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Pyrolytic $S \rightarrow N$ Methyl Migration of *N,N*-Dimethyl-*N′*-(4-methyl-2-thiazolyl)-*S*-methylisothiourea

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N,N-Dimethyl-*N′*-(4-methyl-2-thiazolyl)-*S*-methylisothiourea (**1a**) was pyrolyzed at 155 °C for 14 h. *N,N*-Dimethyl-*N′*-(3,4-dimethyl-4-thiazolin-2-ylidene)thiourea (**2a**) was identified as a main product. A similar pyrolytic methyl migration from isothiourea-*S* to thiazole-*N* was demonstrated in derivatives of **1a**, but not in derivatives of *N*-monomethyl-*N′*-(2-thiazolyl)-*S*-methylisothiourea. The results are interpreted in terms of predominant species in an equilibrium between (*E*) and (*Z*) forms.

Keywords——methyl migration; pyrolysis; rearrangement; *N*-(2-thiazolyl)thiourea; *N*-(2-thiazolyl)-*S*-methylisothiourea; *N*-(3-methyl-4-thiazolin-2-ylidene)thiourea

In an effort to establish *N*-(2-thiazolyl)thioureas as a new series of chelating ligands,²⁾ we prepared *N*-methyl-*N′*-(3-methyl-4-thiazolin-2-ylidene)-*S*-methylisothiourea by methylation of the corresponding thiourea or *N*-methyl-*N′*-(2-thiazolyl)-*S*-methylisothiourea.³⁾ In an attempt to obtain the corresponding compound of *N,N*-dimethylthiourea, *N,N*-dimethyl-*N′*-(2-thiazolyl)thioureas were treated with various methylating agents. According to the methylating agents and the reaction conditions, either the *S*-methylated compound (*S*-methylisothiourea) or the thiazole-*N*-methylated compound was obtained. In the course of the investigation, we found a pyrolytic methyl transfer reaction from *S*-methylisothiourea to (3-methyl-4-thiazolin-2-ylidene)thiourea.

Rearrangement of methyl *p*-dimethylaminobenzenesulfonate to *p*-trimethylammonium benzenesulfonate zwitterion was found by Kuhn and Ruelius.⁴⁾ Bergman *et al.*⁵⁾ extensively studied the methyl migration and found that the reaction was intermolecular and proceeded at a considerably faster rate in a crystal than it did in solution. The reaction rate enhancement was explained in terms of proper orientation of the molecules in the crystal.

The pyrolytic methyl migration of *S*-methylisothioureas was also intermolecular and proceeded smoothly without any solvent. The present paper is concerned with the $S \rightarrow N$ methyl migration.

Results and Discussion

N,N-Dimethyl-*N′*-(4-methyl-2-thiazolyl)-*S*-methylisothiourea (**1a**) was heated at 155 °C for 14 h. Chromatography of the pyrolytic products gave a yellow crystalline compound, which was identified as *N,N*-dimethyl-*N′*-(3,4-dimethyl-4-thiazolin-2-ylidene)thiourea (**2a**) by comparing its physicochemical properties with those of an authentic sample synthesized from 2-imino-3,4-dimethyl-4-thiazoline and *N,N*-dimethylthiocarbamoyl chloride. Similarly, pyrolysis of *N,N*-dimethyl-*N′*-(4,5-dimethyl-2-thiazolyl)-*S*-methylisothiourea (**1b**) and *N,N*-diethyl analogs of **1a** and **1b** (**1c** and **1d**) gave the corresponding (3-methyl-4-thiazolin-2-ylidene)thioureas (**2b**, **2c**, and **2d**, respectively) (Chart 1). The results indicate that the reactions include pyrolytic $S \rightarrow N$ migration of a methyl group.

