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Studies on Organic Sulfur Compounds. XIV.[1] The Reaction of N-Alkoxycarbonyl-N′-(2-thiazolyl)thioureas with Some Oxidants[2]

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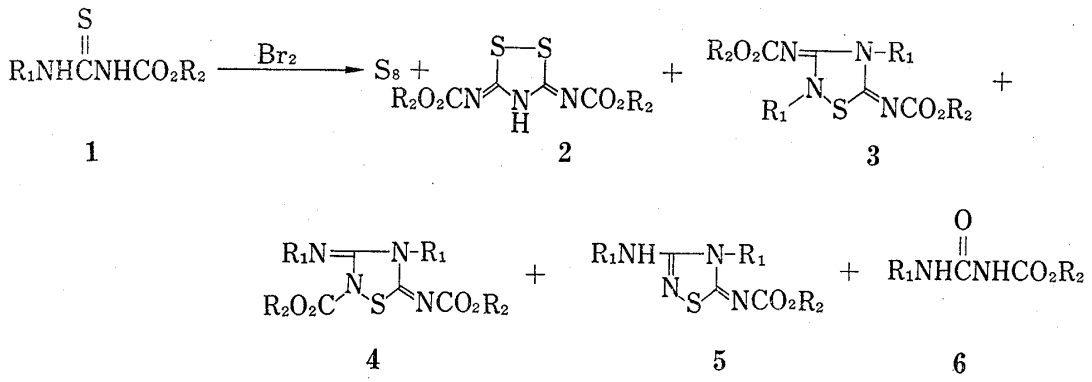
N-Alkoxycarbonyl-N′-(2-thiazolyl)thioureas were reacted with some oxidants, such as bromine, benzoyl peroxide, hypobromous acid and N-bromosuccinimide, to afford 2-alkoxycarbonylimino-thiazolo[3,2-*b*]thiadiazolines (X). Furthermore, from the reaction mixtures of N-ethoxycarbonyl-N′-(2-thiazolyl)thiourea (**12**) with bromine in chloroform, N-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline hydrobromide monohydrate (**14**) was obtained, which was easily dehydrobrominated to form 2-ethoxycarbonylimino-thiazolo-[3,2-*b*]thiadiazoline (**13**) by treatment with large quantities of water. This paper describes particularly in detail about the structures of **13** and **14**.

There are several reports[4–9] concerning the oxidation reaction of amidinylthioureas and β-imino-thioamides. However, the studies on the oxidation of the thioureas containing a heterocyclic moiety have not been appeared. In the previous paper,[1] we reported the reaction of alkoxycarbonylthioureas (**1**) with bromine to afford sulfur and five other products (**2**, **3**, **4**, **5** and **6**). This paper describes the oxidation of some N-(2-thiazolyl)thioureas which are structurally regarded as a kind of amidinylthiourea.



In the reaction of N-ethyl-N′-(2-thiazolyl)thiourea (**7**) with equimolecular quantities of bromine in chloroform, only N-ethyl-N′-(5-bromothiazol-2-yl)thiourea (**8**) was isolated. Furthermore, this product was converted oxidatively to N-ethyl-N′-(5-bromothiazol-2-yl)urea

1) Part XIII: M. Nagano, M. Oshige, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2396 (1973).
2) This was presented at the 5th Symposium of Heterocyclic Chemistry, Gifu, Novemver, 1972. Abstract Paper, pp. 73—76.
3) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
4) F. Kurzer, *J. Chem. Soc.*, **1955**, 1.
5) P.K. Srivastava and Y. Ramachandra Rao., *J. Indian Chem. Soc.*, **40**, 803 (1963).
6) J. Goerdeler and M.W. Pohland, *Chem. Ber.*, **94**, 2950 (1961).
7) J. Goerdeler and H. Horm, *Chem. Ber.*, **96**, 1551 (1963).
8) J. Goerdeler and U. Keuser, *Chem. Ber.*, **97**, 3106 (1964).
9) J. Goerdeler and J. Gnad, *Chem. Ber.*, **98**, 1531 (1965).

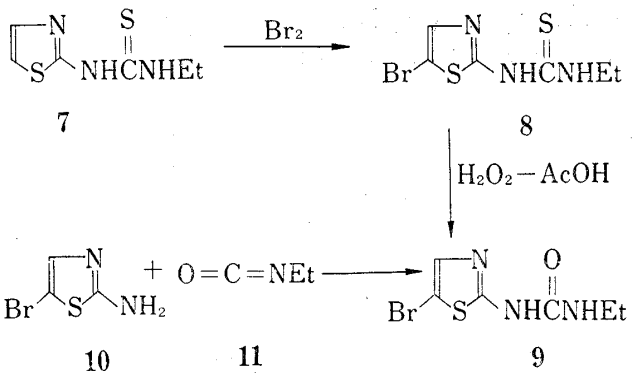


Chart 1

(**9**), which was obtained by the addition reaction of 2-amino-5-bromothiazole (**10**) to ethyl isocyanate (**11**), by treatment with hydrogen peroxide.

