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Studies on Organic Sulfur Compounds. IX.[1] The Reaction of Ethoxycarbonyl Isothiocyanate with 4,5-Substituted 2-Aminothiazoles[2]

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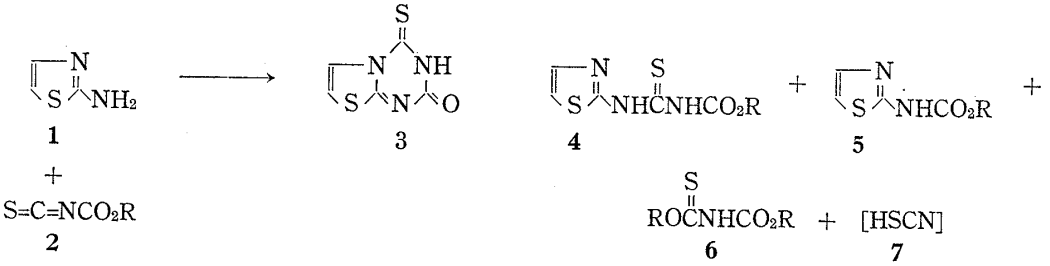
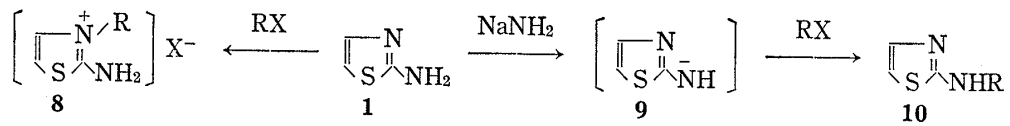
The Reactions of ethoxycarbonyl isothiocyanate (**23**) with 4,5-substituted 2-aminothiazoles (**24**) afforded thiazolo [3,2-*a*]-*s*-triazine-4-thio-2-ones (**25**), N-alkoxycarbonyl-N′-(2-thiazolyl)thioureas (**26**), alkyl-N-(2-thiazolyl)carbamates (**27**), ethyl-N-ethoxycarbonyl thiocarbamate (**28**) and thiocyanic acid (**7**). However, in the cases of the amines whose pKa values were smaller than that of 2-aminothiazole (**24-a**) or the amines which had some substituents on the 4-position of **24**, the corresponding cyclic compounds (**25**) could not be obtained. A series of these phenomena was discussed in connection with basicities of 2-aminothiazoles (**24**) and the steric hindrance of the substituents on the 4-position of **24**.

In the previous paper,[1] the reactions of alkoxycarbonyl isothiocyanates (**2**) with 2-aminothiazole (**1**) were reported to give thiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**3**), N-alkoxycarbonyl-N′-(2-thiazolyl)thioureas (**4**), alkyl-N-(2-thiazolyl)carbamates (**5**), alkyl-N-alkoxycarbonyl thiocarbamates (**6**) and thiocyanic acid (**7**). In these reactions, there seemed to be some relationships among the processes of the formation of the three products (**3**, **4** and **5**). We are particularly interested in investigating the mechanism of the formation of **3**.

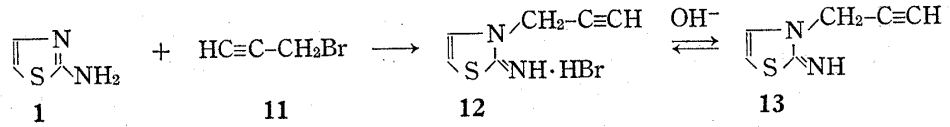


The studies on the tautomeric problems of 2-aminothiazoles have been undertaken by many chemists. It is known that the basicity of 2-aminothiazole (**1**) is lower than that of aniline, and a proton adds preferentially to the ring nitrogen atom, thus **8** is formed by the alkylation of **1** with alkyl halides, except under strongly alkaline conditions where the intermediate anion (**9**) probably reacts with alkyl halides to give **10**.[4] Iwai and Hiraoka[5] ob-



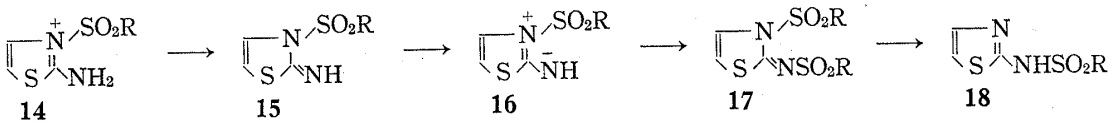
tained 2-imino-3-(2-propynyl)-4-thiazoline (**13**) from 2-aminothiazole (**1**) and 2-propynyl bromide (**11**) by a similar reaction. It has been reported that the reactions of 2-amino-

1) Part VIII: M. Nagano, T. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), 20, 2618 (1972).
2) The Third Sympodium of Heterocyclic Compounds, Tokyo, November 1970. Perliminary Report, p. 33.
3) Location: *Hiromachi, Sinagawa-ku, Tokyo.*
4) A.R. Katritzky and J.M. Lagowski, "Heterocyclic Chemistry," Methuen, London, 1960, p. 233—234.
5) I. Iwai and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), 12, 813 (1964).



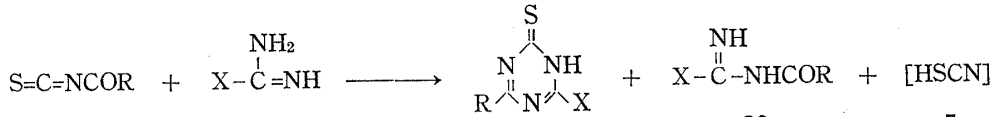
1 11 12 13

thiazole (**1**) and sulfonyl halides generally afford disulfonyl compounds (**17**) and monosulfonyl compounds (**18**).[6–10] Angyal[11] has explained the machanism of the formation of **17** and **18** wherein the first reaction product would be the cation (**14**) which in the alkaline medium would lose a proton to yield **15**, and this intermediate **15** would react readily with a second molecule of a sulfonyl halide to yield **17** which would be easily hydrolyzed to **18** by acids or bases. It has been also shown that the rate of the reaction of 2-amino-4-phenylthiazole with toluene-*p*-sulfonyl chloride is very slow; not only the disubstituted product but also the monosubstituted product is slowly formed.[11] Goerdeler, *et al.*[12–15] have reported that in the



14 15 16 17 18

reactions of acyl isothiocyanates (**19**) with amidines (**20**) (or amidinoids), which lead to triazine thiones (**21**), the lower the basicity of **20** and the carbonyl activity of **19** are, the greater the yield of **21** is; and on the contrary, the higher the basicity of (**20**) and the activity of **19** are, the greater the yields of acyl amidines (**22**) and thiocyanic acid (**7**) are. From above in-



19 20 21 22 7

formation, presumably the basicity and substituent groups at the 4-position of 2-aminothiazole may exert some influence on such an addition reaction. We wish now to report the reactions of ethoxycarbonyl isothiocyanate (**23**) and some 4,5-substituted 2-aminothiazoles.

