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Studies on Thiazole and Thiazoline Derivatives (XVII) Methylation of N-Alkyl (or N, N-dialkyl)-N′-(2-thiazolyl) thiourea derivatives.[1]

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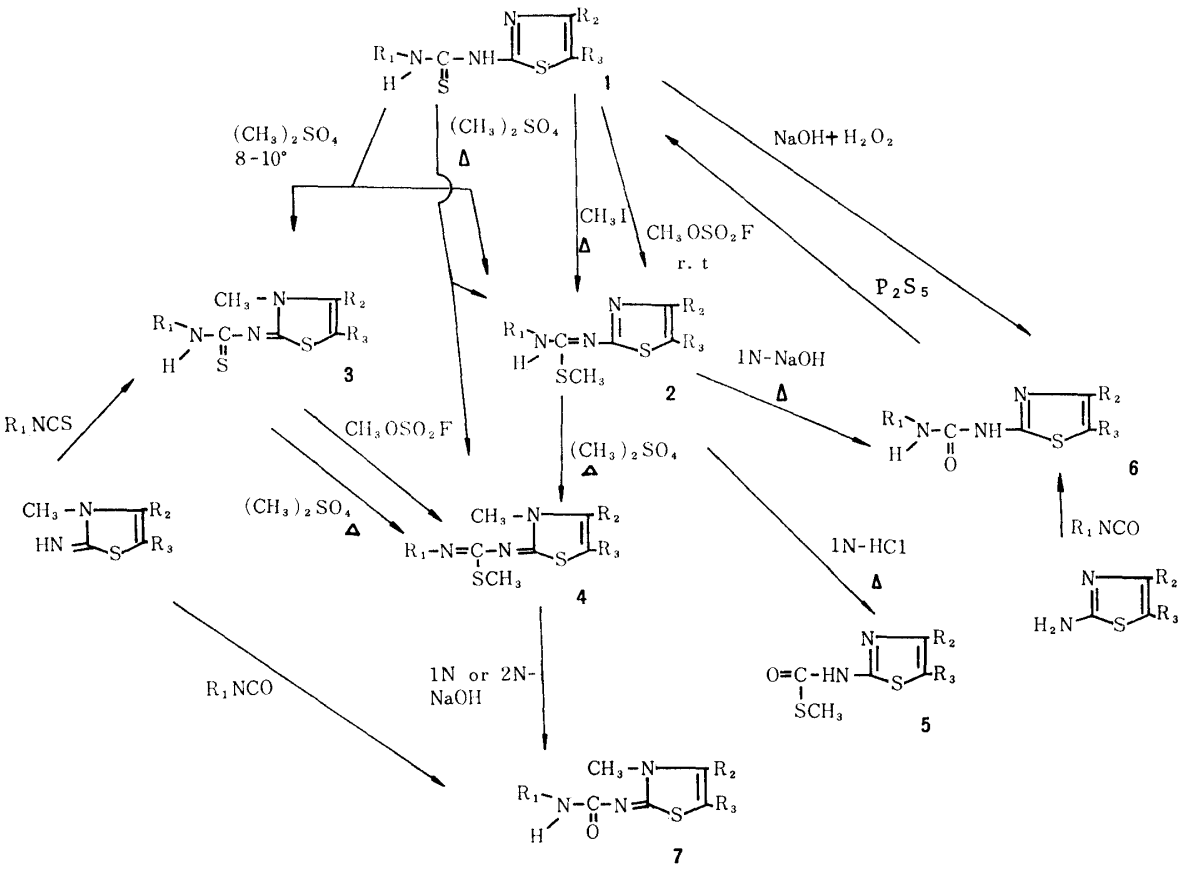
As shown in Scheme 1 and 2, methylation of title compounds was examined by various kinds of methyl agents. S-methyl derivatives and ring N-methyl derivatives as mono-methyl substituent and ring N,S-dimethyl derivatives as di-methyl substituents were obtained and the structure of these compounds was identified by NMR, Mass, IR, elemental analysis, and the hydrolyzed products of their methyl derivatives. Among them, we found that when S-methyl derivatives, N,N-dimethyl-N′-(4-methyl (or 4,5-dimethyl)thiazole)-S-methylisothiourea, were heated at 155—160°, ring N-methyl derivatives, N,N-dimethyl-N′-(3,4-dimethyl(or 3,4,5-trimethyl) thiazole-2-ylidene) thiourea were obtained. A detailed methyl rearrangement will be reported elsewhere at a later date.

For many years we have synthesized ureido and thioureido derivatives of thiazoles, thiazolines and oxazolines, and studied relationships between their biological activities and structures, as well as their chelate formation with metalic ions such as Pd^{2+}, Cu^{2+}, Hg^{2+}, Au^{3+} etc[2]. Thioureido derivatives exhibited effectively biological activity, but showed an oral toxicity in rat. This communication describes methylation of thioureido thiazole derivatives as shown in Scheme 1, 2 and Table I. The effects depending upon the reaction conditions with various methyl agents such as $(CH_3)_2SO_4$, CH_3OSO_2F (magic methyl) and CH_3I were examined and identified the structure of their products. In the case of N-Alkylthioureidothiazoles, **1a** to **1e**, possible positions of methylation are four as marked→(arrow) in Scheme 3 and N,N-dialkylthioureidothiazoles, **1f**, **g**, are two. On the other hand dimethyl-substituents of compounds **1** may be also considered for methylation.

To a solution of **1a** in 2N–NaOH solution was added an equivalent of $(CH_3)_2SO_4$ (or molar ratio of 1: 2), the mixture was left at 8—10° for several hours. The resulting yellow precipitate was filtered and neutralized with $NaHCO_3$ solution to afford free base

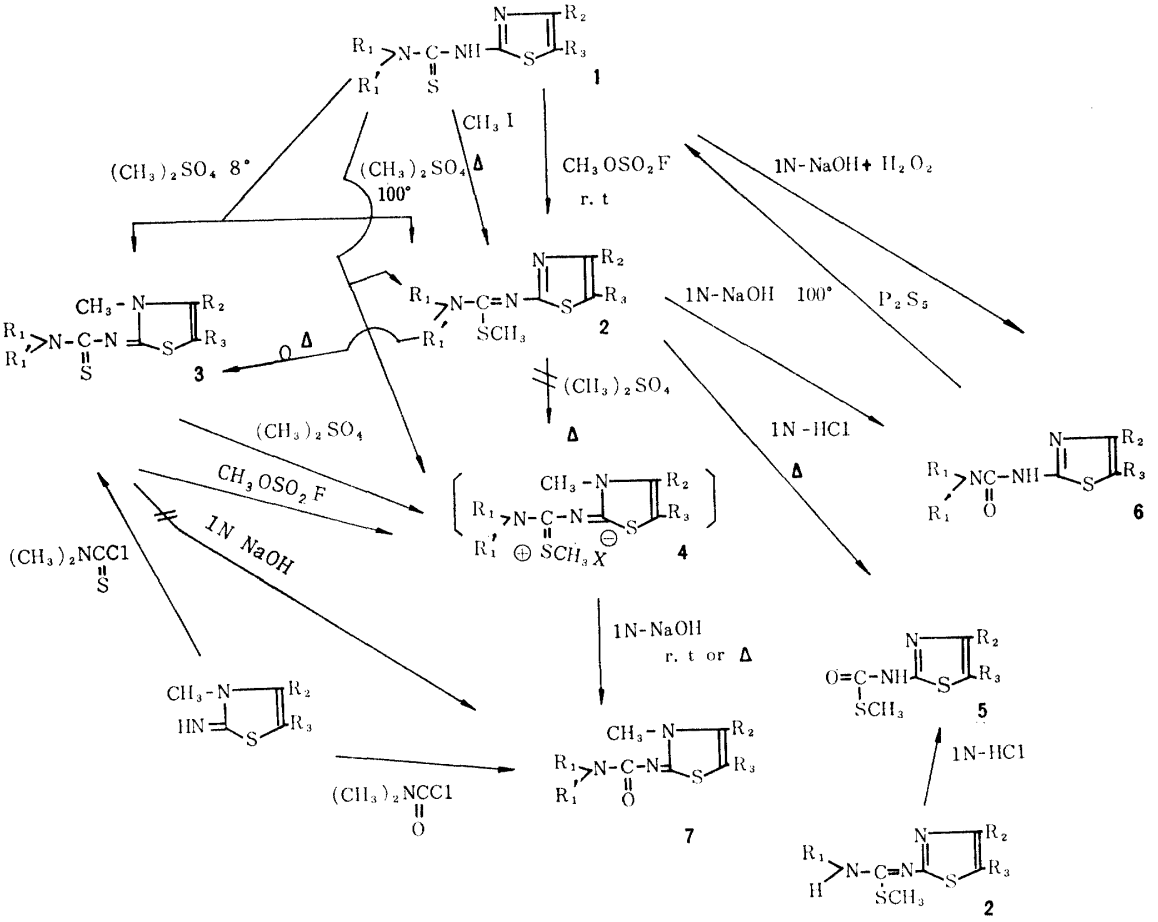
1) Y. Yamamoto and R. Yoda, S-methylation were presented at the 98 Annual Meeting of the Yakugakukai April 4 (1978) (preprints 283p, 1978)