N-Ethoxycarbonyl-N′-(2-thiazolyl) thiourea[10] (**12**) was reacted with bromine in acetic acid, and the reaction solution was neutralized with ammonia water to give 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline (**13**). When **12** was treated with bromine in chloroform, the resulting solid was recrystallized to afford 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline hydrobromide monohydrate (**14**). The structures of **13** and **14** are discussed in detail in this paper. The molecular formula of **13** was expressed as $C_7H_7O_2N_3S_2$ by the elemental analysis and the mass spectrum: $M^+=229$, and the infrared (IR) spectrum showed a strong peak at 1580 cm^{-1}, but no absorption band appeared in the range of 1800 to 1600 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum consisted of a triplet at δ 1.29 due to three methyl

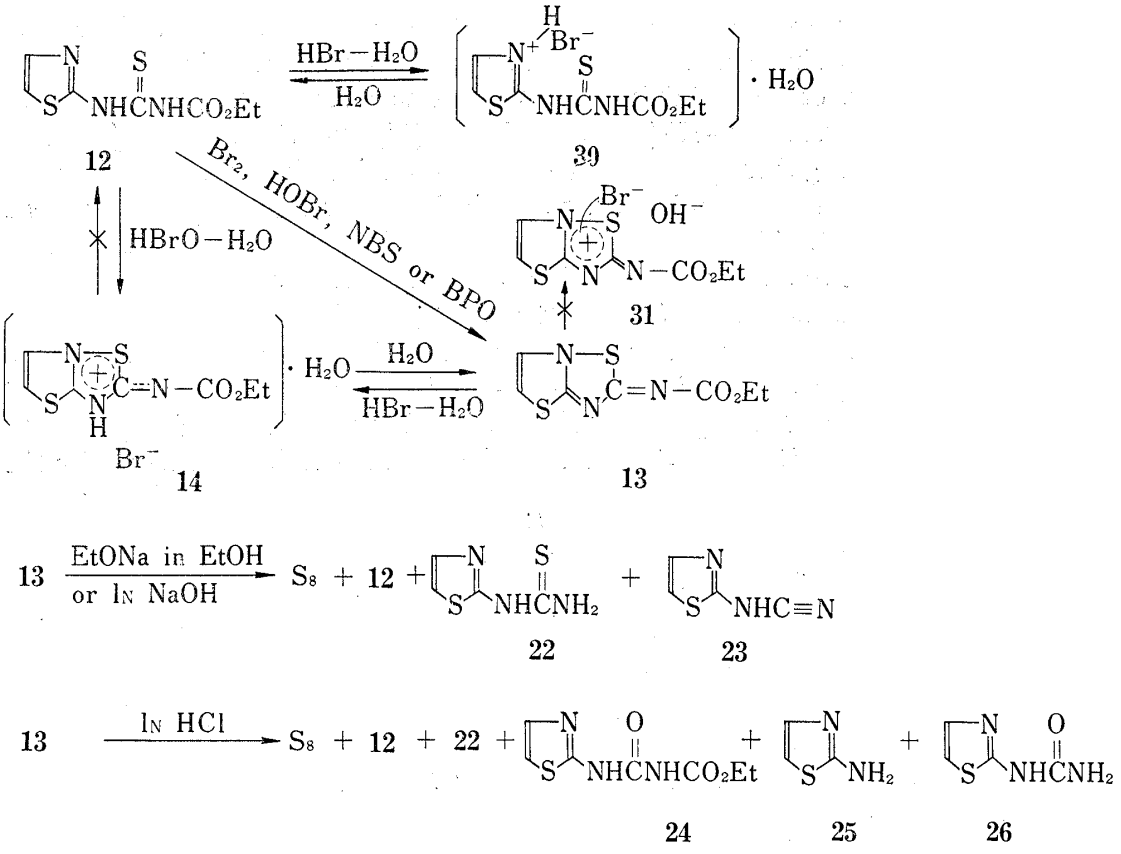


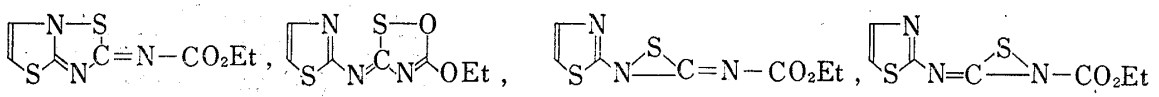
Chart 2

protons ($J=7.0$ Hz), a quartet at δ 4.27 due to two methylene protons ($J=7.0$ Hz) and a pair of doublets at δ 7.55 and 8.18 corresponding to two ring protons ($J=4.8$ Hz). In the ultraviolet (UV) spectrum, the absorption maximum at 308 mμ shifted to 295 mμ on the addition of hydrochloric acid. These data suggested that the structure of **13** may be one

10) M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 2618 (1972).