Ethoxycarbonyl isothiocyanate (**23**) was treated with 5-alkyl-2-aminothiazoles (**24-b**, **24-c**, **24-d**, and **24-e**), whose pK_a values were larger than that of 2-aminothiazole (pK_a: 5.34), to afford 7-alkylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-ones (**25-b**, **25-c**, **25-d**, and **25-e**), N-ethoxycarbonyl-N′-(5-alkyl-thiazol-2-yl)thioureas (**26-b**, **26-c**, **26-d**, and **26-e**), ethyl-N-(5-alkylthiazol-2-yl)carbamates (**27-b**, **27-c**, **27-d**, and **27-e**), ethyl-N-ethoxycarbonyl thiocarbamate (**28**) and thiocyanic acid (**7**). The rates of the reactions of **23** with 2-amino-4-methyl-thiazole (**24-j**, pK_a: 5.86) and 2-amino-4,5-dimethylthiazole (**24-m**, pK_a: 6.29) were so fast that the starting amines could not be recovered, and the thiazolyl thioureas (**26-j** and **26-m**) were isolated in good yields, followed by small amounts of the thiazolyl carbamates (**27-j** and **27-m**) and N-ethoxycarbonyl thiocarbamate (**28**); but, in spite of their larger pK_a values, the corresponding thiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one could not be obtained in each case (Chart 2). 2-Amino-5-phenylthiazole (**24-f**, pK_a: 4.78) was reacted with (**23**) to afford N-ethoxy-

6) Brit. Patent 533, 495 Feb. 14, 1941.
7) W.G. Raiziss and W.L. Clemence, *J. Amer. Chem. Soc.*, **63**, 3124 (1941).
8) P.C. Price and H.R. Reitsema, *J. Org. Chem.*, **12**, 269 (1947).
9) V.C. Deliwala, K. Ganapachi, and W.M. Shirsat, *Proc. Indian Acad. Sci.*, **18A**, 360 (1943).
10) T.S. Angyal, O.W. Morris, and K.W. Warburton, *Aust. J. Sci. Res.*, **A5**, 368 (1952).
11) T.S. Angyal, *Aust. J. Sci. Res.*, **A5**, 374 (1952).
12) J. Goerdeler, *Q. Report on Sulfur Chemistry*, **5**, 169 (1970).
13) J. Goerdeler and J. Neuffer, *Tetrahedron Letters* **1967**, 2791.
14) J. Goerdeler and J. Neuffer *Chem. Ber.*, **104**, 1580 (1971).
15) J. Goerdeler and J. Neuffer, *Chem. Ber.*, **104**, 1606 (1971).

carbonyl-N′-(5-phenyl-thiazol-2-yl)thiourea (**26-f**), ethyl-N-(5-phenyl-thiazol-2-yl)carbamate (**27-f**), **28** and **7**. On the other hand, in the case of 2-amino-4-phenylthiazole (**24-k**, pK_a: 4.32) only one product, namely 1-ethoxycarbonyl-3-(4-phenyl-thiazol-2-yl)thiourea (**26-k**), was obtained in good yield despite its smaller pK_a value than that of (**24-f**), but thiocyanic acid (**7**) could not be formed. However, even in the cases of 5-bromo-(**24-g**), 5-thiocyanato-(**24-h**), and 5-nitro-2-aminothiazole (**24-i**), whose pK_a values were smaller than that of 2-amino-4-phenylthiazole (**24-k**), the thiazolyl thioureas (**26-g**, **26-h**, and **26-i**), the thiazolyl carbamates (**27-g**, **27-h**, and **27-i**), (**28**) and (**7**) were produced in each case. Furthermore, in the case of 2-aminobenzothiazole (**24-l**), whose pK_a value was similar to that of (**24-k**), two compounds (**26-l**) and (**27-l**), besides starting amine, were isolated (Chart 2).