2) Y. Yamamoto, K. Horiuchi, R. Yoda, K. Kubo, and Y. Murakami, Kyoritsu Yakka Daigaku Kenkyu Nempo (abbriviated hereafter: Kyoyaku nempo) **18**, 64 (1973), CA **80**, 140793n (1974). Y. Yagi, K. Horiuchi, R. Yoda, Y. Yamamoto, and Y. Murakami, Nippon Kagaku Kaishi, 831 (1975), CA **83**, 125678x (1975).



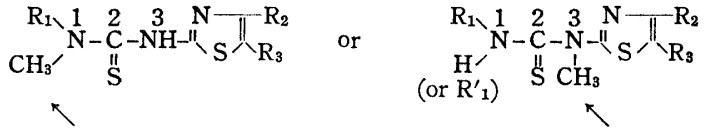
Scheme 1

(mp 42—102°) which had a widely distributed melting point. On the TLC (solvent: ether) of raw products with 42—102°, two spots appeared showing *Rf*-values 0.75 and 0.29 and these data suggested the mixture of two derivatives. For the purpose of characterization, the crude products were separated by an ethanol-soluble product having *Rf* value of 0.75 and the other one as ethanol-insoluble product having *Rf*-value of 0.29. Based on spectroscopic data the former was identified N-methyl-N′-(2-thiazolyl)-S-methylisothiourea, **2a**, (S-methyl derivatives) and the latter, N-methyl-N′-(3-methyl-4-thiazolyl-2-ylidene)thiourea, **3a**, (ring N-methyl derivatives). Thermal reaction of **1a** with an equivalent of $(CH_3)_2SO_4$ in the absence of solvents gave S-methyl derivative **2a** and N-methyl-N′-(3-methyl-4-thiazolin-2-ylidene)-S-methylisothiourea(ring N,S-dimethyl derivative) **4a**. Methyl group was introduced to both sulfur of thiocarbonyl group and nitrogen at the 3 position of thiazole ring. Only trace amounts of ring N-methyl derivative **3a** was observed on TLC. Mono-methyl substituents, S-methyl or ring N-methyl derivatives, were furthermore reacted with various kinds of methyl agents to afford ring N,S-dimethyl derivatives. Compounds **4** were given high yields.



Scheme 2

On the other hand we expected methylation of 1-nitrogen and 3-nitrogen of thioureido group, isomeric to each other, as shown below (marked→). However these methylated

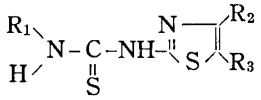
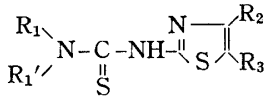
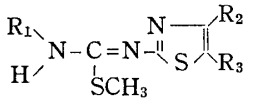
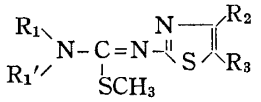
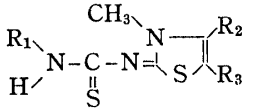
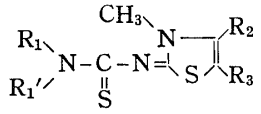
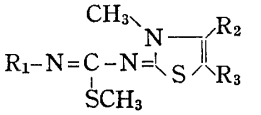
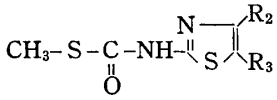


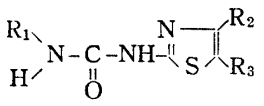
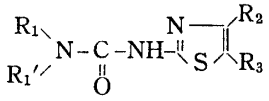
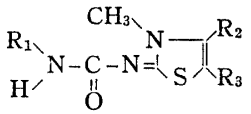
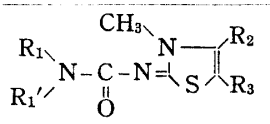
products were not obtained, these compounds had already reported *via* another route.[3,6] Next, an equimolar mixture of compound **1** and CH_3OSO_2F (or a small excess of CH_3OSO_2F) was stirred at room temperature for several days and resulting precipitate was collected. After neutralization of 1N–NaOH solution, white crystals of S-methyl derivatives were afforded.

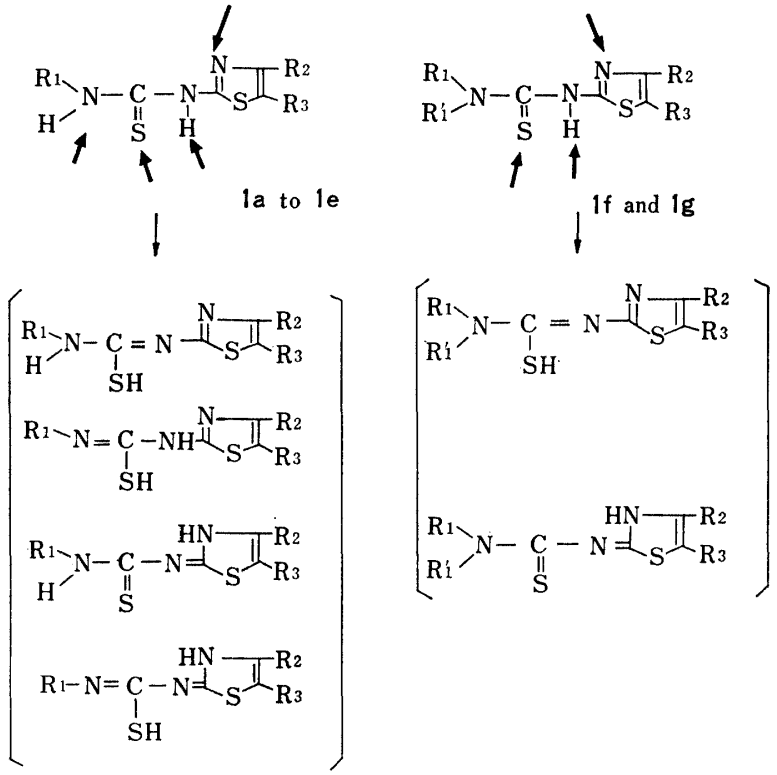
In order to confirm structures of S-methyl derivatives, **2** were hydrolyzed with 1N–NaOH solution at *ca.* 100° and was given white crystals which showed at 1680 cm^{-1} for a strong

3) Y. Yamamoto, H. Nakamura, R. Yoda, M. Inoue, and S. Kato, Kyoyaku nempo, **12**, 116 (1967), CA **69**, 96554g (1968). R. Yoda and Y. Yamamoto, ibid. **18**, 37 (1973), CA **81**, 77824b (1974). Y. Yamamoto, R. Yoda, and K. Sekine, Chem. Letters, 1299 (1977).