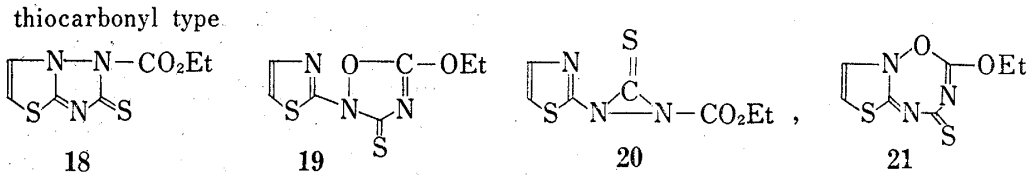
of the eight structures which comprise four sulfide types (**13**, **15**, **16** and **17**) and four thiocarbonyl types (**18**, **19**, **20** and **21**). To confirm the structure of **13** as belonging to either of

sulfide type



13 15 16 17

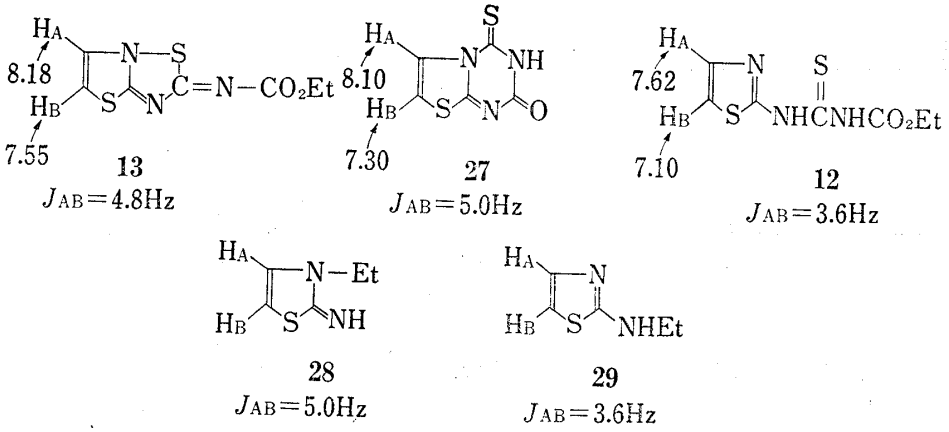
thiocarbonyl type



18 19 20 21

these two types, **13** was allowed to hydrolize in the presence of a base and an acid. The compound (**13**) was treated with sodium ethoxide in ethyl alcohol or 1N sodium hydroxide to afford sulfur, **12**, N-(2-thiazolyl)thiourea (**22**) and 2-cyanaminothiazole (**23**). These products were confirmed on the basis of the elemental analyses and spectral data. Among these reaction products, **22** was also obtained in a good yield by treatment of **12** with 1N sodium hydroxide under the same reaction conditions as those mentioned above. The formation of **12** in the reaction of **13** with a base suggests that **13** has a certain oxidative power. The compound (**13**) was reacted with equimolecular amounts of phenylhydrazine to give **12** in 93% yield.

A solution of **13** in acetone containing 1N hydrochloric acid was refluxed for 2 hr to afford sulfur, **12**, **22**, N-ethoxycarbonyl-N'-(2-thiazolyl)urea (**24**), 2-aminothiazole (**25**) and N-2-thiazolylurea (**26**). Among these products, **25** or **26** was obtained in a good yield by the hydrolysis of **12** or **23** with 1N hydrochloric acid, respectively, under the same reaction conditions as those in the case of **13**. These experiments make it clear that **13** doesn't correspond to a thiocarbonyl type, but to a sulfide type. In order to determine the structure of **13** corresponding to one of the four structures (**13**, **15**, **16** and **17**), the chemical shifts and the coupling constants of the two ring protons of **13** were compared with those of the two ring protons of other model compounds, namely thiazolo[3,2-*a*]-*s*-triazine-4-thio-2-one (**27**; δ 8.10 and 7.30, J_{AB}=5.0 Hz),[10] **12** (δ 7.62 and 7.10, J_{AB}=3.6 Hz), 3-ethyl-2-iminothiazoline (**28**; J_{AB}=5.0 Hz)[11] and 2-(ethylamino)thiazole (**29**; J_{AB}=3.6 Hz).[12] The high resolution technique for the mass



spectrum of **13** shows that the peaks at *m/e* 229 ($C_7H_7O_2N_3S_2$, mol.wt.,obs.=228.993, mol. wt.,calc.=228.998), *m/e* 185 ($C_5H_3ON_3S_2$, mol.wt.,obs.=184.972, mol.wt.,calc.=184.972),

11) J. Drucy, *J. Helv. Chim. Acta*, **24E**, 226 (1941).
12) I.A. Kaye and C.L. Parris, *J. Org. Chem.*, **17**, 737 (1952).