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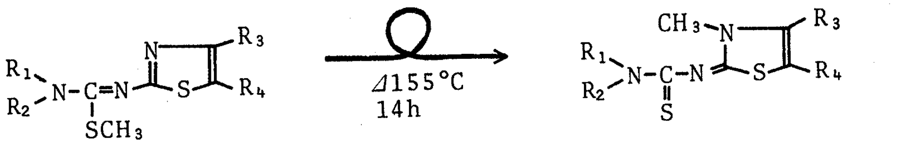

1a: $R_1=R_2=R_3=CH_3$, $R_4=H$
1b: $R_1=R_2=R_3=R_4=CH_3$
1c: $R_1=R_2=C_2H_5$, $R_3=CH_3$, $R_4=H$
1d: $R_1=R_2=C_2H_5$, $R_3=R_4=CH_3$

2a: $R_1=R_2=R_3=CH_3$, $R_4=H$
2b: $R_1=R_2=R_3=R_4=CH_3$
2c: $R_1=R_2=C_2H_5$, $R_3=CH_3$, $R_4=H$
2d: $R_1=R_2=C_2H_5$, $R_3=R_4=CH_3$

Chart 1

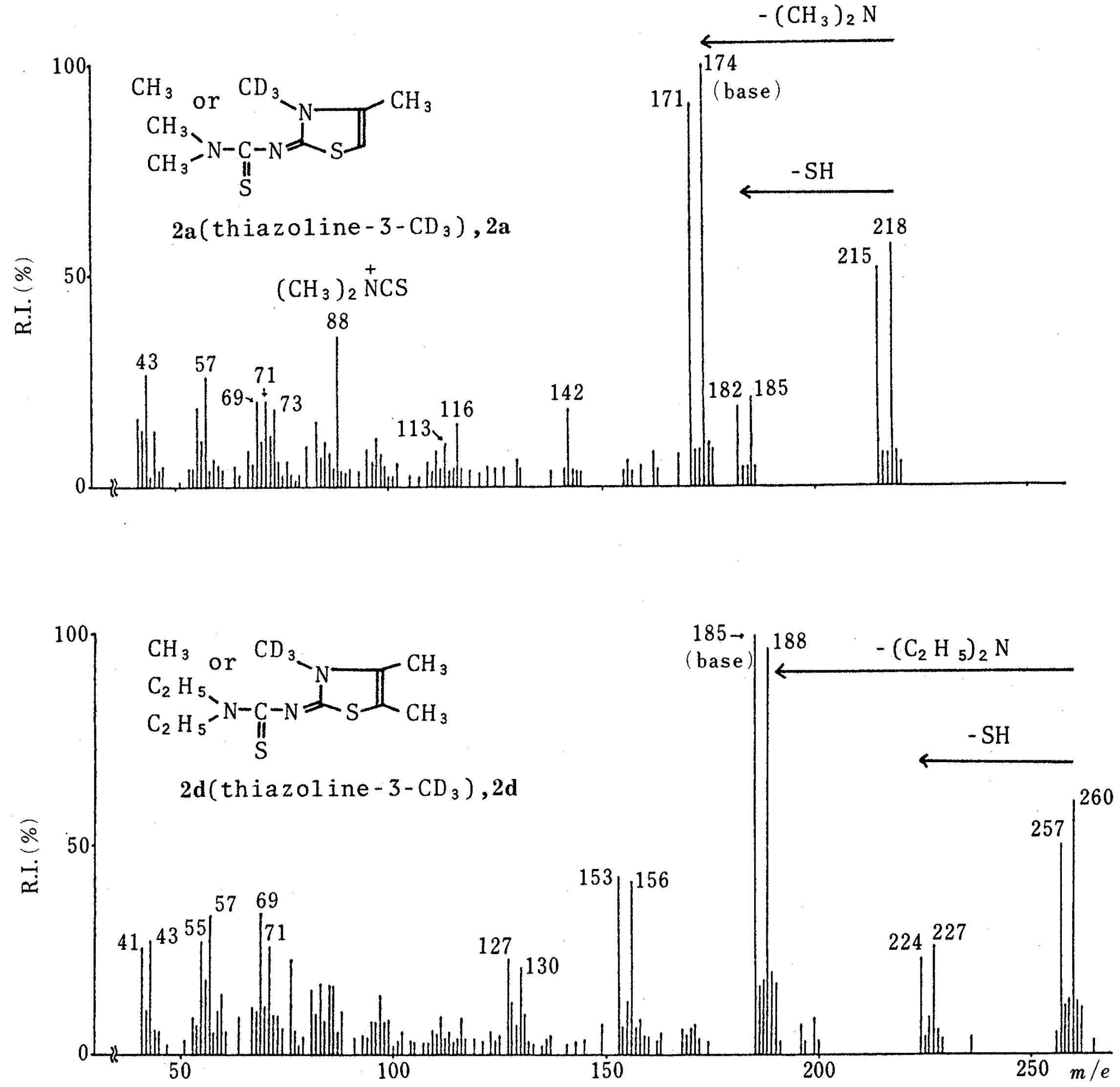

Fig. 1. Mass Spectra of **2a** and **2d**

In order to confirm the migration, *S*-deuteromethylisothiourea, **1a** (S-CD_3), was prepared and subjected to pyrolysis. Compound **2a** (thiazoline-3-CD_3) was obtained as a main product.