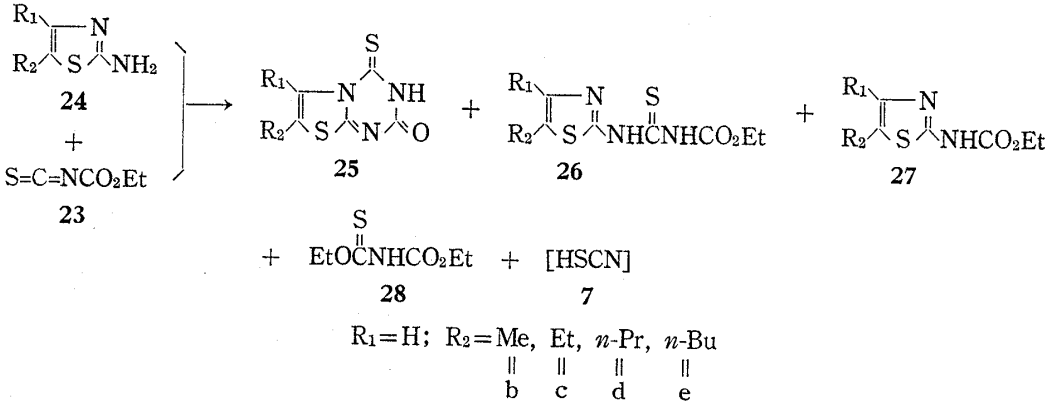


Chart 1

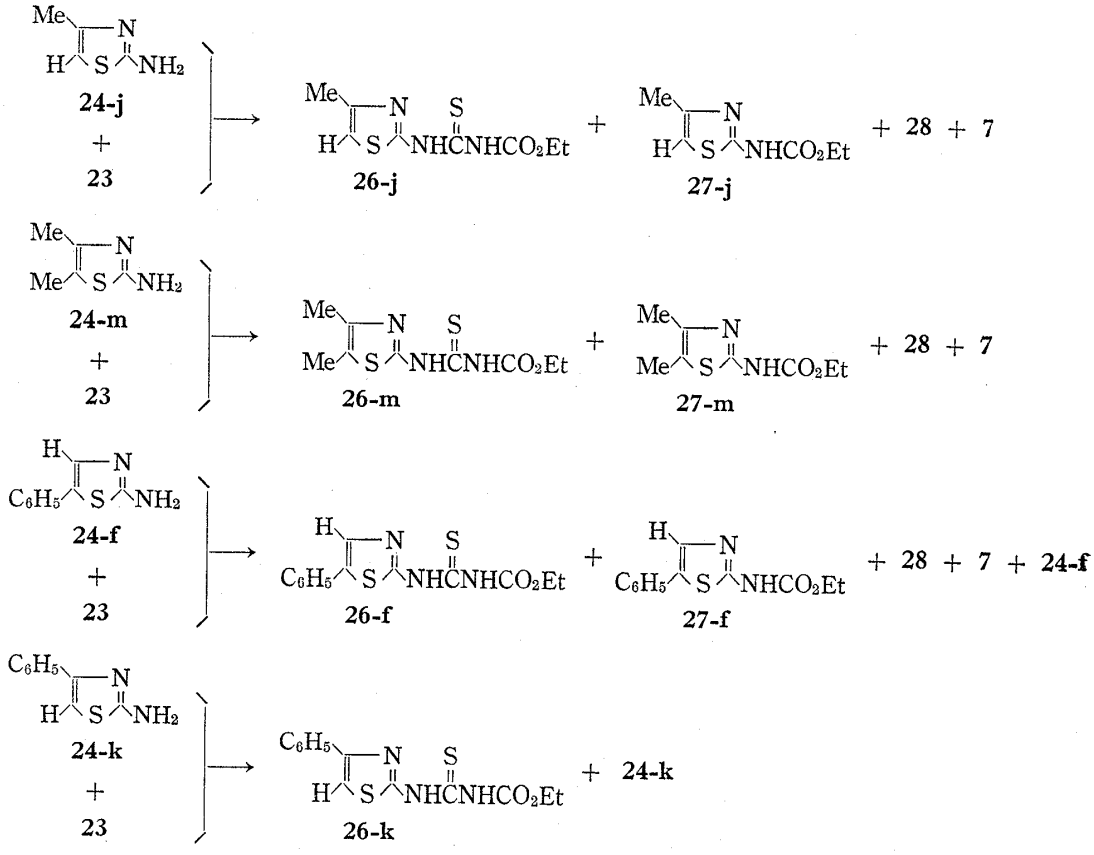


Chart 2

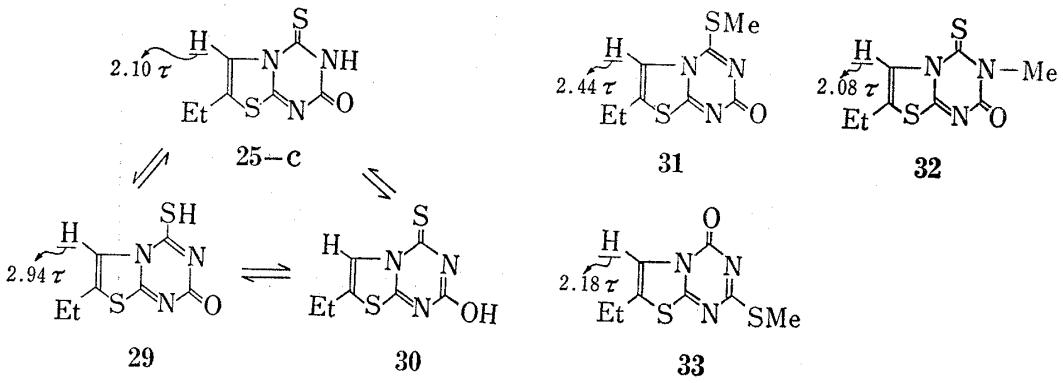
It was observed in nuclear magnetic resonance (NMR) spectra that the three thiazolo-[3,2-*a*]-*s*-triazine-2-thio-4-ones (**25-b**, **25-c**, and **25-d**), which were obtained by the reactions

Table I. The pK_a Values of 2-Aminothiazoles and Isolated Yields of the Products

24	pKa (temp. °C)	25		26		27		28	HSCN	Recovered Compd. (24)
$R_1=R_2=H$ (**24-a**)	5.34 (5.39)[16] (26)	29.0 (%)	(**25-a**)	50.0 (%)	(**26-a**)	7.0 (%)	(**27-a**)	2.8 (%)	+	not isolated
$R_1=H$, $R_2=Me$ (**24-b**)	5.88 (25)	39.1	(**25-b**)	43.2	(**26-b**)	6.8	(**27-b**)	2.8	+	not isolated
$R_1=H$, $R_2=Et$ (**24-c**)	5.89 (26)	36.9	(**25-c**)	40.5	(**26-c**)	6.5	(**27-c**)	2.8	+	not isolated
$R_1=H$, $R_2=n$-Pr (**24-d**)	5.89 (26)	36.9	(**25-d**)	42.5	(**26-d**)	6.7	(**27-d**)	2.3	+	not isolated
$R_1=H$, $R_2=n$-Bu (**24-e**)	5.91 (27)	38.1	(**25-e**)	39.2	(**26-e**)	6.6	(**27-e**)	3.4	+	not isolated
$R_1=H$, $R_2=C_6H_5$ (**24-f**)	4.78 (27)	not isolated		69.1	(**26-f**)	8.9	(**27-f**)	0.7	+	10.2 (%)
$R_1=H$, $R_2=Br$ (**24-g**)	3.54 (26.5)	not isolated		43.8	(**26-g**)	2.3	(**27-g**)	0.8	+	42.3
$R_1=H$, $R_2=SCN$ (**24-h**)	2.65 (26)	not isolated		36.5	(**26-h**)	2.6	(**27-h**)	0.6	+	50.9
$R_1=H$, $R_2=NO_2$ (**24-i**)	0.93 (27)	not isolated		28.0	(**26-i**)	2.3	(**27-i**)	1.0	+	57.5
$R_1=Me$, $R_2=H$ (**24-j**)	5.81 (26)	not isolated		87.5	(**26-j**)	4.3	(**27-j**)	1.2	+	not isolated
$R_1=C_6H$, $R_2=H$ (**24-k**)	4.32 (26)	not isolated		77.5	(**26-k**)	not isolated		not isolated	trace	8.3 (%)
(**24-l**)	4.32 (4.51)[16] (27)	not isolated		66.5	(**26-l**)	15.3	(**27-l**)	not isolated	+	6.5
$R_1=R_2=Me$ (**24-m**)	6.29 (26)	not isolated		84.8	(**26-m**)	6.0	(**27-m**)	1.4	+	not isolated

16) A. Albert. R. Goldace, and J. Philips, *J. Chem. Soc.*, **1948**, 2240.

of ethoxycarbonyl isothiocyanate (**23**) with 5-alkyl-2-aminothiazoles (**24-b**, **24-c**, and **24-d**), existed in two tautomeric forms in a solvent. For example, the peak of 6-H of 7-ethylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**25-c**) was observed at 2.10 τ and 2.94 τ with an intensity ratio of 2 to 1 in dimethyl sulfoxide (DMSO). The two tautomers of this cyclic compound were supposed to be the keto-forms (**25-c** and **29**) rather than the enol-form (**30**) on the basis of the IR spectrum (>C=O: 1690 cm^{-1}), and by the comparison with the chemical shifts of the 6-H of 7-ethyl-4-methylthiothiazolo[3,2-*a*]-*s*-triazine-2-one (**31**: 2.44 τ), 7-ethyl-3-methylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**32**: 2.08 τ) and 7-ethyl-2-methylthiothiazolo-[3,2-*a*]-*s*-triazine-4-one (**33**: 2.18 τ) in DMSO.