m/e 184 ($C_5H_2ON_3S_2$, mol.wt.,obs.=183.964, mol. wt.,calc.=183.964), *m/e* 157 ($C_4H_3N_3S_2$, mol.wt.,obs.=156.977, mol.wt.,calc.=156.977), *m/e* 152 ($C_5H_2ON_3S$, mol.wt.,obs.=151.990, mol.wt.,calc.=151.992), *m/e* 142 ($C_4H_2N_2S$, mol.wt.,obs.=141.964, mol.wt.,calc.=141.966), *m/e* 130 ($C_3H_2N_2S_2$, mol.wt.,obs.=129.966, mol.wt.,calc.=129.966), *m/e* 125 ($C_4H_3N_3S$, mol. wt.,obs.=125.005, mol.wt.,calc.=125.005), *m/e* 115 (C_3HNS_2, mol.wt.,obs.=114.951, mol. wt.,calc.=114.955) and *m/e* 104 ($C_2H_2NS_2$, mol.wt.,obs.=103.967, mol.wt.,calc.=103.963) correspond to the fragments of the structures in Fig. 1. From these facts, the most suitable

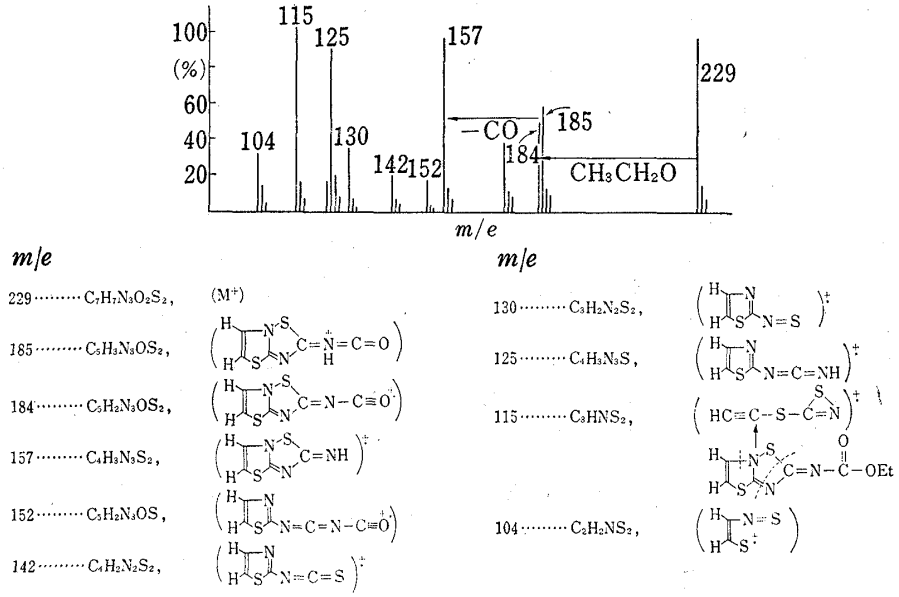


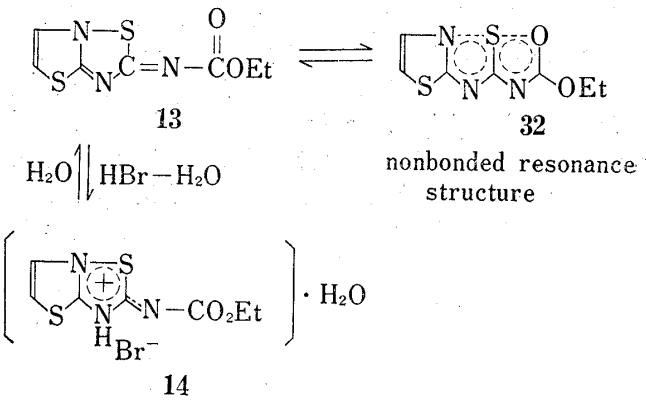
Fig. 1. Mass Spectrum of 2-Ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline (**13**)

structure representing **13** would be 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline. The compound (**13**) was also easily prepared by using other oxidants, such as hypobromous acid (HBrO), N-bromosuccinimide (NBS) and benzoyl peroxide, instead bromine. However, in the reaction of **12** with hydrogen peroxide (H_2O_2), **13** could not be obtained, but only **24** was isolated in a good yield. The yields of **13** in the reaction of **12** with various oxidants are summarized in Table I.

TABLE I. Yields of 2-Ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline (**13**) in the Reaction of **12** with some Oxidants

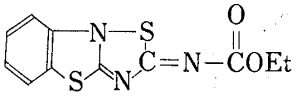
Oxid. reagents	Solvents	Yield (%)
Br_2	AcOH	65(%)
Br_2	$CHCl_3$	90(%)
HBrO	$CHCl_3$	83(%)
NBS	EtOH	79(%)
BPO	dichloroethane	88(%)
H_2O_2(30%)	AcOH	not isolated

but **13** was recovered unchanged. Furthermore, the IR spectrum of N-ethoxycarbonyl-N′-(2-thiazolyl)thiourea hydrobromide monohydrate (**30**), which was obtained by treatment of **12** with 48% hydrobromic acid, was different from that of **14**. From these facts, the compound (**14**) was regarded as the hydrobromide of **13**, namely 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline hydrobromide monohydrate. It is very interesting that the IR absorption band of the carbonyl bond of 13 appears at 1580 cm^{-1} and that of **14**, which is formed by the protonation of **13**, appears in a normal absorption range (1680 cm^{-1}). If the structure of **13** has a nonbonded resonance structure (**32**) in a fairly high extent, the difference between the IR spectrum of **13** and that of **14** could be reasonably explained.