After pyrolysis of a mixture of **1a** (S-CD_3) and **1d**, two products were separated and identified as **2a** and **2d** from their physicochemical properties. Mass spectra of the products are shown in Fig. 1. Two molecular peaks attributable to CH_3 and CD_3 compounds are

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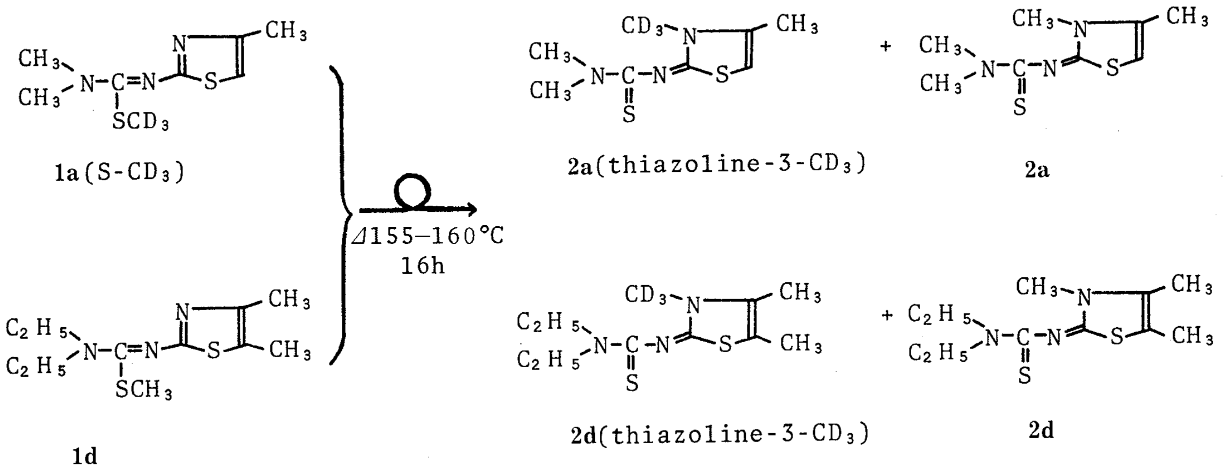

Chart 2

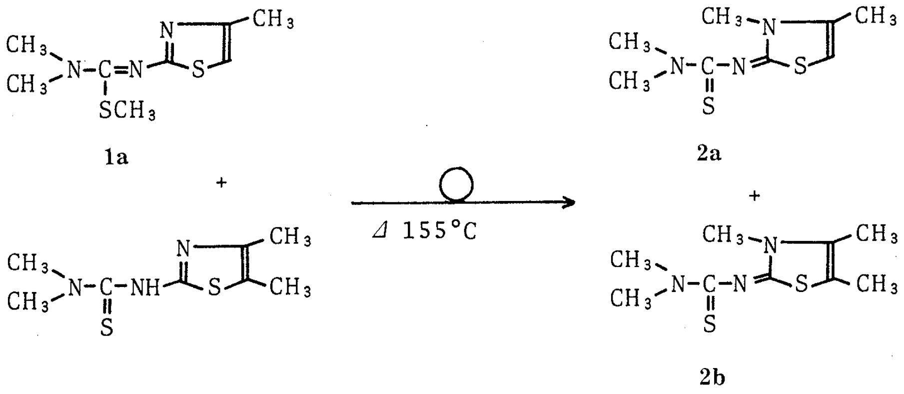

Chart 3

clearly observed in the spectra of both products. The reactions are shown in Chart 2. The formation of **2a** and **2d** (thiazoline-3-CD_3) suggests that the reaction involves intermolecular transfer of the methyl group.