From above mentioned facts, it became clear that in the reaction of ethoxycarbonyl isothiocyanate (**23**) with 2-aminothiazoles (**24**), the rates of the reactions were dependent on the basicity of the amines (**24**), but the sorts and the yields of the reaction products might be attributed to both the basicity of (**24**) and the steric hindrance of the substituent groups at 4-position of (**24**). However, the mechanism of the formation of three compounds (**25**, **26**, and **27**) remains to be solved. The structures of the isolated products were confirmed on the basis of analytical and spectral data. The pK_a values of 2-aminothiazoles and the yields of isolated products are summarized in Table I.

Experimental[17]

pK_a Measurements——The p*K*a values of 2-aminothiazoles (24) were determined by the spectrophotometric method[18] in aqueous solution containing 4% alcohol.[19]

General Method for the Reactions of Ethoxycarbonyl Isothiocyanate (23) with 4,5-Substituted 2-Aminothiazoles (24)——To a solution of 2-aminothiazoles (0.01 mole) in AcOEt (30 ml), a solution of ethoxycarbonyl isothiocyanate (0.011 mole) in AcOEt (20 ml) was added dropwise at 0—5°, and the mixture was allowed to stand over night and then the reaction solution was refluxed for 2 hr, washed with aqueous $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. After removal of the solvent under reduced pressure, the residue was eluted with AcOEt–benzene on silica gel, and the isolated compounds were refined by recrystallization.

Reaction of 23 with 2-Amino-5-methyl-thiazole (24-b)——1.45 g of **23** was treated with 1.16 g of **24-b** to afford four compounds (**25-b**, **26-b**, **27-b**, and **28**). 7-Methyl-thiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**25-b**), 0.78 g, pale yellow needles from acetone, mp 250—252° (decomp.). *Anal.* Calcd. for $C_6H_5ON_3S_2$: C, 36.19; H, 2.53; N, 21.10; S, 32.19. Found: C, 36.10; H, 2.47; N, 21.37; S, 32.01. Mass Spectrum: M^+= 199. IR ν_{max}^{Nujol} cm^{-1}: 3150 (>NH), 1690 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 7.76 and 7.66 (1:4, d, J= 1.0: methyl protons), 2.94 and 2.08 (1:3, q, J=1.0: methyn proton), *ca.* 1.0 and *ca.* −2.60 (1:3, broad: >NH). N-Ethoxycarbonyl-N′-(5-methyl-thiazol-2-yl)thiourea (**26-b**). 1.11 g, pale yellow prisms from benzene, mp 173—174°. *Anal.* Calcd. for $C_8H_{11}O_2N_3S_2$: C, 39.15; H, 4.52; N, 17.12; S, 26.13. Found:

17) All melting points were uncorrected. NMR spectra were obtained in the specified solvents on a Varian A-60 spectrometer. Mass spectrum was determined on a JEOL JMS-OISG spectrometer.
18) A. Albert and E.P. Serjent, "Ionization Constants of Acids and Bases," Methuen, London, 1962.
19) p*K*a Measurements were carried out on the Beckman model DB spectrometer at the temperature shown in Table I.

C, 39.23; H, 4.44; N, 17.22; S, 26.33. IR ν_{max}^{Nujol} cm^{-1}: 3180 (>NH), 1730 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.62 (3H, t, J=7.0), 7.51 (3H, d, J=1.5), 5.56 (2H, q, J=7.0), 2.56 (1H, q, J=1.5), *ca.* 1.54 (1H), *ca.* −3.12 (1H). UV λ_{max}^{EtOH} mμ (ε): 232 (8500), 261.5 (16800), 313 (11200). Ethyl N-(5-methylthiazol-2-yl)-carbamate (**27-b**)*, 0.124 g, colorless needles from isopropyl ether, mp 149—150°. *Anal.* Calcd. for $C_7H_{10}O_2N_2S$: C, 45.16; H, 5.14; N, 15.05; S, 17.19. Found: C, 45.48; H, 5.49; N, 15.00; S, 17.04. IR ν_{max}^{Nujol} cm^{-1}: 3180 (>NH), 1718 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.60 (3H, t, J=7.0), 7.64 (3H, d, J=1.5), 5.68 (2H, q, J=7.0), 2.97 (1H, q, J=1.5), *ca.* −2.30 (1H). UV λ_{max}^{EtOH} mμ (ε): 262.5 (9800). *This compound (**27-b**) agreed with the sample prepared from (**24**-b) and methyl chloroformate in the presence of triethyl amine.[20] Ethyl N-ethoxycarbonyl thiocarbamate (**28**) (0.05 g) agreed with the sample prepared by treatment of **23** with ethyl alcohol.[1] Thiocyanic acid (**7**) was detected by the color reaction with ferric chloride.