Some other N-alkoxycarbonyl-N′-(2-thiazolyl)thioureas were allowed to react with bromine under same reaction conditions as those in the case of **12** to give the corresponding thiazolothiadiazoline derivatives in good yields. The yields of 2-alkoxycarbonylimino-thiazolo-[3,2-*b*]thiadiazolines (X) are summarized in Table II.

Table II. Yields of 2-Alkoxycarbonylimino-thiozolo-[3,2-*b*]thiadiazolines (X)

Compd. No.	R_1	R_2	R_3	mp (°C)	Yield (%)
34	H	H	Me	167—168	91
13	H	H	Et	165—166	90
36	H	H	*n*-Pr	139—141	93
38	H	H	iso-Pr	156—158	91
40	H	H	*t*-Bu	120—122	92
42	H	H	iso-Bu	125—126	93
44	H	Me	Et	181—183	91
46	H	Et	Et	175—177	92
48	H	*n*-Pr	Et	172—174	91
50	H	*n*-Bu	Et	168—170	92
52	H	Br	Et	194—196	88
54	Me	H	Et	187	87
56	Ph	H	Et	210—212	67
58				205—207	87

Experimental[13]

Synthesis of N-Ethyl-N′-(2-thiazolyl)thiourea (7)——The mixtures of 2-aminothiazole (**25**; 30.0 g) and ethyl isothiocyanate (22.5 g) in AcOEt (200 ml) were refluxed for 2 days, and the precipitated crystals were

13) All melting points were uncorrected. NMR spectra were obtained in the specified solvents on a Varian A-60 spectrometer with tetramethyl silane as an internal standard. Mass spectra were determined on a JEOL-JMS-OISG spectrometer.

collected on a glass filter and recrystallized from benzene to give 25.0 g of N-ethyl-N′-(2-thiazolyl)thiourea (**7**), colorless needles, mp 136—137°. *Anal.* Calcd. for $C_6H_9N_3S_2$: C, 38.50; H, 4.80; N, 22.45; S, 34.20. Found: C, 38.10; H, 4.71; N, 22.10; S, 34.11. IR ν_{max}^{Nujol} cm^{-1}: 3160 and 3120 (>NH). NMR (DMSO-d_6) δ (J=Hz): 1.08 (3H, t, J=7.0), 5.23 for two methylene protons (–NH–C<u>H</u>$_2$–CH_3, d, q, J_1=5.0, J_2=7.0), 7.06 (1H, d, J=3.8), 7.40 (1H, d, J=3.8), *ca.* 0.44 (2H, broad).

Reaction of N-Ethyl-N′-(2-thiazolyl)thiourea (7) with Bromine——To a solution of **7** (5.6 g) in $CHCl_3$ (450 ml), bromine (5.1 g) in $CHCl_3$ (50 ml) was added dropwise at room temperature, and then the reaction solution was stirred for 1 hr at room temperature followed by refluxing for 1 hr. After removal of $CHCl_3$, the residue was poured into ice water and neutralized with ammonia water. The precipitate was recrystallized from benzene to afford 3.5 g of N-ethyl-N′-(5-bromothiazole-2-yl)thiourea (**8**) as colorless needles, mp 162—163°. *Anal.* Calcd. for $C_6H_8N_3S_2Br$: C, 27.07; H, 3.02; N, 15.78; S, 24.09; Br, 30.02. Found: C, 27.22; H, 2.96; N, 15.60; S, 24.36; Br, 30 11. IR ν_{max}^{Nujol} cm^{-1}: 3330 and 3220 (>NH). NMR (DMSO-d_6) δ (J=Hz): 1.12 (3H, t, J=7.0), 3.51 for two methylene protons (–NH–C<u>H</u>$_2$–CH_3, d, q, J_1=4.5, J_2=7.0), 7.46 (1H, s), *ca.* 8.43 (1H, broad), *ca.* 11.52 (1H, broad).

Oxidation of N-Ethyl-N′-(5-bromothiazol-2-yl)thiourea (8) with Hydrogen Peroxides——To a solution of **8** (0.27 g) in AcOH (20 ml), 30% H_2O_2 (10 ml) was added dropwise at a range of 5 to 10°, and the reaction mixture was poured into ice water (150 ml), and the precipitate was collected on a glass filter and dried to be recrystallized from AcOEt to afford 0.12 g fo N-ethyl-N′-(5-bromothiazol-2-yl)urea (**9**), colorless needles, mp 197—199° (decomp.). *Anal.* Calcd. for $C_6H_8ON_3SBr$: C, 28.81; H, 3.22; N, 16.79; S, 12.81; Br, 31.94. Found: C, 28.86; H, 3.26; N, 16.42; S, 12.67; Br, 32.13. IR ν_{max}^{Nujol} cm^{-1}: 3230, 3165 and 3110 (>NH). NMR (DMSO-d_6) δ (J=Hz): 1.10 (3H, t, J=7.0,) 3.16 for two methylene protons (–NH–C<u>H</u>$_2$–CH_3, d, q, J_1=4.5, J_2=7.0), 7.32 (1H, s), *ca.* 6.46 (1H, broad), *ca.* 10.54 (1H, broad).