From the pyrolytic products of a mixture of **1a** and *N*,*N*-dimethyl-*N*′-(4,5-dimethyl-2-thiazolyl)thiourea, both of the possible thiazole-*N*-methylated thioureas were formed (Chart 3). The result shows that the *S*-methylisothiourea acts as a methylating agent towards the thiazolylthiourea derivative.

A similar *S*→*N* migration of the ethyl group was demonstrated in the *S*-ethyl analog of **1a**. *N*,*N*-Dimethyl-*N*′-(4-methyl-2-thiazolyl)-*S*-ethylisothiourea was pyrolyzed to form *N*,*N*-dimethyl-*N*′-(3-ethyl-4-methyl-4-thiazolin-2-ylidene)thiourea.

N-Methyl-(2-thiazolyl)-*S*-methylisothioureas (**3a**—**c**) were pyrolyzed under conditions similar to those used for the *N*,*N*-dimethylisothiourea analogs and the products were analyzed by means of thin layer chromatography. The spots of the methyl-migrated compounds (**4a**—**c**) were not found in the chromatograms (Chart 4). Pyrolysis of an equimolar mixture of **1a** and **3b** gave **2a**, but not **4b**.

The results clearly indicate that the pyrolytic *S*→*N* methyl migration takes place in *N*,*N*-dimethyl-*N*′-thiazolyl-*S*-methylisothioureas but not in *N*-monomethyl analogs. A tentative interpretation of the phenomena is as follows (Charts 4 and 5).

In these isothiourea and thiourea derivatives, S, C, and two N atoms of the thiourea moiety are presumably coplanar with the thiazole moiety. The compounds should be present as an equilibrium mixture of (*E*) and (*Z*) forms as shown in Chart 5. For *N*,*N*-dimethyl derivatives, the (*E*) form must be favored, since the two bulky groups are brought closer

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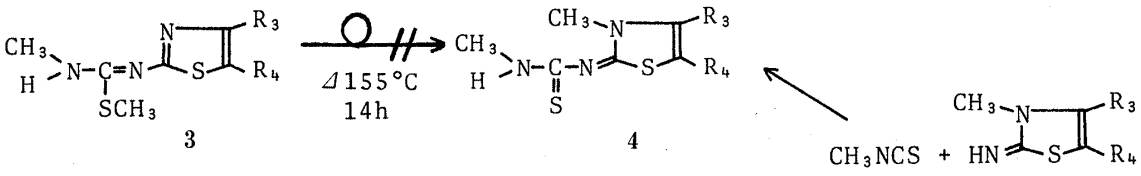