Table I Substituents of thioureidothiazole derivatives.

structures	compd. No.	substituents	ref.	UV $\lambda_{max}^{2\text{-PrOH}}$ nm ($\varepsilon \times 10^{-3}$)
	**1a**	$R_1=CH_3$, $R_2=R_3=H$	3)	254.5(10.4) 289 (20.4)
	1b	$R_1=R_2=CH_3$, $R_3=H$	3)	255 (8.9) 292.5(19.7)
	1c	$R_1=C_2H_5$, $R_2=CH_3$, $R_3=H$	mp 242 (dioxane)	258 (9.9) 294 (19.6)
	1d	$R_1=(CH_3)_2H$, $R_2=CH_3$, $R_3=H$	mp 171.5 (EtOH)	259 (9.9) 294.5(18.5)
	1e	$R_1=R_2=R_3=CH_3$	mp 207 (EtOH)	256 (8.2) 298 (18.0)
	**1f**	$R_1=R_1'=R_2=CH_3$, $R_3=H$	3)	293 (7.9) 329 (15.4)
	1g	$R_1=R_1'=R_2=R_3=CH_3$	3)	289 (8.1) 332 (15.7)
	**2a**	$R_1=CH_3$, $R_2=R_3=H$		
	2b	$R_1=R_2=CH_3$, $R_3=H$		
	2c	$R_1=C_2H_5$, $R_2=CH_3$, $R_3=H$		
	2d	$R_1=(CH_3)_2CH$, $R_2=CH_3$, $R_3=H$		
	2e	$R_1=R_2=R_3=CH_3$		
	**2f**	$R_1=R_1'=R_2=CH_3$, $R_3=H$		
	2g	$R_1=R_1'=R_2=R_3=CH_3$		
	**3a**	$R_1=CH_3$, $R_2=R_3=H$		
	3b	$R_1=C_2H_5$, $R_2=R_3=H$		
	3c	$R_1=(CH_3)_2CH$, $R_2=R_3=H$		
	3d	$R_1=R_2=CH_3$, $R_3=H$	4)	
	3e	$R_1=C_2H_5$, $R_2=CH_3$, $R_3=H$	4)	
	3f	$R_1=(CH_3)_2CH$, $R_2=CH_3$, $R_3=H$	4)	
	3g	$R_1=R_2=R_3=CH_3$		
	**3h**	$R_1=R_1'=R_2=CH_3$, $R_3=H$		
	3i	$R_1=R_1'=R_2=R_3=CH_3$		
	**4a**	$R_1=CH_3$, $R_2=R_3=H$		
	4b	$R_1=R_2=CH_3$, $R_3=H$		
	4c	$R_1=C_2H_5$, $R_2=CH_3$, $R_3=H$		
	4d	$R_1=(CH_3)_2CH$, $R_2=CH_3$, $R_3=H$		
	4e	$R_1=R_2=R_3=CH_3$		
	**5a**	$R_2=R_3=H$		
	5b	$R_2=CH_3$, $R_3=H$		
	5c	$R_2=R_3=CH_3$		

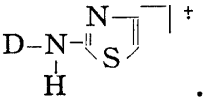
	**6a**	$R_1=CH_3$, $R_2=R_3=H$	5)	260 (19.1)
	6b	$R_1=R_2=CH_3$, $R_3=H$	5)	262.5(8.5)
	6c	$R_1=(CH_3)_2CH$, $R_2=CH_3$, $R_3=H$		
	6d	$R_1=R_2=R_3=CH_3$	5)	271.5(10.3)
	**6e**	$R_1=R_1'=R_2=CH_3$, $R_3=H$		
	**7a**	$R_1=CH_3$, $R_2=R_3=H$		
	7b	$R_1=R_2=CH_3$, $R_3=H$	4)	
	7c	$R_1=C_2H_5$, $R_2=CH_3$, $R_3=H$	4)	
	7d	$R_1=(CH_3)_2CH$, $R_2=CH_3$, $R_3=H$		
	**7e**	$R_1=R_1'=R_2=CH_3$, $R_3=H$		



Scheme 3 Methylation position and prototropy of thioureido derivatives.

amide vibration in IR spectra. These hydrolyzed products were identical with the known N-Alkyl-N′-(2-thiazolyl)ureido derivatives, **6**.[5] Thiourea derivatives **1** was oxidized with H_2O_2 in 1N–NaOH solution to give also compounds **6**. Then, in order to confirm structures of ring N,S-dimethyl derivatives, **4** were also hydrolyzed by the same treatment as just above mentioned. These hydrolyzed products were identical with the known N-Alkyl-N′-(3-methylthiazol-2-ylidene)ureido derivatives **7**.[4] In connection with elimination of SCH_3 group T.A. Briody *et al.* reported recently that elimination-addition mechanism was due to the base catalyzed conversion of S-Alkylisothioureas to ureas.[7]

On heating of S-methyl derivative **2a** with 1N–HCl solution at around 100°, a HCl-salt was afforded which was neutralized to yield a free base as white crystals with mp 170—174°. It showed a molecular ion peak at *m/e* 174 (Relative intensity: 40%) and a fragment peak at *m/e* 126 (49%) which was corresponding to $[M^+–CH_3SH]$ and at *m/e* 100 (63%) corresponding to 2-aminothiazole cation. In the 100 MHz NMR spectrum ($CDCl_3$) it showed signals at δ 2.48 (s, 3H, CH_3), δ 7.58 and δ 6.89 (m, 1H, CH, 4 and 5 position of thiazole ring, respectively) and δ 13.16 (broad, 1H, NH, disappeared after D_2O exchange). Compound with mp 170—174° was indentified as 2-(methylthiocarbonyl)-aminothiazole **5a** by above mentioned data and elemental analysis. Compound **5a** in the mixture of DMSO-d_6 and D_2O was heated at 100° for deuteration. The deutrated compound **5a** showed a molecular ion peak at *m/e* 175 and then a base peak at *m/e* 101

probably for  .

Methylation of N,N-dimethyl thioureido derivatives, **1f** and **1g**, was also examined by the same manners as shown in Scheme 2. However ring N,S-dimethyl derivatives **4** were not isolated as intermediates. After stirring the mixture of **3h** and methyl agents at room temperature, red oily material obtained was neutralized with 1N–NaOH solution and **7e** with mp 154° was obtained. Compound **7e** was synthesized independently by the reaction of 2-imino-4-methyl-4-thiazoline with N,N-dimethylcarbamoyl chloride. IR and NMR data of this compound agreed with those of **7e** with mp 154°. These data may be explained that, on the first stage ring N,S-dimethyl derivative of **3h** was obtained as HSO_3F salt and then, S-methyl group of this salt was hydrolyzed with 1N–NaOH solution. On the other hand in similar conditions, the reaction of **3h** in 1N–NaOH solution did not give the expected product for **7e**, the compound **3h** being recovered essentially unreacted. Compound **2a** was irradiated at 150° for 17 hr by ultraviolet ray 253 nm, but did not changed.

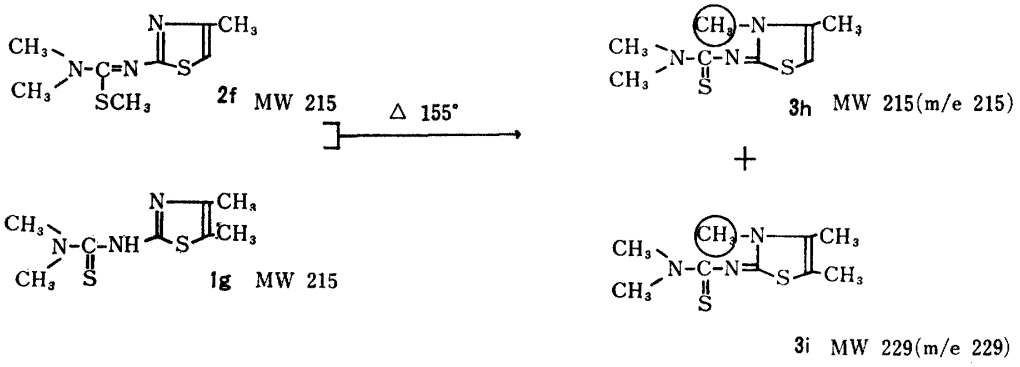
4) Y. Yamamoto, R. Yoda, S. Koda, M. Matsumura, K. Sekine, and Y. Yoshida, Kyoyaku nempo, **20**, 57 (1975), ibid. **21**, 145 (1976).