Synthesis of N-Ethyl-N′-(5-bromothiazol-2-yl)urea (9)——The mixtures of 2-amino-5-bromothiazole (**10**: 1.70 g) and ethyl isocyanate (**11**: 1.0 g) in acetone (50 ml) were refluxed for four days, and after removal of acetone, the resulting residue was eluted with AcOEt–benzene on silica gel to give 1.04 g of N-ethyl-N′-(5-bromothiazol-2-yl)urea (**9**).

Reaction of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea (12) with Bromine——a) To a solution of **12** (2.31 g) in acetic acid (30 ml), bromine (1.68 g) in acetic acid (10 ml) was added dropwise at 10°, and the reaction solution was stirred for 1 hr at room temperature and subsequently poured into ice water (500 ml). After the aqueous solution was neutralized with ammonia water, the resulting solid was recrystallized from ethyl alcohol to afford 1.50 g of 2-ethoxycarbonyl-thiazolo[3,2-*b*]thiazoline (**13**), colorless needles, 168—169°(decomp.). *Anal.* Calcd. for $C_7H_7O_2N_3S_2$: C, 36.69; H, 3.08; N, 18.34; S, 27.92. Found: C, 36.29; H, 3.01; N, 18.41; S, 28.03. UV λ_{max}^{EtOH} mμ (ε): 308 (17000).

b) To a solution of **12** (2.31 g) in $CHCl_3$ (250 ml), bromine (1.68 g) was added at room temperature, and the reaction mixture were stirred for 1 hr at room temperature followed by refluxing for 1 hr. After removal of $CHCl_3$, the resulting solid was recrystallized from EtOH to give 1.58 g of 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline hydrobromide monohydrate (**14**), colorless prisms, mp 137—139° (decomp.). *Anal.* Calcd. for $C_7H_{10}O_3N_3S_2Br$: C, 25.61; H, 3.07; N, 12.80; S, 19.53; Br, 24.34. Found: C, 25.73; H, 3.20; N, 12.80; S, 19.69; Br, 24.74.

Reaction of 2-Ethoxycarbonyl-thiazolo[3,2-*b*]thiadiazoline (13) with Sodium Ethoxide——To a solution of 2.31 g of **13** in 50 ml of EtOH, ethanolic sodium ethoxide, which was prepared from Na (0.3 g) and EtOH (50 ml), was added under ice cooling, and the reaction mixture was stirred for 4 hr at room temperature, and after removal of EtOH under reduced pressure, the residue was poured into ice water (100 ml) and neutralized with 1N HCl. The reaction products were extracted with $CHCl_3$ (200 ml), and the $CHCl_3$ layer was washed with H_2O, dried over anhyd. Na_2SO_4, and after removal of drying agent and solvent, the residue was eluted with AcOEt–benzene on silica gel to afford 0.12 g of sulfur, 1.2 g of **12**, 0.1 g of **22** and 0.5 g of **23**. N-(2-Thiazolyl)thiourea (**22**), colorless needles from AcOEt, mp 186—188°. *Anal.* Calcd. for $C_4H_5N_3S_2$: C, 30.19; H, 3.17; N, 26.41; S, 40.23. Found: C, 30.37; H, 3.21; N, 26.18; S, 40.15. Mass Spectrum: M^+=159. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3270, 3170 and 1608 (>NH and –NH_2). NMR (DMSO-d_6) δ (J=Hz): 7.14 (1H, d, J=4.0), 7.46 (1H, d, J=4.0), *ca.* 8.76 (2H, broad), *ca.* 10.60 (1H, broad). 2-Cyanaminothiazole (**13**), colorless needles from AcOEt–benzene, mp 146—148° (decomp.). *Anal.* Calcd. for $C_4H_3N_3S$: C, 38.40; H, 2.42; N, 33.60; S, 25.58. Found: C, 38.26; H, 2.67; N, 32.24; S, 25.13. IR ν_{max}^{Nujol} cm^{-1}: 31.00 (>NH). NMR (DMSO-d_6) δ (J=Hz): 6.78 (1H, d, J=4.0), 7.24 (1H, d, J=4.0), *ca.* 13.30 (1H, broad). UV λ_{max}^{EtOH} mμ (ε): 230 (2300), 284 (13400).

Reaction of 2-Ethoxycarbonyl-thiazolo[3,2-*b*]thiadiazoline (13) with Sodium Hydroxide——A suspension of 2.29 g of **13** in 50 ml of 1N NaOH solution was stirred for 4 hr at room temperature followed by neutralizing with 1N HCl, and the reaction mixtures were extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4, and after removal of drying agent and solvent, the residue was chromatographed on silica gel (AcOEt–benzene) to afford 0.08 g of sulfur, 0.11 g of **12**, 0.93 g of **22** and 0.42 g of **23**.