Reaction of 23 with 2-Amino-5-ethylthiazole (24-c)——1.45 g of (**23**) was treated with 1.30 g of 2-amino-5-ethylthiazole (**24-c**) to afford three compounds (**25-c**, **26-c**, and **27-c**) besides 0.05 g of (**28**). 7-Ethylthiazolo[3,2-*a*]*s*-triazine-4-thio-2-one (**25-c**), 0.785 g, colorless needles from acetone, mp 212—214° (decomp.). *Anal.* Calcd. for $C_7H_7ON_3S_2$: C, 39.44; H, 3.31; N, 19.72; S, 30.01. Found: C, 39.68; H, 3.39; N, 19.37; S, 29.57. IR ν_{max}^{Nujol} cm^{-1}: 3200 (>NH), 1690 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 8.82 and 8.78 (1: 2, t, J=7.0, methyl protons), 6.28 and 6.26 (1: 2, q, d, J_1=7.0, J_2=1.3, methylene protons), 2.94 and 2.10 (1: 2, t, J=1.3: methyn proton), *ca.* 0.84 and −1.98 (1: 2, broad, –NH). UV λ_{max}^{EtOH} mμ (ε): 245 (8600), 284 (11900), 314 (5300). N-Ethoxycarbonyl-N′-(5-ethylthiazol-2-yl)thiourea (**26-c**), 1.05 g, colorless needles from ethyl acetate, mp 166—167° (decomp.). *Anal.* Calcd. for $C_9H_{13}O_2N_3S_2$: C, 41.70; H, 5.06; N, 16.21; S, 24.68. Found: C, 41.49; H, 5.23; N, 16.19; S, 24.71. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1740 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.70 (3H, t, J=7.0), 8.68 (3H, t, J=7.0), 7.77 (2H, q, d, J_1=7.0, J_2=1.0), 5.68 (2H, q, J=7.0), 2.75 (1H, t, J=1.0), *ca.* 1.60 (1H), *ca.* −2.56 (1H). UV λ_{max}^{EtOH} mμ (ε): 232.5 (8600), 261 (17000), 312 (10800). Ethyl N-(5-ethyl-thiazol-2-yl)carbamate (**27**-c)*, 0.13 g, colorless needles from isopropyl ether, mp 104—105°. *Anal.* Calcd. for $C_8H_{12}O_2N_2S$: C, 47.99; H, 6.04; N, 13.99; S, 15.98. Found: C, 47.84; H, 6.22; N, 13.82; S, 15.92. IR ν_{max}^{Nujol} cm^{-1}: 3200 (=NH), 1730 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.71 (3H, t, J=7.0), 8.65 (3H, t, J=7.0), 8.23 (2H, q, d, J_1=7.0, J_2=1.0), 5.67 (2H, q, J=7.0), 2.96 (1H, t, J=1.0), *ca.* −1.0 (1H). *This compound (**27-c**) agreed with the sample prepared from **24-c** and ethyl chloroformate in the presence of triethyl amine.[20]

Methylation of 7-Ethylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (24-c) with Methyl Iodide——A mixture of 2.13 g of **24-c**, methyl iodide (1.8 g), triethyl amine (1.2 g) and AcOEt (50 ml) was refluxed for 5 hr, and the reaction mixture was washed with satd. aqueous $NaHCO_3$ solution and then H_2O, dried over anhyd. Na_2SO_4. After removal of solvent the residue was eluted with AcOEt–benzene over silica gel to afford two products (**31** and **32**). 7-Ethyl-4-methylthiothiazolo[3,2-*a*]-*s*-triazine-2-one (**31**), 0.65 g, colorless needles from benzene, mp 170—171°. *Anal.* Calcd. for $C_8H_9ON_3S_2$: C, 42.29; H, 3.99; N, 18.50; S, 28.17. Found: C, 42.40; H, 4.30; N, 18.31; S, 28.25. IR ν_{max}^{Nujol} cm^{-1}: 1666 (>C=O), 1617 (>C=N- or >C=C<). NMR (DMSO-d_6) τ (J=Hz): 8.77 (3H, t, J=7.5), 7.35 (3H, s), 7.25 (2H, q, t, J_1=7.5, J_2=1.3), 2.44 (1H, t, J=1.3). UV λ_{max}^{EtOH} mμ (ε): 244.3 (16100), 273.5 (14500). 7-Ethyl-3-methylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**32**)*, 1.13 g, colorless needles from AcOEt, mp 148—149°. *Anal.* Calcd. for $C_8H_9ON_3S_2$: C, 42.29; H, 3.99; N, 18.50; S, 28.17. Found: C, 42.62; H, 4.24; N, 18.05; S, 27.92. IR ν_{max}^{Nujol} cm^{-1}: 1696 (>C=O), 1622 (>C=C< or >C=N-). NMR (DMSO-d_6) τ (J=Hz): 8.77 (3H, t, J=7.5), 7.25 (2H, q, t, J_1=7.5, J_2=1.2), 6.39 (3H, s), 2.08 (1H, t, J=1.2). UV λ_{max}^{EtOH} mμ (ε): 242.5 (6600), 268 (11400), 291.2 (15300). *0.8 g of **32** was oxidized with Hg $(AcO)_2$ to give 0.4 g of **34**. 7-Ethyl-3-methylthiazolo[3,2-*a*]-*s*-triazine-2,4-dione (**34**), colorless needles from acetone, mp 168—169°. *Anal.* Calcd. for $C_8H_9O_2N_3S$: C, 45.50; H, 4.30; N, 19.90; S, 15.15. Found: C, 45.52; H, 4.33; N, 19.63; S, 14.93. IR ν_{max}^{Nujol} cm^{-1}: 1740 (>C=O), 1670 (>C=O), 1620 (>C=C< or >C=N-). NMR (DMSO-d_6) τ (J=Hz): 8.79 (3H, t, J=7.0), 7.28 (2H, q, t, J_1=7.0, J_2=1.3), 6.78 (3H, s), 2.48 (1H, t, J=1.3). UV λ_{max}^{EtOH} mμ (ε): 240 (5800), 288 (9700).

Preparation of 7-Ethyl-2-methylthio-thiazolo[3,2-*a*]-*s*-triazine-4-one (**33**)——2.59 g of N-ethoxycarbonyl-N′-(5-ethyl-thiazol-2-yl)thiourea (**26**-c) was heated at 170—180° under N_2 gas for 5 minutes, and the residue was solved in acetone (100 ml). To the solution methyl iodide (1.8 g) and triethyl amine (1.2 g) were added, and the mixture was refluxed for 3 hr, and the reaction mixture was washed with satd. aqueous $NaHCO_3$, H_2O and dried over anhd. Na_2SO_4. After removal of solvent, the residue was recrystallized from benzene to afford 0.4 g of (**33**) as colorless needles of mp 135—137°. *Anal.* Calcd. for $C_8H_9ON_3S_2$: C, 42.29; H, 3.99; N, 18.50; S, 28.17. Found: C, 42.37; H, 3.72; N, 18.34; S, 28.15. IR ν_{max}^{Nujol} cm^{-1}: 1702 (>C=O), 1600 (>C=C< or >C=N–). NMR (DMSO-d_6) τ (J=Hz): 8.72 (3H, t, J=7.5), 7.50 (3H, s), 7.12 (2H, q, d, J_1=7.5, J_2=1.3), 2.18 (1H, t, J=1.3). UV λ_{max}^{EtOH} mμ (ε): 246 (7000), 267 (8100), 314 (20000).