5) Y. Yamamoto, H. Nakamura, R. Yoda, N. Kaneko, and R. Usuba, Kyoyaku nempo, **11** 42 (1966), CA**68**, 105071f (1968).

6) Y. Yamamoto, R. Yoda, and C. Tamura, Chem. Letters, 1147 (1975).

7) T.A. Briody, A.F. Hegarty and F.L. Scott, Tetrahedron, 33, 1469 (1977).

However **2a** was heated at 150° for 140 hr in pyridine to afford only trace amount of ring N,S-dimethyl derivative which was observed on TLC. Its formation of this dimethyl derivative may be explained that after being eliminated of methyl group of S-methyl derivatives, this eliminated methyl group was transferred to nitrogen at the 3-position of a thiazole ring of S-methyl derivative and the resulting N,S-dimethyl derivative was obtained. In the case of N,N-dimethylthioureidothiazole **1f**, after methylation with CH_3OSO_2F by the same manner a raw product was neutralized saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The solvent was removed under reduced pressure and the residual oily material was distilled *in vacuo* (**2f**, bp 154°/0.35 mmHg). S-methyl derivative **2f** was heated at 155° without the addition of solvent and a raw product was purified by silica-gel chromatography using acetone-$CHCl_3$ (1 : 2). Treatment with decolorizing carbon, yellow needles with mp 204° were afforded. After treatment as described above, **2g** gave also pale-yellow crystals having mp 224° (EtOH). These compounds were synthesized independently by the reaction of 2-imino-3,4-dimethyl(or 3,4,5-trimethyl)thiazole with N,N-dimethylthiocarbamoylchloride or **4** with $(CH_3)_2SO_4$. IR, UV, NMR and mixed mp determination of these compounds agreed with those of the compounds having mp 204° and 224°, respectively. Therefore the structure of compound having of mp 204° was identified as N,N-dimethyl-N′-(3,4-dimethyl-4-thiazolin-2-ylidene)thiourea **3h** and mp 224°, N,N-dimethyl-N′-(3,4,5-trimethyl-4-thiazolin-2-ylidene)thiourea **3i**. We found these were isomeric products which were formed by easy rearrangement of methyl group of isothiourea **2f** or **2g**. In order to clarify whether this transfer mechanism of methyl group was caused either intramolecular rearrangement or intermolecular one, cross reaction was carried out as shown in Scheme 4. Cross reaction products of yellow needles in the Mass spectrum showed a molecular ion peak at *m/e* 229 which was *m/e* 14 more than that of starting materials having *m/e* 215 as shown in Fig. 2. However it was difficult to isolate each of cross products as usual manners.



Scheme 4 Cross reaction of **2f** and **1g**.

UV absorption curves

Compairing with starting materials (thioureido derivatives) S-methyl derivatives indi-

cated blue shifts of about 20—30 nm in the first absorption maximum and red shifts of about 15 nm in the second absorption maxmum were observed as shown in Table I, II, and Fig. 1. On the other hand ring N-methyl derivatives showed red shifts of *Ca.* 30 nm both in the first and second absorption maxmum, but the ring N,S-dimethyl derivatives indicated that blue shifts of 10 nm in the first absorption maxmum and red shifts of 16—20 nm in the second absorption maxmum. In the case of S-methyl derivatives of N,N-dimethylthioureido it indicated larger red shifts of 40—67 nm in the first absorption maxmum and no change or red shifts of 10 nm in the second absorption maxmum.

Mass

Thioureido derivatives **1** (starting materials) showed those own characteristic fragment peaks of [M^+–RNH], [M^+–RN] and [M^+–SH]. S-methyl derivatives showed a stable base peak corresponding to [M^+–CH_3S] and no fragment peaks of [M^+–RNH] and [M^+–RN] as mentioned above. N,N-dimethylthioureido derivatives, **2f** and **2g** exhibited a molecular ion at *m/e* 215 (base), 229 (86%), respectively, and had at *m/e* 168 (98%), 182 (base) for [M^+–CH_3S], respectively. Ring N-methyl derivatives **3h** and **3i** had a base peak at *m/e* 171, 185 for [M^+–$(CH_3)_2N$], at *m/e* 182 (31%), 196 (6%) for [M^+–SH] and both had a peak at *m/e* 88 for $(CH_3)_2N^+CS$ which was a characteristic one for N,N-dimethylthioureido derivatives.

Table II-A Physical properties of compounds **2**.

Comp. No.	mp (recryst. solvent)	Formula (MW)	Anal. Calcd. (found) C	H	N	UV 2-PrOH max nm(ε×10⁻³)
2a	48～9 (EtOH)	$C_6H_9N_3S_2$ 187.287	38.48 (38.65	4.84 4.67	22.44 22.14)	226.0(6.0) 305.5(18.0)
2b	69～70 (EtOH+H_2O)	$C_7H_{11}N_3S_2$ 201.314	41.76 (41.59	5.51 5.45	20.87 20.62)	231.5(6.9) 309.5(17.1)
2c	158～9 * (EtOH+H_2O)	$C_8H_{13}N_3S_2$ 215.341	37.83 (37.89	3.63 3.57	18.91 * 18.88)	230sh(6.8) 308 (17.6)
2d	40 (EtOH+H_2O)	$C_9H_{15}N_3S_2$ 229.368	47.13 (48.25	6.59 6.92	18.32 16.92)	236.0(6.3) 311.0(17.7)
2e	52 (EtOH)	$C_8H_{13}N_3S_2$ 215.341	44.62 (44.65	6.09 6.15	19.51 19.41)	215sh(7.1) 310.0(19.2)
2f	126 * (EtOH+H_2O)	$C_8H_{13}N_3S_2$ 215.341	37.83 (37.61	3.63 3.50	18.91 * 18.20)	245.0(8.1) 316.5(7.2)
2g	103～4 * (EtOH+H_2O)	$C_9H_{15}N_3S_2$ 229.368				246.0(7.6) 330.0(7.1)

* Picrate, sh (shoulder)

Table II-B Physical properties of compounds **3**.

Comp. No.	mp (recryst. solvent)	Formula (MW)	Anal. Calcd. (found) C	H	N	UV 2-PrOH max nm(ε × 10^{-3})
3a	154~6 (EtOH)	$C_6H_9N_3S_2$ 187.287	38.48 (38.52	4.84 4.69	22.44 22.41)	287.0(8.0) 323.5(16.0)
3b	112~4 (EtOH)	$C_7H_{11}N_3S_2$ 201.314	41.76 (41.74	5.51 5.53	20.87 20.84)	291.0(8.7) 323.0(16.2)
3c	137~8 (EtOH)	$C_8H_{13}N_3S_2$ 215.341	44.62 (44.71	6.09 6.26	19.51 19.58)	290.5(10.2) 324.0(17.5)
3d	215 (EtOH)	$C_7H_{11}N_3S_2$ 201.314	41.76 (42.24	5.51 5.30	20.87 20.93)	290.0(6.8) 326.0(15.4)
3e	213 (EtOH)	$C_8H_{13}N_3S_2$ 215.341	44.62 (44.81	6.09 5.95	19.51 19.63)	291 (10.0) 327 (18.5)
3f	181 (EtOH)	$C_9H_{15}N_3S_2$ 229.368	47.13 (47.08	6.59 6.51	18.32 18.53)	290.0(9.3) 327.5(18.5)
3g	232 ($CHCl_3$)	$C_8H_{11}N_3S_2$ 215.341	44.62 (44.61	6.09 6.11	19.51 19.58)	284.0(5.0) 331.0(16.6)
3h	204~6 (EtOH)	$C_8H_{11}N_3S_2$ 215.341	44.62 (44.62	6.09 6.07	19.51 19.23)	295sh(9.5) 327 (17.7)
3i	224~6 (EtOH)	$C_9H_{15}N_3S_2$ 229.368	47.13 (47.36	6.59 6.83)		291.5(8.5) 332.5(17.4)

NMR (in $CDCl_3$ solvent)

S-methyl derivatives **2a, b, e** exhibited SCH_3 signal at about δ 2.43—2.47 which were a sharp singlet. On the other hand N,S-dimethyl derivatives **4a-c** exhibited SCH_3 signal at δ 2.49—2.53 which were observed at some lower field than that of S-methyl derivatives and a signal due to $N\text{-}CH_3$ at the 3-position of thiazole ring was observed a sharp singlet at δ 3.43—3.57.