Reaction of 1-Ethoxycarbonyl-3-(2-thiazolyl)thiourea (12) with Sodium Hydroxide——A suspension of **12** (2.31 g) in 1N NaOH solution (50 ml) was stirred for 4 hr at room temperature and neutralized with 1N HCl. The precipitate was collected on a glass filter followed by washing with H_2O to give 1.47 g of **22**.

Reaction of 2-Ethoxycarbonyl-thiazolo[3,2-*b*]thiadiazoline (13) with Phenylhydrazine——After a mixture of **13** (2.29 g) and phenylhydrazine (1.10 g) in EtOH (100 ml) was stirred for 3 hr, EtOH was evaporated under reduced pressure, and the residual solid was washed with ethyl ether to afford 2.15 g of **12**.

Reaction of 2-Ethoxycarbonylimino-thiazolo[3,2-*b*]thiazoline (13) with Hydrochloric Acid——A suspension of 2.29 g of **13** in 60 ml of 1N HCl solution was refluxed for 3 hr and neutralized with sodium carbonate, and H_2O was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel (AcOEt–benzene) to afford 0.14 g of sulfur, 0.735 g of **12**, 0.123 g of N-ethoxycarbonyl-N′-(2-thiazolyl)urea (**24**),[14] 0.136 g of **22**, 0.257 g of 2-aminothiazole (**25**) and 0.375 g of **26**. N-(2-Thiazolyl)urea (**26**), colorless needles from AcOEt, mp 203° (decomp.). *Anal.* Calcd. for $C_4H_5ON_3S$: C, 33.57; H, 3.52; N, 29.37; S, 22.36. Found: C, 33.28; H, 3.55; N, 28.96; S, 22.33. IR ν_{max}^{Nujol} cm^{-1}: 3490, 3320, 3260 and 3180 (>NH and $-NH_2$), 1720 (>C=O). NMR (DMSO-d_6) δ (J=Hz): *ca.* 6.36 (2H, broad), 7.04 (1H, d, J=4.0), *ca.* 7.36 (1H, d, J=4.0), *ca.* 10.40 (1H, broad).

Reaction of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea (12) with Hydrochloric Acid——A suspension of 0.23 g of **12** in 20 ml of 1N HCl solution was refluxed for 3 hr and neutralized with Na_2CO_3, and H_2O was evaporated under reduced pressure. The residue was dried and chromatographed on silica gel (benzene–AcOEt) to afford 0.10 g of sulfur and 0.04 g of Sulfur 2-aminothiazole (**25**).

Reaction of 2-Cyanaminothiazole (23) with Hydrochloric Acid——A suspension of 0.125 g of **23** in 10 ml of 1N HCl solution was refluxed for 3 hr and neutralized with Na_2CO_3, and H_2O was evaporated under reduced pressure. The residue was dried and chromatographed on silica gel (AcOEt) to afford 0.123 g of N-(2-thiazolyl)urea (**26**).

Reaction of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea (12) with Hypobromous Acid (HBrO)——To a solution of 2.31 g of **12** in $CHCl_3$ (300 ml), HBrO–H_2O, which was prepared from HgO (yellow, 3.0 g) and 3% Br_2–H_2O (3.0 g), was added dropwise under ice cooling and further, the reaction solution was stirred for 1 hr at same temperature. After removal of $CHCl_3$ under reduced pressure below 20°, the resulting residue was poured into H_2O (200 ml) and the precipitate was collected on a glass filter and dried in a vacuum to afford 1.80 g of 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline (**13**).

Reaction of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea (12) with Benzoyl Peroxide (BPO)——To a solution of 2.31 g of **12** in dichloroethane (200 ml), 2.90 g of BPO was added under ice cooling, and the reaction solution was stirred for 3 hr at room temperature, and after removal of solvent, the resulting residue was washed with ether and benzene to give 2.06 g of 2-ethoxycarbonyliminothiazolo[3,2-*b*]thiadiazoline (**13**).

Reaction of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea (12) with N-Bromosuccinimide (NBS)——To a solution of 2.31 g of **12** in EtOH (100 ml), 2.14 g of NBS was added under ice cooling, and after removal of EtOH under reduced pressure, the residue was washed with ether and dissolved in $CHCl_3$ (200 ml). The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4, and $CHCl_3$ was removed to afford 1.83 g of 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline (**13**).

Reaction of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea (12) with Hydrogen Peroxide (H_2O_2)——To a solution of 2.31 g of **12** in AcOH (50 ml), 30% H_2O_2 (10 ml) was added dropwise at a range of 10 to 15°, and the reaction mixture was poured into ice water (200 ml) and neutralized followed by extracting with $CHCl_3$ (200 ml). The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4, and after removal of drying agent and solvent, the resulting solid was recrystallized to afford 1.63 g of N-ethoxycarbonyl-N′-(2-thiazolyl)urea (**24**).