Reaction of 23 with 2-Amino-5-*n*-propylthiazole (24-d)——1.45 g of **23** was treated with 1.42 g of (**24-d**) to afford three products (**25-d**, **26-d** and **27-d**) besides 0.04 g of (28). 7-*n*-Propylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**25**-d), 0.84 g, colorless needles from AcOEt, mp 192—193°. *Anal.* Calcd. for $C_8H_9ON_3S_2$: C, 42.27; H, 3.99; N, 18.49; S, 28.21. Found: C, 42.08; H, 4.17; N, 18.30; S, 27.80. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1680 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 9.05 and 9.03 (1: 2, *t*, J=7.0, methyl protons), 8.39

20) U.S.A. Patent 2850503 Sept. 2, 1958.

and 8.36 (1: 2, $J_1=J_2=7.0$: methylene protons), 7.54 (2H, t, d, $J_1=7.0$, $J_2=1.0$, methylene protons: overlap to the peaks of DMSO), 2.91 and 2.06 (1: 2, t, $J=1.0$, methyn proton), *ca.* 0.97 and *ca.* −1.78 (1: 2, broad: >NH). N-Ethoxycarbonyl-N′-(5-*n*-propylthiazol-2-yl)thiourea (**26-d**), 1.16 g, colorless needles from benzene, mp 119—121° (decomp.). *Anal.* Calcd. for $C_{10}H_{15}O_2N_3S_2$: C, 43.95; H, 5.53; N, 15.37; S, 24.43. Found: C, 43.95; H, 5.66; N, 15.15; S, 24.11. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 9.03 (3H, t, $J=7.0$), 8.66 (3H, t, $J=7.0$), 8.29 (2H, q, t, $J_1=J_2=7.0$), 7.23 (2H, t, d, $J_1=7.0$, $J_2=1.0$), 5.62 (2H, q, $J=7.0$), 2.75 (1H, t, $J=1.0$), *ca.* 1.52 (1H), *ca.* −2.64 (1H). UV λ_{max}^{EtOH} mμ (ε): 233 (8300), 261.5 (15400), 314 (11500). Ethyl-N-(5-*n*-propylthiazol-2-yl)carbamate (**27-d**)*, 0.13 g, colorless needles from *n*-hexane–benzene, mp 118—119°. *Anal.* Calcd. for $C_9H_{14}O_2N_2S$: C, 50.46; H, 6.59; N, 13.08; S, 14.94. Found: C, 50.10; H, 6.59; N, 12.72: S, 14.92. IR ν_{max}^{Nujol} cm^{-1}: 3210 (>NH), 1740 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 9.02 (3H, t, $J=7.0$), 8.62 (3H, t, $J=7.0$), 8.31 (2H, q, t, $J_1=J_2=7.0$), 7.36 (2H, t, d, $J_1=7.0$, $J_2=1.0$), 5.66 (2H, q, $J=7.0$), 2.92 (1H, t, $J=1.0$), *ca.* −2.48 (1H). UV λ_{max}^{EtOH} mμ (ε): 263.5 (10300). *This compound (**27**-d) agreed with the sample prepared from **24-d** and ethyl chloroformate in the presence of triethyl amine.

Reaction of 23 with 2-Amino-5-*n*-butylthiazole (24-e)——1.45 g of **23** was treated with 1.42 g of **24-e** to afford three products (**25-e**, **26-e** and **27-e**) besides 0.06 g of (28). 7-*n*-Butylthiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**25-e**), 0.92 g, colorless needles from benzene, mp 174—175°. *Anal.* Calcd. for $C_9H_{11}ON_3S_2$: C, 44.81; H, 4.60; N, 17.42; S, 26.53. Found: C, 44.53; H, 4.65; N, 17.31; S, 26.53. IR ν_{max}^{Nujol} cm^{-1}: 2170 (>NH), 1690 (-C=O). NMR (DMSO-d^6) τ (J=Hz): 9.14 (3H, t, $J=6.2$), 8.92—8.16 (4H, m), 7.28 (2H, t, d, $J_1=7.0$, $J_2=1.0$), 2.10 (1H, t, $J=1.0$), *ca.* −3.04 (1H). N-Ethoxycarbonyl-N′-(5-*n*-butylthiazolol-2-yl)thiourea (**26-e**), 1.125 g, colorless needles from ethyl acetate, mp 103—104°. *Anal.* Calcd. for $C_{11}H_{17}O_2N_3S_2$: C, 45.99; H, 5.97; N, 14.63; S, 22.08. Found: C, 45.78; H, 5.84; N, 14.52; S, 21.71. IR ν_{max}^{Nujol} cm^{-1}: 3200 (-NH), 1732 (=C=O). NMR ($(CD_3)_2C=O$]τ(J=Hz): 9.06 (3H, t, $J=7.0$), 8.48 (3H, t, $J=7.0$), 8.88—8.06 (4H, m), 7.18 (2H, t, d, $J_1=7.0$, $J_2=1.0$), 5.65 (2H, q, $J=7.0$), 2.72 (1H, t, $J=1.0$), *ca.* −0.42 (1H), *ca.* −2.90 (1H). UV λ_{max}^{EtOH} mμ (ε): 232 (8100), 262 (16800), 314 (11700). Ethyl N-(5-*n*-butylthiazolol-2-yl)carbamate (**27-e**)*, 0.15 g, colorless needles from *n*-hexane–benzene, mp 91—92°. *Anal.* Calcd. for $C_{10}H_{16}O_2N_2S$: C, 52.62; H, 7.07; N, 12.27; S, 14.02. Found: C, 52.17; H, 7.04; N, 12.13; S, 14.10. IR ν_{max}^{Nujol} cm^{-1}: 3220 (>NH), 1730 (>C=O). NMR ($CDCl_3$), (J=Hz): 0.06 (3H, t, $J=6.2$), 8.92—7.98 (4H, m), 8.62 (3H, t, $J=7.0$), 8.23 (2H, t, d, $J_1=7.0$, $J_2=1.0$), 5.65 (2H, q, $J=7.0$), 2.92 (1H, t, $J=1.0$), *ca.* −2.76 (1H). UV λ_{max}^{EtOH} mμ (ε): 263.5 (10400). *This compound (**27-e**) agreed with the sample prepared from 2-amino-5-*n*-butylthiazole (**24-e**) and ethyl chloroformate in the presence of triethyl amine.