Further investigation on mechanism is now in progress.

We are grateful to Miss Tomoko Takahashi for Mass, and Miss Midori Yamazaki and Michiko Yoshida for their assistance in experimental works. We also wish to acknowledge the staff of Department of Physical Chemistry for elemental analysis and the staff of Department of Pharmacology for screening tests, the Central Research Laboratories, Sankyo CO., Ltd..

Table Ⅱ-C Physical properties of compounds **4** and **5**.

Comp. No.	mp (recryst. solvent)	Formula (MW)	Anal. Calcd. (found) C	H	N	S	UV 2-PrOH max nm($\varepsilon \times 10^{-3}$)
4a	87～9 (EtOH+H_2O)	$C_7H_{11}N_3S_2$ 201.314	41.76 (41.57	5.51 5.30	20.90 20.89)		246.0(6.5) 307.0(14.0)
4b	122 (EtOH+H_2O)	$C_8H_{13}N_3S_2$ 215.341	44.62 (44.55	6.09 6.76	19.51 19.38)		244.0(5.4) 313.0(12.1)
4c	105～6 (EtOH+H_2O)	$C_9H_{15}N_3S_2$ 229.368	47.13 (47.11	6.59 6.59	18.32 18.28)		244.0(5.6) 312.0(13.5)
4d	115 (EtOH+H_2O)	$C_{10}H_{17}N_3S_2$ 243.395	49.35 (49.39	7.04 6.99	17.26 17.55)		243.0(5.2) 359 (13.5)
4e	201 ($CHCl_3$)	$C_9H_{15}N_3S_2$ 229.368	47.13 (47.05	6.59 6.84	18.32 18.26)		240.0(5.4) 316.0(12.7)
5a	170～4 (EtOH)	$C_5H_6N_2OS_2$ 174.244	34.47 (34.48	3.47 3.45	16.08 15.94	36.80 35.75)	270.5(15.9) 310sh(1.0)
5b	166～7 (EtOH+H_2O)	$C_6H_8N_2OS_2$ 188.271	38.28 (38.10	4.28 4.80	14.88 14.75	34.06 33.89)	276 (11.3) 320sh(1.0)
5c	163 (*n*-hexane)	$C_7H_{10}N_2OS_2$ 202.298	41.56 (41.70	4.98 5.20)	13.85		283.0(11.4) 320sh(2.5)

Table Ⅱ-D Physical properties of compounds **6e** and **7**.

Comp. No.	mp (recryst. solvent)	Formula (MW)	Anal. Calcd. (found) C	H	N	UV 2-PrOH max nm($\varepsilon \times 10^{-3}$)
6e	103 (cyclohexane)	$C_7H_{11}N_3OS$ 185.249	45.39 (45.89	5.99 6.12)	22.68	265.0(8.5) 297.0(3.7)
7a	92～3 (toluene)	$C_6H_9N_3OS$ 171.22	42.09 (42.15	5.30 5.19	24.54 24.26)	241.0(3.0) 289.0(11.9)
7b	189～90 (H_2O)	$C_7H_{11}N_3OS$ 185.249	45.39 (45.23	5.99 5.94	22.68 22.21)	237.0(3.4) 293.0(16.4)
7c	121 (H_2O)	$C_8H_{11}N_3OS$ 199.276	48.22 (48.14	6.58 6.49	21.09 20.92)	239.0(3.4) 292.0(17.3)
7d	95 (H_2O)	$C_9H_{15}N_3OS$ 213.303	50.68 (49.42	7.09 7.08	19.70 16.50)	240.5(2.4) 292.5(11.8)
7e	154 (*n*-hexane)	$C_8H_{13}N_3OS$ 199.276	48.22 (48.26	6.58 6.59	21.09 20.93)	226.5(4.6) 295.0(18.0)

Table Ⅲ-A Mass spectra data of compounds **2** and **3**. *m/e*(Relative Intensity : %)

2a	187(22, M^+), 140(base, M^+-SCH_3), 125(5), 113(28), 100(3), 99(6), 86(6), 74(14)
2b	201(76, M^+), 154(base, M^+-SCH_3), 127(49), 114(5), 113(8), 99(12), 88(15), 74(27)
2c	215(66, M^+), 168(base, M^+-SCH_3), 140(base), 113(21), 74(19), 72(21), 71(23)
2e	215(32, M^+), 168(base, M^+-SCH_3), 141(13), 127(4), 100(4), 86(7), 85(7), 74(5)
2f	215(base, M^+), 168(98, M^+-SCH_3), 153(64), 145(23), 88(23), 83(33), 73(11), 72(22), 71(18)
2g	229(86, M^+), 182(base, M^+-SCH_3), 167(43), 159(20), 149(8), 128(2), 127(3), 126(6), 86(17), 83(21)
3g	215(92, M^+), 185(base, M^+-CH_3NH), 182(77, M^+-SH), 153(38), 141(29), 127(33), 114(12), 99(11), 85(27)
3h	215(90, M^+), 182(M^+-SH), 171(base, $M^+-(CH_3)_2N$), 139(26), 113(19), 88(27), 73(20), 72(15), 71(9)
3i	229(62, M^+), 196(9, M^+-SH), 185(base, $M^+-(CH_3)_2N$), 153(19), 128(2), 127(11), 88(16), 86(6)

Table Ⅲ-B Mass spectra data of compounds **4, 5, 6e** and **7e**.

4a	201(7, M^+), 154(base, M^+-SCH_3), 139(7), 99(8), 86(5), 73(7), 72(5)
4b	215(33, M^+), 170(23), 169(35), 168(base, M^+-SCH_3), 153(30), 113(12), 88(27), 82(14), 73(24), 72(28)
4c	229(12, M^+), 182(base, M^+-SCH_3), 154(71), 139(9), 113(6), 82(7), 74(11), 73(8)
4d	243(11, M^+), 196(48, M^+-SCH_3), 154(base), 140(5), 74(8), 73(7)
4e	229(70, M^+), 182(base, M^+-SCH_3), 167(57), 155(3), 152(7), 141(16), 127(24), 88(50), 86(36), 85(56)
5a	174(30, M^+), 146(20), 126(49, M^+-CH_3SH), 100(63), 99(11), 86(5), 75(base, CH_3SCO^+), 58(86)
5b	188(base, M^+), 173(17, M^+-CH_3), 160(38), 141(18), 140(50), 127(4), 114(91), 88(18), 86(12), 75(89, CH_3SCO^+)
5c	202(base, M^+), 174(15), 154(40, M^+-CH_3SH), 128(54), 100(6), 86(17), 85(44), 75(38, CH_3SCO^+), 72(2), 71(16)
6e	185(42, M^+), 141(26, $M^+-(CH_3)_2N$), 114(4), 72(base, ), 71(4)
7e	199(22), 156(8), 155(base, $M^+-(CH_3)_2N$), 72(13)

Table Ⅳ-A NMR spectra data by JNM-NH 100(100 Hz).