3a : $R_3=R_4=H$
3b : $R_3=CH_3, R_4=H$
3c : $R_3=R_4=CH_3$

4a : $R_3=R_4=H$
4b : $R_3=CH_3, R_4=H$
4c : $R_3=R_4=CH_3$

Chart 4

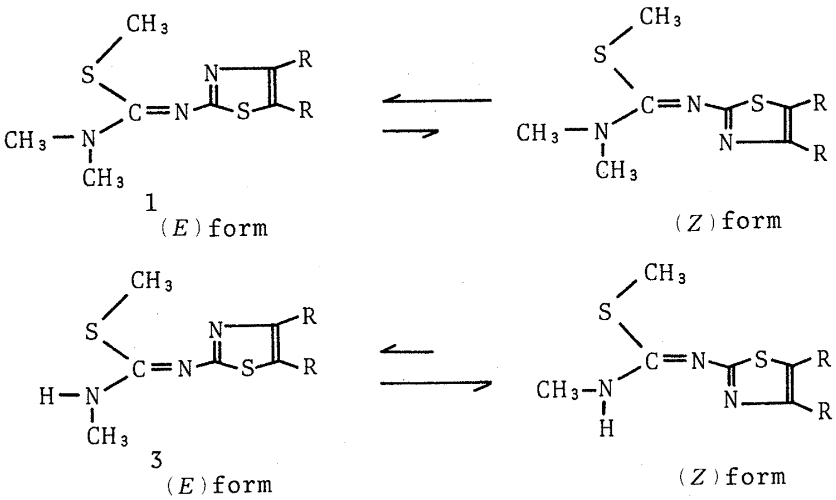

Chart 5

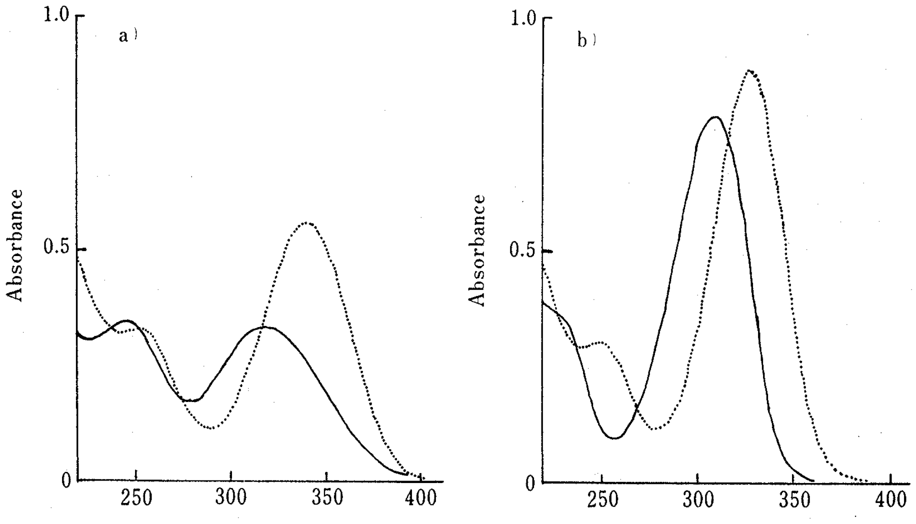

Fig. 2. Absorption Spectra of a) **1a** and b) **3b**

Solid lines are spectra in neutral methanol and dotted lines are those in acidic methanol.

together in the (*Z*) form. On the other hand, the (*Z*) form must be stabilized by an intramolecular hydrogen bond between the NH and thiazole N atoms and it may be the predominant form in *N*-monomethyl derivatives.

Absorption spectra of **1a** and **3b** in acidic and neutral methanol solutions are shown in Fig. 2. The spectra in acidic solutions are attributed to the species protonated at the thiazole

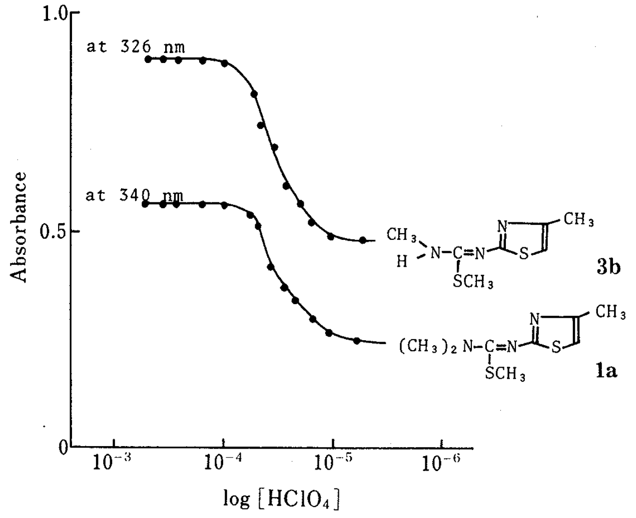

Fig. 3. Spectrophotometric Titration Curves of **1a** and **3b** in Methanol with $HClO_4$

Table I. Physicochemical Properties of *N*-Monoalkyl Derivs. and *N*,*N*-Dialkyl Derivs.