Reaction of 2-Amino-5-phenylthiazole (24-f) and 23——In the reaction of 1.45 g of **23** and 1.77 g of **24-f**, two compounds (**26-f** and **27-f**), besides 0.18 g of **24-f** and 0.02 g, of **28**, could be isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(5-phenylthiazol-2-yl)thiourea (**26-f**), 2.12 g, colorless needles from ethyl acetate, mp 159—160° (decomp.). *Anal.* Calcd. for $C_{13}H_{13}O_2N_3S_2$: C, 50.81; H, 4.26; N, 13.68; S, 20.82. Found: C, 51.68; H, 4.27; N, 13.13; S, 20.54. IR ν_{max}^{Nujol} cm^{-1}: 3140 (>NH), 1728 (>C=O). NMR [$(CD_3)_2C=O$] τ (J=Hz): 8.65 (3H, t, $J=7.0$), 5.64 (2H, q, $J=7.0$), 2.78—2.14 (5H, m), 2.10 (1H, s), *ca.* −0.56 (1H, m), *ca.* −2.94 (1H, m). UV λ_{max}^{EtOH} mμ (ε): 267 (16400), 333 (11500). Ethyl N-(5-phenylthiazol-2-yl)carbamate (**27-f**)*, 0.22 g, colorless needles from ethyl acetate, mp 201—202°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.06; H, 4.87; N, 11.29; S, 12.89. Found: C, 57.69; H, 4.88; N, 11.00; S, 12.85. IR ν_{max}^{Nujol} cm^{-1}: 3200 (>NH), 1728 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.58 (3H, t, $J=7.0$), 5.62 (2H, q, $J=7.0$), 2.78—2.26 (5H, m), 2.43 (1H, s), *ca.* −2.70 (1H). UV λ_{max}^{EtOH} mμ (ε): 297.5 (18800). *This compound (**27-f**) agreed with the sample prepared from **24-f** and ethyl chloroformate in the presence of triethyl amine.

Reaction of 23 with 2-Amino-5-bromothiazole (24-g)——In the reaction of 1.45 g of **23** and 1.79 g of **24-g**, two products (**26-g** and **27-g**), besides 0.76 g of **24-g** and 0.015 g of **28**, were isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(5-bromothiazol-2-yl)thiourea (**26-g**), 1.38 g, pale yellow needles from acetone, mp 175° (decomp.). *Anal.* Calcd. for $C_7H_8O_2N_3S_2Br$: C, 27.10; H, 2.60; N, 13.55; S, 20.68; Br, 25.76. Found: C, 27.14; H, 2.70; N, 13.36; S, 20.68; Br, 25.98. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1720 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.71 (3H, t, $J=7.0$), 5.72 (2H, q, $J=7.0$), 2.28 (1H, s), *ca.* −1.96 (2H). UV λ_{max}^{EtOH} mμ (ε): 262.5 (16200), 314 (11000). Ethyl N-2-(5-bromothiazolyl)carbamate (**27-g**), 0.058 g, colorless needles from ethyl acetate, mp 175—176°. *Anal.* Calcd. for $C_6H_7O_2N_2SBr$: C, 28.69; H, 2.80; N, 11.15; S, 12.76; Br, 31.82. Found: C, 29.02; H, 2.79; N, 11.15; S, 12.76; Br, 31.87. IR ν_{max}^{Nujol} cm^{-1}: 3180 (>NH), 1728 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.60 (3H, t, $J=7.0$), 5.64 (2H, q, $J=7.0$), 2.74 (1H, s), *ca.* −2.18 (1H). UV λ_{max}^{EtOH} mμ (ε): 266 (8600).

Reaction of 23 with 2-Amino-5-thiocyanatothiazole (24-h)——In the reaction of 1.45 g of **23** and 1.57 g of **24-h**, two products (**26-h** and **27-h**), besides 0.8 g of **24-h** and 0.011 g of **28**, were isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(5-thiocyanatothiazol-2-yl)thiourea (**26-h**), 1.10 g, pale yellow needles from acetone, mp 189—191° (decomp.). *Anal.* Calcd. for $C_8H_8O_2N_4S_3$: C, 33.34; H, 2.80; N, 19.44; S, 33.31. Found: C, 33.60; H, 2.84; N, 18.99; S, 32.91. IR ν_{max}^{Nujol} cm^{-1}: 3190 (>NH), 2130 (SCN), 1715 (>C=O). NMR (DMF) τ (J=Hz): 8.66 (3H, t, $J=7.0$), 5.64 (2H, q, $J=7.0$), 1.88 (1H, s), *ca.* −2.10 (1H), *ca.* −3.30 (1H). UV λ_{max}^{EtOH} mμ (ε): 248 (15600), 263 (15200), 314 (10800). Ethyl-N-(5-thiocyanato-2-yl)thiourea (**27-h**)*, 0.05 g, pale yellow prisms from benzene, mp 194—196°. *Anal.* Calcd. for $C_7H_7O_2N_3S_2$:

C, 36.69; H, 3.08; N, 18.34; S, 27.92. Found: C, 36.24; H, 3.00; N, 18.32; S, 27.79. IR ν_{max}^{Nujol} cm^{-1}: 3120 (>NH), 2150 (SCN), 1730 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.58 (3H, t, J=7.0), 5.62 (2H, q, J=7.0), 2.32 (1H, s), *ca.* −1.36 (1H). UV λ_{max}^{EtOH} mμ (ε): 271 (11500). *This compound (**27-h**) agreed with the sample prepared from **24-h** and ethyl chloroformate in the presence of triethyl amine.

Reaction of 23 with 2-Amino-5-nitrothiazole (24-i)——In the reaction of 1.45 g of **23** and 1.45 g of **24-i**, two products (**26-i** and **27-i**), besides 0.83 g **24-i** and 0.018 g of **28**, were isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(5-nitrothiazol-2-yl)thiourea (**26-i**), 0.80 g, pale yellow needles from ethyl acetate, mp 173—174° (decomp.). *Anal.* Calcd. for $C_7H_7O_4N_4S_2$: C, 30.44; H, 2.92; N, 20.29; S, 23.17. Found: C, 30.43; H, 2.83; N, 20.54; S, 23.42. IR ν_{max}^{Nujol} cm^{-1}: 3150 (>NH), 1730 (>C=O). NMR [$(CD_3)_2C$=O] τ (J=Hz): 8.65 (3H, t, J=7.0), 5.51 (2H, q, J=7.0), 1.46 (1H, s), *ca.* −0.92 (1H), *ca.* −3.32 (1H). UV λ_{max}^{EtOH} mμ (ε): 240 (15700), 277.5 (11900). 354 (10300), 432.5 (5900). Ethyl-N-(5-nitrothiazol-2-yl)carbamate (**27-i**)*, 0.05 g, pale yellow needles from ethyl acetate, mp 197—198°. *Anal.* Calcd. for $C_6H_7O_4N_3S$: C, 33.19; H, 3.24; N, 19.35; S, 14.73. Found: C, 33.61; H, 3.34; N, 11.05; S, 14.67. IR ν_{max}^{Nujol} cm^{-1}: 3160 (>NH), 1735 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.58 (3H, t, J=7.0), 5.54 (2H, q, J=7.0), 1.72 (1H, s), *ca.* −1.60 (1H). UV λ_{max}^{EtOH} mμ (ε): 231 (6600), 340 (11400), 417.5 (2600). *This compound (**27-i**) agreed with the sample prepared from **24-i** and ethyl chloroformate in the presence of triethyl amine.