Compd. No. (solvent)	$S\underline{CH_3}$	$\underline{CH_3}\!\!\diagdown\!\!N\!\!\diagup\!\!H$	$\underline{CH_3}CH_2\!\!\diagdown\!\!N\!\!\diagup\!\!H$	$CH_3\underline{CH_2}\!\!\diagdown\!\!N\!\!\diagup\!\!H$	$\underline{CH_3}\!\!\diagdown\!\!N\!\!\diagup\!\!\underline{CH_3}$	$\underline{CH_3}\!\!\diagdown\!\!N-$	$N\!\!-\!\!\underline{H}$	$N\!\!-\!\!\underline{CH_3}$	$N\!\!-\!\!\underline{CH_3}$	$\underline{CH_3}$	NH
2a	2.47	3.00					7.21, 6.67				9.87
($CDCl_3$)	(s, 3H)	(d, J=5.0, 3H)					(d, 1H), (d, 1H)				(b, 1H)
2b	2.45	3.03						2.26	6.27		10.16
($CDCl_3$)	(s, 3H)	(d, J=5.0, 3H)						(b, J=1.0, 3H)	(1H)		(b, 1H)
2c	2.45		1.27	3.24～3.45				2.26	6.24		10.26
($CDCl_3$)	(s, 3H)		(t, J=7.0, 3H)	(m, 2H)				(d, J=1.0, 3H)	(d, J=1.0, 1H)		(b, 1H)
2e	2.43	2.99								2.14, 2.20	10.07
($CDCl_3$)	(s, 3H)	(d, J=5.0, 3H)								(s, 3H), (s, 3H)	(b, 1H)
2f	2.16				3.14			2.26	6.28		
($CDCl_3$)	(s, 3H)				(s, 6H)			(d, J=1.0, 3H)	(d, J=1.0, 1H)		
2g	2.18				3.18					2.24～2.54	
($CDCl_3$)	(*)				(s, 6H)					(m*, 9H)	
3h					3.28～3.48 (6H)	3.55 (s, 3H)		2.26 (d, J=1.0, 3H)	6.08 (1H)		
($CDCl_3$)											
3i					3.22～3.46 (b, 6H)	3.52 (s, 3H)				2.13 (s, 6H)	
($CDCl_3$)											
6e					2.95			2.20	6.31		8.70～9.10
($CDCl_3$)					(s, 6H)			(d, J=1.0, 3H)	(d, J=1.0, 1H)		(b, 1H)
7e					3.08	3.49		2.19	5.98		
($CDCl_3$)					(s, 6H)	(s, 3H)		(d, J=1.0, 3H)	(d, J=1.0, 1H)		

Table IV-B NMR spectra data.

Compd. No. (solvent)	$S\underline{CH_3}$	$\underline{CH_3}\diagdown N=$	$\underline{CH_3}CH_2-N=$	$CH_3\underline{CH_2}-N=$	$\underline{CH_3}\diagdown N-\diagup$	$N-\underline{C}(\underline{H})=\underline{C}(\underline{H})$	$N-\underline{C}(\underline{CH_3})=\underline{C}(H)$	$N-\underline{C}(\underline{CH_3})=\underline{C}(\underline{H})$	$\underline{C}(\underline{CH_3})=\underline{C}(\underline{CH_3})$	$\underline{NH}$
4a	2.53	3.08			3.57	6.35, 6.80				
($CDCl_3$)	(s, 3H)	(s, 3H)			(s, 3H)	(d, J=4.5, 1H) (〃)				
〃	2.48	3.10			3.56	6.43, 7.11				
(DMSO-d_6)	(s, 3H)	(s, 3H)			(s, 3H)	(d, J=4.5, 1H) (〃)				
4b	2.50	3.18			3.47		2.18	5.85		
($CDCl_3$)	(s, 3H)	(s, 3H)			(s, 3H)		(d, J=1.0, 3H)	(1H)		
〃	2.44	3.04			3.44		2.18	6.12		
(DMSO-d_6)	(solvent overlap)	(s, 3H)			(s, 3H)		(d, J=1.0, 3H)	(1H)		
4c	2.49		1.28	*	*3.30～3.47		2.19	5.87		
($CDCl_3$)	(s, 3H)		(t, J=7.0, 3H)		(m, 5H)		(d, J=1.0, 3H)	(1H)		
〃	2.45		1.21		3.48		2.21	6.14		
(DMSO-d_6)	(solvent overlap)		(t, J=7.0, 3H)		(s, 3H)		(d, J=1.0, 3H)	(1H)		
4e (DMSO-d_6 + $CDCl_3$)	2.41	3.03			3.43				2.07	
	(s, 3H)	(s, 3H)			(s, 3H)				(6H)	
5a	2.48					6.89, 7.58				13.16
($CDCl_3$)	(s, 3H)					(m, 1H) (〃)				(b, 1H)
5b	2.40						6.40	2.38		13.5
($CDCl_3$)	(3H)						(1H)	(3H)		(b, 1H)
5c	2.44								2.28	
($CDCl_3$)	(3H)								(6H)	

Table V-A IR spectra of compounds **2.** (KBr disk, cm^{-1})

com-pounds	−3000	3000 −1800	1800 −1600	−1500	−1400	−1300	−1200	−1000	−800	−600	−400
2a	3100w	2925w		1580vs 1575vs 1562vs 1545sh	1485m 1440 s 1428 s	1370m 1320m	1205m	1160w 1130m 1070m 1040w	870m	710m	595sh 525sh
2b	3180m 3100m	2910m		1580vs 1570vs 1540sh 1525m 1510sh	1430vs	1380vs 1320m 1300m	1280m 1205 s	1150m 1125 s 1058m 1050m 1000w	980w 860m 853m 810w	740m 730m 710 s 635m	520w
2d				1580br 1545vs 1530 s 1510 s	1470 s 1445vs 1420 s	1390m 1370m 1350m 1335m 1328sh 1308 s	1275m 1200m	1170m 1155m 1130vs 1060sh	990m 970m 950sh 930sh 900w 880w 860m 805w	730w 720w 700 s 675sh 640m 615w	560w 550w 470w
2e		2910m 2850m		1573vs 1559vs 1539sh 1520sh 1505w	1495w 1489w 1462m 1438 s 1424 s	1381m 1372 s 1369sh 1338m 1313m	1290m 1268m 1203m	1173m 1139m	1092w 1048m 969w 893w 808w	737w 711m 681m 638w 621w 609w	528w 514w

abbreviation : vs (very strong), s (strong), m (medium), w (weak), sh (shoulder), br (broad).

Table V-B IR spectra of compounds 4. (KBr disk, cm^{-1})

com-pounds	−3000	−1800	−1600	−1500	−1400	−1300	−1200	−1000	−800	−600	−400
4a	3095m 3060m	2900m 2830m 2315m		1570sh 1560 s 1515vs 1505vs	1410m	1390 s 1365m 1350m	1265w 1240m 1215m	1100m 1045m 1025m	955m 853w 823w	770m 725w 685m 650w 630m 610m	530w 502w
4b	3100w	2910w 2830w	1650w	1570 s 1560 s 1540sh 1505vs	1475sh 1435m 1410 s	1380vs 1360m 1340m 1315m	1290w 1265w 1245w 1220 s	1170w 1110w 1070m 1040w 1020m 1005sh	970w 890m 830w 810sh	753w 720w 705m 690w 650w	553w 535w 450w
4c	3105w	2970w 2915w 2858w 2815w	1600w	1553 s 1528vs	1430m 1414m	1385w 1372w 1351m 1335m	1283w 1265w 1239w 1210m	1176w 1100w 1069w 1036m	936m 880w 828w	746w 720w 709w 690w 642w	550w 533w 447w
4d	3095w	2960m 2923w 2845w	1600w	1568vs 1520vs	1468w 1451w 1434w 1420m	1391w 1378w 1365m 1349m 1332m	1291w 1245w 1218m	1180w 1158w 1142m 1119w 1060w 1008w	974m 900m 858w 830w	740w 721w 692w 649w	565w 553w 538w 478w
4e		2980w 2950w 2915m 2840m 2320m	1634w	1563vs 1503vs	1472sh 1463sh 1455m 1435m 1414vs	1381vs 1358vs 1312sh	1290m 1262w 1242vs	1196w 1111m 1062 s 1020m	958w 879 s	767m 678w 648w 618w	558w 551w 523w 517w 460w