Compd. No.	^{1}H-NMR ($CDCl_3$) δ		UV $\lambda_{max}^{2\text{-PrOH}}$		Compd. No.	^{1}H-NMR ($CDCl_3$) δ		UV $\lambda_{max}^{2\text{-PrOH}}$	
	$S\underline{CH}_3$	$(\underline{CH}_3)_2N$	nm	ε		$S\underline{CH}_3$	$\underline{CH}_3NH$	nm	ε
N,*N*-Dimethyl-*N*′-(4-methyl-2-thiazolyl)-thiourea	—	3.30	293	8.3×10^3	*N*-Monomethyl-*N*′-(4-methyl-2-thiazolyl)-thiourea	—	3.03 (DMSO-d_6)	255	8.9×10^3
			329	16.4				290	20.4
1a	2.16	3.14	245	8.1	**3a**	2.47	3.00	226	6.0
			316	7.2				305	18.1
1b	2.18	3.18	246	7.6	**3b**	2.45	3.03	230	7.9
			325	7.1				310	16.5
1d	2.25	—	248	7.7	**3c**	2.43	2.99	225	7.1
			328	7.2				310	19.2

N, whereas those in neutral solutions are attributed to the thiazole-unprotonated species. Protonation of thiourea N is not expected to have a marked effect on the spectra.

Figure 3 shows the spectrophotometric titration curves in methanol (with various concentrations of $HClO_4$) of the compounds based on the absorption bands assigned to the thiazole protonated species. The curves indicate that the thiazole N is more basic in **1a** than **3b**. These results suggest that the basicity as well as the reactivity in the methyl migration are lower in the thiazole N of **3b**, probably because the more stabilized (*Z*) form is predominant.

Data from nuclear magnetic resonance spectra are listed in Table I. Chemical shifts of protons of the *S*-methyl group appear at higher field in the *N*,*N*-dimethyl derivatives than in the *N*-monomethyl derivatives. This is in conformity with the above assumption, since higher field shifts due to the ring current of thiazole are expected for the methyl protons in (*E*) form. Similar higher field shifts of *S*-methyl protons of *cis*- aryl-*S*-methylisothioureas than of *trans* isomers were reported.[6]

The above assumption is tentative and requires confirmation. Further work is in progress.

Experimental

Thiourea and isothiourea derivatives (**1**—**4**) were prepared according to the method given in the previous paper.[3]

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Their physicochemical properties were described therein. Compound **1a** (S-CD_3) was prepared by methylation of *N*,*N*-dimethyl-*N*′-(4-methyl-2-thiazolyl)thiourea with CD_3I.

A JEOL JMS-D100 mass spectrometer, a JEOL JNM-NH 100 NMR-spectrometer [100 MHz], and a Shimadzu UV-200s double beam spectrometer were used throughout the present study.

A typical pyrolytic procedure is as follows: **1d** (300 mg, liquid) was placed in a flask equipped with a condenser and was heated with stirring for 14 h in a silicon-oil bath maintained at 155 °C. A brown solid was obtained upon cooling to room temperature. The brown solid was washed with EtOH and subjected to chromatography on silica-gel eluted with acetone–$CHCl_3$ (1 : 2). A yellow crystalline compound was separated from the eluate and recrystallized from EtOH, yield 20 mg, mp 131 °C. The compound was identified as **2d** by elemental analysis and by comparing its physicochemical properties with an authentic sample.

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], **II**, 271 (1982); R. Yoda, Y. Yamamoto, and Y. Murakami, *ibid.*, **II**, 75 (1983).
3) Y. Yamamoto and R. Yoda, *Annual Report of the Kyoritsu College of Pharmacy*, **24**, 21 (1979).
4) R. Kuhn and H. W. Ruelius, *Chem. Ber.*, **83**, 420 (1950).
5) C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, P. Y. Lau, G. Wood, and R. G. Bergman, *J. Am. Chem. Soc.*, **99**, 851 (1977).
6) G. Tóth, I. Tóth, and L. Toldy, *Tetrahedron Lett.*, **1969**, 5299.