sh	13.9 7.5	215 (95)	171 (base)	88 (15)
		5b	CH_3	Ph	178	Ⓗ	292 340sh	13.7 7.0	277 (base)	233 (72)	88 (23)
	X=O	**5c**	CH_3	CH_3	155	Ⓗ	297	13.8	199 (47)	155 (base)	72 (11)
		5d	CH_3	Ph	191	EtOH– H_2O	314	19.2	261 (63)	217 (base)	72 (6)
	X=S	**5e**	C_2H_5	Ph	153	EtOH	294	13.1	305 (65)	233 (base)	116 (3)
6	X=S	**6a**	CH_3	CH_3	204	Ⓗ	296sh 328	7.9 15.0	215 (63)	171 (base)	88 (17)
		6b	CH_3	Ph	222	EtOH	295sh 333	8.0 17.4	277 (72)	233 (base)	88 (17)
	X=O	**6c**	CH_3	CH_3	156	Ⓗ	295	16.9	199 (23)	155 (base)	72 (13)
		6d	CH_3	Ph	127	Ⓗ	302	16.0	261 (33)	217 (base)	72 (22)
	X=S	**6e**	C_2H_5	Ph	136	EtOH– H_2O	298sh 333	9.4 19.0	305 (65)	233 (base)	116 (7)
7	X=S	**7a**	CH_3	Ph	94	Ⓗ	273	11.5	265 (35)	221 (5)	88 (base)

sh; shoulder.
a) Analyses were within ±0.2% of the theoretical values.
b) The crude product was purified by column chromatography.

TABLE II. Yields in the Reaction of **1a** or **1b** with **2a**

Reactants (g)		Conditions Solvent (ml)		Reaction time (h)	Yields (mg)			
1a	**2a**				**3a**	**4a**	**5a**	**6a**
3.85	3.71	Ether[a]	130	142	—	170	37	—
3.85	3.71	Ether[b]	110	122	—	600	4	37
5.13	2.47	*n*-Pentane	355	121	486	600	—	34
5.13	2.47	Benzene	165	145	—	410	119	110
5.13	2.47	Ether[c]	100	163	—	640	158	—
1b	**2a**				**3b**	**4b**	**5b**	**6b**
0.5	0.32	Ether[d]	50	142	—	—	Trace	25
2.25	0.74	Ether	80	96	—	—	—	100
2.61	0.85	Ether	63	24	—	—	10	260
3	0.99	Ether	110	116	310	Trace	—	—
3	0.99	Ether	100	135	98	—	11	220
3.19	1.03	Ether	100	111	37	Trace	7	35

a) Pyridine 2.37 g was added.
b) $(C_2H_5)_3N$ 3.04 g was added.
c) Strictly free from peroxide.
d) $(C_2H_5)_3N$ 0.3 g was added.

equimolar amount of P_2S_5 was added. The mixture was refluxed for 7 h and evaporated to dryness. The residue was dissolved in H_2O (30 ml) with heating, then the solution was allowed to cool. The white product (**5a**) was collected and recrystallized from ligroin. Yield, 520 mg. In a similar way, **5b** and **5d** were prepared from phenylthiourea.

1,1-Dimethyl-3-(4-methyl-3-phenyl-2(3*H*)thiazolylidene)thiourea (6b)——2-Imino-4-methyl-3-phenyl-4-thiazoline was prepared from phenylthiourea and monochloroacetone,[5] and was dissolved in EtOH (310 mg/20 ml). After dropwise addition of **2a** (200 mg) to the above solution, the mixture was stirred for 49.5 h at room temperature. The precipitate was recrystallized from EtOH. Yield 30 mg. Other thiourea (**6a**, **e**) and urea (**6c**, **d**) derivatives were prepared similarly.

^{15}N-Labeled Thiazolines——Phenyl isothiocyanate (7.1 g) was added dropwise to aqueous NH_3 (18.01%, 5 ml) enriched with ^{15}N (^{15}N atom, 50.8%) at room temperature. The mixture was stirred at room temperarure for 4.5 h and excess NH_3 was removed by heating in a boiling water bath. Phenylthiourea was precipitated after cooling, and was recrystallized from EtOH (6.8 g). Monochloroacetone (2.8 g) was added dropwise to a suspension of the product in H_2O (4.5 g/40 ml) at room temperature. The mixture was heated at 90—95 °C for 5.5 h, cooled, and made alkaline with 40% NaOH. The yellow precipitate was recrystallized from *n*-hexane (yield, 3.29 g) and it was confirmed to be 4-methyl-3-^{15}N-2-phenylaminothiazole (**1b***) (^{15}N, 44.6%) by mass spectroscopic analysis as well as by other physicochemical data. The reaction of **1b*** and **2a** gave **3b*** (^{15}N, 49.2%). Heating of **3b*** in dioxane containing HCl gave **6b*** (^{15}N, 47.7%).

1,1,3-Trimethyl-3-(4-methyl-2-thiazolyl)urea (4c)——An EtOH solution of **4a** (250 mg/40 ml) was made alkaline with 4% NaOH and kept at 0—5 °C. Aqueous hydrogen peroxide (35%) was added and the mixture was stirred for 1 h at 0—5 °C then for 1.5 h at room temperature. The white precipitate was removed and the filtrate was made acidic by addition of 15% HCl, concentrated *in vacuo* and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. The oily product was purified by chromatography on a silica gel column with acetone–$CHCl_3$ (1 : 2). White crystals were obtained.

Acknowledgements Thanks are due to the members of the Department of Physical Chemistry, the Central Research Laboratories, Sankyo Co., Ltd., for elemental analysis.

References and Notes

1) Deceased September 6th, 1983.
2) R. Yoda, K. Akiyama, Y. Yamamoto, and Y. Murakami, *Bunseki Kagaku*, **30**, 160 (1981); R. Yoda, *Mikrochim. Acta* [Wien], **1982** II, 271; R. Yoda, Y. Yamamoto, and Y. Murakami, *ibid.*, **1983** II, 75.
3) Y. Yamamoto, H. Nakamura, R. Yoda, M. Inoue, and S. Kato, *Annual Reports of Kyoritsu College of Pharmacy*, **12**, 116 (1967); Y. Yamamoto, H. Nakamura, and R. Yoda, *ibid.*, **15**, 31 (1970); R. Yoda and Y.

Yamamoto, *ibid.*, **18**, 36 (1973); Y. Yamamoto, K. Sekine, and T. Takahashi, Proceedings of the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977, II-87.
4) Y. Yamamoto, R. Yoda, and C. Tamura, *Chem. Lett.*, **1975**, 1147; Y. Yamamoto, R. Yoda, K. Koguchi, T. Takahashi, and N. Motomura, *Annual Reports of Kyoritsu College of Pharmacy*, **26**, 25 (1981).
5) H. Beyer and G. Ruhlig, *Chem. Ber.*, **89**, 107 (1956).