Table V-C IR spectra of compounds **3**, **5**, **6e** and **7e**. (KBr disk, cm^{-1})

compounds	−3000	−1800	−1600	−1500	−1400	−1300	−1200	−1000	−800	−600	−400
3g	3230vs 3010m	2925m 2900m 2825w	1630w	1562w 1543sh 1525vs 1512vs 1502vs	1466 s 1450 s 1410 s	1388vs 1375 s 1350 s 1328m	1298sh 1283m 1235vs 1215m 1203sh	1138m 1052w 1025w	956w 884m	706w 650w	562w 531w 468w
3h	3070m	2590m		1596m 1524vs	1418m	1378vs 1358vs 1300m	1287vs 1217m	1132m 1115m 1110m 1050m	920m 879m 823w	735w 649w 632w	594w 540w 512w 454w
3i		2900m	1632w	1548sh 1528sh 1510vs 1505vs	1498vs 1478vs 1458sh 1412m	1370vs 1347vs 1310 s	1290 s 1237m	1128m 1105m 1095m 1045w	989w 920m 871m 842w	765w 635w	558w
5a	3160m	2925m 2850m 2700m 2325m	1675vs 1654m	1585 s 1560m 1540m	1490w 1440m 1420w	1375w 1320m	1282vs 1230w	1165vs 1075w 1060m	970w 895m 870w 815w	770m 718w 710w 700m 690w 655m 615m	520w
5b	3400m 3100 s	2999m 2895 s	1664 s	1530vs	1431m	1376m 1306vs	1258vs 1150vs	1006m	974m 885 s 850m	740m 727m 663m 633m	
5c	3110m 3000m	2905m	1665 s	1565m 1545vs 1528vs 1509sh	1435m	1300m	1273 s 1255 s 1225m	1172sh 1150vs	980br 895m 870m	690w 655w 605w	
6e	3140br	2905br	1689vs 1665vs 1650vs 1644vs	1562vs 1547vs 1530vs 1500vs	1485sh 1439vs 1405 s	1360vs 1307vs	1290vs 1265vs	1171vs 1145 s 1138 s 1065m 1040m	970m 885 s 842m	770m 740m 718 s 705sh 685m 620m	
7e	3070m	2900m	1665w 1640w	1590vs 1545m 1530 s	1483 s 1458m 1430m 1415 s	1390vs 1370vs	1275m 1265m 1208 s	1190 s 1050m 1025m	905m 830w 815w	770m 710w 635w	540w 465w

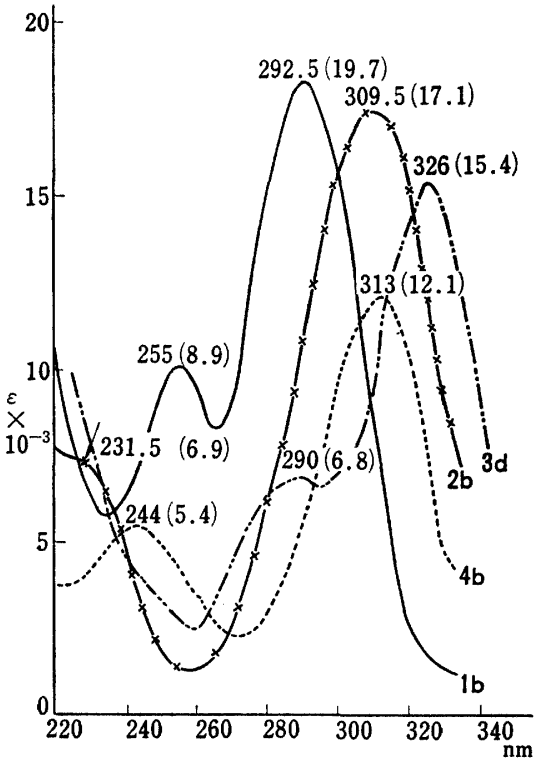


Fig. 1 UV Absorption Spectra of **1b**, **2b**, **3d**, and **4b** in 2-PrOH.

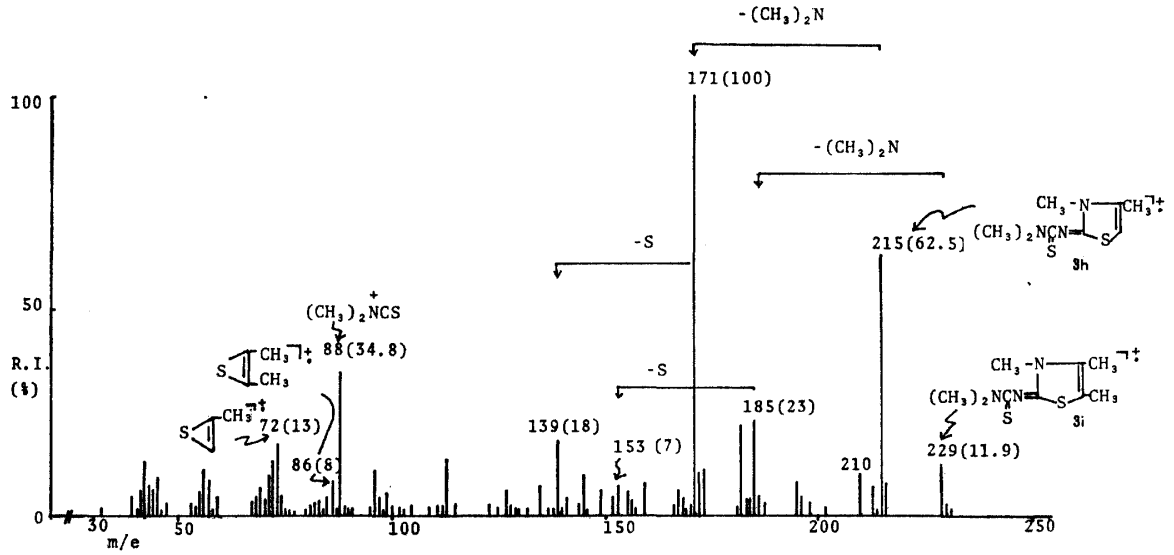


Fig. 2 Mass spectra of cross products **3h** and **3i**.

Experimental

Melting points were taken on a Yanako micro melting-point apparatus and are uncorrected. Infrared spectra were obtained with a Hitachi EPI-G3 spectrometer, ultraviolet spectra, with a Shimadzu double beam spectrophotometer UV-200s and nuclear magnetic resonance spectra with a Nihon Denshi JNM-NH 100 [100 MHz] with tetramethylsilane (TMS) as internal standard. Chemical shift are expressed in δ (ppm). The coupling constants (J) is expressed in Hz. Abbreviation: s: singlet, d: doublet, q: quartet, m: multiplet, b: broad.

Typical procedures for these reaction were as follows.

2a and **3a**: To a solution of **1a** (0.8 g) in 2N-NaOH solution (26 ml), was added $(CH_3)_2SO_4$ (0.58 g) at 10° under stirring. Stirring was continued for 20 min. The resulting yellow-pale crystals were collected and yielded 0.4 g, mp 42—102°. These raw products were isolated as an ethanol-soluble product and an ethanol-insoluble product. The former was identified compound **2a**, mp 48—49° (from EtOH), the latter compound **3a**, mp 156—158° (from EtOH). When the molar ratio of 1: 2 (**1a**: $(CH_3)_2SO_4$) was examined by the same manner, raw products having mp 42—102° yielded 1.5 g.

3a and **4a**: An equimolar of **1a** (0.5 g) and $(CH_3)_2SO_4$ (0.35 g) was heated at 90° for 20 min. The white precipitate was filtered, identified as compound **3a** having *Rf*-value 0.49 (ether). Neutralization of filtrate with 2N-NaOH solution **4a** having *Rf*-value 0.49 (ether) yielded. When the molar ratio of 1: 2 (**1a**: $(CH_3)_2SO_4$) was heated at 94° for 15 min, the mixture of **3a** and **4a** also were yielded by the same treatment as just above mentioned.