Reaction of 23 with 2-Amino-4-methylthiazole (24-j)——In the reaction of 1.45 g of **23** and 1.16 g of **24-j**, two products (**26-j** and **27-j**), besides 0.022 g of **28**, were isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(4-methylthiazol-2-yl)thiourea (**26-j**), 2.14 g, colorless needles from isopropyl ether, mp 140—141° (decomp.). *Anal.* Calcd. for $C_8H_{11}O_2N_3S_2$: C, 39.17; H, 4.52; N, 17.12; S, 26.15. Found: C, 39.09; H, 4.56; N, 17.32; S, 26.01. IR ν_{max}^{Nujol} cm^{-1}: 3200 (>NH), 1725 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.66 (3H, t, J=7.0), 7.61 (3H, d, J=1.0), 5.68 (2H, q, J=7.0), 3.38 (1H, q, J=1.0), *ca.* 0.89 (1H), *ca.* −2.70 (1H). UV λ_{max}^{EtOH} mμ (ε): 228 (10000), 264 (14900), 3310 (10700). Ethyl-N-(4-methylthiazol-2-yl)-carbamate (**27-j**)*, 0.08 g, colorless needles from isopropyl ether, mp 103—104°. *Anal.* Calcd. for $C_7H_{10}O_2N_2S$: C, 45.16; H, 5.41; N, 15.05; S, 17.19. Found: C, 44.46; H, 5.50; N, 15.20; S, 17.10. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1720 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.66 (3H, t, J=7.0), 7.62 (3H, d, J=1.0), 5.68 (2H, q, J=7.0), 3.53 (1H, q, J=1.0), *ca.* −0.92 (1H). UV λ_{max}^{EtOH} mμ (ε): 261.7 (7800). *This compound (**27-j**) agreed with the sample prepared from **24-j** and ethyl chloroformate in the presence of triethyl amine.

Reaction of 23 with 2-Amino-4-phenylthiazole (24-k)——In the reaction of 1.45 g of **23** and 1.76 g **24-k**, only one product **26-k**, besides 0.14 g of **24-k**, was isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(4-phenylthiazol-2-yl)thiourea (**26-k**), 2.47 g, pale yellow needles from benzene, mp 181—182° (decomp.). *Anal.* Calcd. for $C_{13}H_{13}O_2N_3S_2$: C, 50.79; H, 4.26; N, 13.67; S, 20.86. Found: C, 50.85; H, 4.45; N, 13.61; S, 20.68. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1736 (>C=O). NMR [$(CD_3)_2C$=O] τ (J=Hz): 8.65 (3H, t, J=7.0), 5.60 (2H, q, J=7.0), 2.72—2.40 (3H, m), 2.48 (1H, s), 2.16—1.88 (2H, m), *ca.* −0.45 (1H), *ca.* −3.22 (1H). UV λ_{max}^{EtOH} mμ (ε): 236 (26500), 264 (27600), 320 (10300).

Reaction of 23 with 2-Aminobenzothiazole (24-l)——In the reaction of 1.45 g of **23** and 1.50 g of **24-l**, two compounds (**26-l** and **27-l**), besides 0.098 g of **24-l**, were isolated by column coromatography on silica gel. N-Ethoxycarbonyl-N′-(2-benzothiazolyl)thiourea (**26**-l), 1.87 g, pale yellow prisms from acetone, mp 189—190° (decomp.). *Anal.* Calcd. for $C_{11}H_{11}O_2N_3S_2$: C, 46.92; H, 3.94; N, 14.99; S, 22.78. Found: C, 46.97; H, 4.09; N, 14.86; S, 22.64. IR ν_{max}^{Nujol} cm^{-1}: 3200 (>NH), 1720 (>C=O). NMR (DMF) τ (J=Hz): 8.65 (3H, t, J=7.0), 5.64 (2H, q, J=7.0), 2.78—1.78 (4H, m), *ca.* −1.88 (1H), *ca.* −3.17 (1H). UV λ_{max}^{EtOH} mμ (ε): 258.5 (23800), 307 (22400). Ethyl-N-(2-benzothiazolyl)carbamate (**27-l**)*, 0.34 g, colorless needles from isopropyl ether, mp 213—214°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2S$: C, 54.05; H, 4.54; N, 12.61; S, 14.40. Found: C, 53.99; H, 4.60; N, 12.62; S, 14.32. IR ν_{max}^{Nujol} cm^{-1}: 3150 (>NH), 1727 (>C=O). NMR (DMF) τ (J=Hz): 8.67 (3H, t, J=7.0), 5.72 (2H, q, J=7.0), 2.90—1.88 (4H, m), *ca.* −2.12 (1H). UV λ_{max}^{EtOH} mμ (ε): 265 (14700). *This compound (**27-l**) agreed with the sample prepared from **24-l** and ethyl chloroformate in the presence of triethyl amine.

Reaction of 23 with 2-Amino-4,5-dimethylthiazol (24-m)——In the reaction of 1.45 g of **23** with 1.30 g of **24-m**, two compounds (**26-m** and **27-m**), besides 0.026 g of **28**, were isolated by column chromatography on silica gel. N-Ethoxycarbonyl-N′-(4,5-dimethylthiazol-2-yl)thiourea (**26-m**), 2.20 g, colorless needles from ethyl acetate, mp 162—163° (decomp.). *Anal.* Calcd. for $C_9H_{13}O_2N_3S_2$: C, 41.70; H, 5.60; N, 16.21; S, 24.68. Found: C, 41.86; H, 5.10; N, 16.29; S, 24.34. IR ν_{max}^{Nujol} cm^{-1}: 3200 (>NH), 1720 (>C=O). NMR [$(CD_3)_2C$=O] τ (J=Hz): 8.68 (3H, t, J=7.0), 7.78 (3H, s), 7.70 (3H, s), 5.66 (2H, q, J=7.0), *ca.* −0.34 (1H), *ca.* −2.14 (1H). UV λ_{max}^{EtOH} mμ (ε): 228.5 (8600), 264. 5(14800), 320 (10500). Ethyl-N-(4,5-dimethylthiazol-2-yl)carbamate (**27-m**)*, 0.012 g, colorless needles from benzene, mp 139—140°. *Anal.* Calcd. for $C_8H_{12}O_2N_2S$: C, 47.97; H, 6.04; N, 13.99; S, 15.98. Found: C, 47.94; H, 6.01; N, 13.76; S, 16.10. IR ν_{max}^{Nujol} cm^{-1}: 3270 (>NH), 1720 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.66 (3H, t, J=7.0), 7.73 (6H, s), 5.70 (2H, q, J=7.0), *ca.* −1.52 (1H). UV λ_{max}^{EtOH} mμ (ε): 269 (9300). *This compound (**27-m**) agreed with the sample prepared from **24-m** and ethyl chloroformate in the presence of triethyl amine.

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