2a: To a solution of **1a** (0.9 g) in $CHCl_3$ (65 ml), was added CH_3OSO_2F (1.17 g) at room temperature. After stirring for 4.5 hr, the white-yellow precipitate having mp 145° was collected (0.45 g), carefully neutralized with 2N-NaOH solution. S-methyl derivative **2a** was obtained as white crystals. TLC (ether): *Rf*-value 0.76.

4a: To a solution of **2a** (0.4 g) in $CHCl_3$ (5 ml), was added CH_3OSO_2F (0.24 g) at room temperature. After stirring for 3 hr, the white precipitate (raw mp 171°) was collected. The raw product was dissolved in H_2O and made alkaline with 4% NaOH solution. Recrystallization from EtOH+H_2O solution gave compound **4a**, mp 90°.

4a: To a solution of **3a** (0.7 g) in $CHCl_3$ (20 ml), was added CH_3OSO_2F (0.42 g) at room temperature. After stirring for 6 hr, the white crystals (mp 137—138°) was collected and made alkaline with 2N-NaOH solution. Recrystallization from EtOH+H_2O solution gave compound **4a**, mp 89—90°. TLC (ether): *Rf*-value 0.09 (salt), 0.17 (free).

4a: The mixture of compound **2a** (0.3 g) and $(CH_3)_2SO_4$ (0.23 g) was heated at 100° for 5—10 min. The crude product was made alkaline with 4% NaOH solution and white crystals were collected to get **4a**.

4a: The mixture of compound **3a** (0.49 g) and $(CH_3)_2SO_4$ (0.5 g) were heated at 60° for 2—3 min. After treatment as described above, compound **4a** having mp 90—91° was

obtained.

6a: A solution of compound **2a** (0.3 g) in 1N-NaOH solution (14 ml) was heated at 60° for 1 hr. The yellow oily materials was neutralized with 1N-HCl solution. Then unreacted **2a** was filtered off and the filtrate was extracted with $CHCl_3$. After evaporation of solvent, compound **6a** was recrystallized from 2-PrOH, mp 214—218°. TLC (ether): *Rf*-value 0.11.

6a: To a solution of **1a** (0.3 g) in 1N-NaOH (10 ml), was added H_2O_2 (3 ml) at 8°. After standing for 30 min, the white crystals were collected, and recrystallized from 2-PrOH to get **6a** (mp 212—214°) 0.17 g which gave a negative chelate formation with Cu^{2+} ion.

7a: A solution of compound **4a** (0.28 g) in 2N-NaOH solution (10 ml) was heated at 100° for 1 hr. The reaction mixture was neutralized with 1N-HCl solution and extracted with $CHCl_3$. After evaporation of solvent, the yellow crystals were recrystallized from toluene to get **7a**, mp 94—96° (0.15 g).

7a: To a solution of **3a** (0.1 g) in the mixture of H_2O (0.6 ml), EtOH (4 ml) and 0.5 N-NaOH (0.4 ml), was added H_2O_2 (1 ml) at room temperature. The reaction mixture was neutralized with 2N-NaOH solution and extracted with $CHCl_3$. The raw product was recrystallized from toluene to get **7a**, mp 93—94° (0.07 g).

5a: A solution of compound **2a** (1.53 g) in 1N-HCl solution (7 ml) was heated at 160° for 1.5 hr. The raw product was recrystallized from EtOH to get **5a**, mp 179—180° (0.57 g).

2c: To a solution of **1c** (1 g) in EtOH (25 ml), was added CH_3I (2.8 g). The reaction mixture was heated at 67° for 3 hr. After removal of the solvent, the crude product (HI salt) was dissolved in H_2O, neutralized with $NaHCO_3$ solution extracted with $CHCl_3$ and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give yellow oily materials which gave a negative chelate formation with Cu^{2+} ion. TLC (ether): *Rf*-value 0.65, (acetone: $CHCl_3$=1: 2): *Rf*-value 0.65. Picrate: mp 158—159° (from EtOH+H_2O).

2f: To a solution of **1f** (3.0 g) in $CHCl_3$ (200 ml), was added CH_3OSO_2F (5.1 g)(bp_{98} 34—35°) at room temperature. After stirring for 3 days red oily materials were dissolved in H_2O, neutralized with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. After evaporation of $CHCl_3$, raw product of 2.7 g yielded. Picrate: mp 126°.

3h: To a solution of 2-imino-3,4-dimethyl-4-thiazoline (8.52 g) in dry acetone (40 ml), was added N,N-dimethylthiocarbamoyl chloride (7.52 g) in dry acetone (20 ml) at room temperature and stirred for 2 days. The raw product was collected, washed with H_2O and was recrystallized with EtOH, mp 206—207°. TLC (acetone: $CHCl_3$=1: 2): *Rf*-value 0.73.

7e: The raw oily material **2f** form **1f** and $(CH_3)_2SO_4$ in 1N-NaOH solution (10 ml) was heated at 120° for 2 hr. The precipitate was collected and recrystallized from *n*-hexane

to get **7e**, mp 147—149°. TLC (ether): *Rf*-value 0.23.

7e: An equimolar mixture of 2-imino-3,4-dimethyl-4-thiazoline (1.94 g) in dry ether (60 ml), and N,N-dimethylcarbamoyl chloride (1.61 g) in dry ether (20 ml) stirred at room temperature for 15.5 hr. The reaction mixture was filtered, the filtrate was evaporated and washed with water. The white raw product was recrystallized from *n*-hexane to get **7e**, mp 149—151°. TLC (ether): *Rf*-value 0.23.

5b: The oily material **2f** (0.4 g) in 10% HCl solution (6 ml) was heated at 50—55° for 1 hr. The reaction mixture was neutralized with 1N–NaOH solution and recrystallized from EtOH to get **5b**, mp 161—163°.

3h: To a solution of **1f** (2.01 g) in 2N–NaOH solution (65 ml), was added $(CH_3)_2SO_4$ (1.26 g) at 9°. The reaction mixture was stirred for 1 hr. The yellow precipitate was filtered. On the TLC (acetone :$CHCl_3$=1: 2) two spots were appeared at the position of *Rf*-values 0.66 and 0.47. The raw product (0.925 g) was recrystallized from ethanol to yield, ring N-methyl derivative **3h**, mp 202.5°. A trace amount of S-methyl derivative **2f** having *Rf*-value 0.47 g yielded. The filtrate was adjusted pH 4 with 10% HCl solution and the resulting product was identical with **1f** of starting material, which gave a positive chelate formation with Cu^{2+} ion.

7e: To a solution of **3h** (0.4 g) in $CHCl_3$ (20 ml), was added CH_3OSO_2 F(0.64 g) and stirred at room temperature for 2 days. The red oily materials was neutralized with 1N–NaOH solution to give white crystals **7e**, mp 150° (from *n*-hexane). TLC (acetone: $CHCl_3$=1: 2): *Rf*-value 0.54.

3h: Compound **2f** was heated at 155—165° for 14 hr. On the TLC the raw product showed two spots having *Rf*-values 0.55 and 0.39 (ether). The raw cross product was purified by silica-gel column chromatography using acetone-$CHCl_3$ (1: 2) as a eluent. The eluate was evaporated under reduced pressure, and treated with an activated charcoal in EtOH to give compound **3h**, mp 204—205° (12 mg).

Cross reaction of 2f and 1g

The mixture of **2f** (300 mg) and **1g** (150 mg) was heated at 145° for 1.5 hr. The raw cross product was purified by silica-gel column chromatography using acetone–$CHCl_3$ (1: 2) as a eluent. The eluate was evaporated and the yellow precipitate was examined on Mass. As shown in Fig. 2, its Mass data showed a molecular ion peak at *m/e* 229 corresponding to compound **3i** having molecular weight 229.