Synthesis of N-Ethoxycarbonyl-N′-(2-thiazolyl)thiourea Hydrobromide Monohydrate (30)——A mixture of 2.31 g of N-ethoxycarbonyl-N′-(2-thiazolyl)thiourea (**12**) and 5 ml of 48% HBr–H_2O in acetone (5 ml) was stirred for 2 hr at room temperature, and after removal of acetone and H_2O under reduced pressure at 20°, the resulting residue was recrystallized from EtOH–benzene to give N-ethoxycarbonyl-N′-(2-thiazolyl)-thiourea hydrobromide monohydrate (**30**), prisms, mp 139—140° (decomp.), 2.8 g. *Anal.* Calcd. for $C_7H_{12}O_3N_3S_2Br$: C, 25.45; H, 3.66; N, 12.72; S, 19.41; Br, 24.19. Found: C, 25.63; H, 3.75; N, 12.68; S, 19.58; Br, 24.23. IR ν_{max}^{Nujol} cm^{-1}: 3380 and 1625 for absorption bands of a latticewater, 3140 (>NH), 1738 and 1280 (>C(O)–O–). 1.65 g of **30** was suspended in 100 ml of H_2O, and the suspension was stirred for 1 hr at room temperature, and the deposited crystals were collected on a glass filter and dried in a vacuum to afford 1.06 g of **12**.

Synthesis of 2-Ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline Hydrobromide Monohydrate (14)——The mixture of 2.29 g of 2-ethoxycarbonylimino[3,2-*b*]thiadiazoline (**13**) and 5 ml of 48% HBr–H_2O in acetone (100 ml) was stirred for 1 hr at room temperature, and after removal of acetone and H_2O, the resulting residue was recrystallized from EtOH to afford 2.88 g of 2-ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline hydrobromide monohydrate*. *2.38 g of **14** was suspended in 100 ml of H_2O, and stirred for 1 hr, and an insoluble solid was collected on a glass filter and washed with H_2O and dried to give 2.08 g of **13**.

Reaction of 2-Ethoxycarbonylimino-thiazolo[3,2-*b*]thiadiazoline (13) with Hypobromous Acid (HBrO)——To a solution of 2.29 g of **13** in $CHCl_3$ (300 ml) HBrO–H_2O, which was prepared from HgO (yellow, 3.0 g) and 3% Br_2–H_2O (3.0 g), was added dropwise under ice cooling and the mixture was stirred for 1 hr. After

14) M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 74 (1973).

removal of $CHCl_3$ under reduced pressure at 20°, the resulting residue was recrystallized from EtOH to give 1.82 g of **13**.

General Method for the Reaction of N-Alkoxycarbonyl-N′-(2-thiazolyl)thioureas (A) with Bromine——To a solution of N-alkoxycarbonyl-N′-(2-thiazolyl)thioureas (A; 0.01 mole) in $CHCl_3$ (250 ml), bromine (0.0105 mole) in $CHCl_3$ (50 ml) was added dropwise at room temperature, and the reaction mixture was stirred for 1 hr at room temperature followed by refluxing for 1 hr. After removal of solvent, the resulting solid was washed with water until the pH value of the washings became to 6. The neutral substances were recrystallized from a suitable solvent to give 2-alkoxycarbonylimino-thiazolo[3,2-*b*]thiadiazolines (X).

Reaction of N-Methoxycarbonyl-N′-(2-thiazolyl)thiourea (33) with Bromine——2.17 g of **33** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to afford 1.95 g of 2-methoxycarbonylimino-thiazolo[3,2-*b*]thiazoline (**34**), colorless needles from AcOEt, mp 167—168° (decomp.). *Anal.* Calcd. for $C_6H_5O_2N_3S_2$: C, 33.48; H, 2.34; N, 19.52; S, 29.79. Found: C, 33.79; H, 2.50; N, 19.29; S, 29.74. IR ν_{max}^{Nujol} cm^{-1}: 1585, 1292 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 252 (3000), 308 (22400). NMR (DMSO-d_6) δ (*J*=Hz): 3.02 (3H, s), 7.56 (1H, d, *J*=4.8), 8.19 (1H, d, *J*=4.8).

Reaction of N-*n*-Prppoxycarbonyl-N′-(2-thiazolyl)thiourea (35) with Bromine——2.45 g of **35** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to afford 2.30 g of 2-*n*-propoxycarbonyl-imino-thiazolo[3,2-*b*]thiadiazoline (**36**), colorless needles from benzene, mp 139—141° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N_3S_2$: C, 39.49; H, 3.73; N, 17.27; S, 26.36. Found: C, 39.43; H, 3.72; N, 17.29; S, 26.37. IR ν_{max}^{Nujol} cm^{-1}: 1588 and 1288 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 251 (3000), 308 (23000). NMR [$(CD_3)_2CO$] δ (*J*=Hz): 0.98 (3H, t, *J*=6.5), 1.68 (2H, t, q, $J_1=J_2=6.5$), 4.23 (2H, t, *J*=6.5), 7.52 (1H, d, *J*=4.8), 8.10 (1H, d, *J*=4.8).

Reaction of N-iso-Propoxycarbonyl-N′-(2-thiazolyl)thiourea (37) with Bromine——2.45 g of **37** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to give 2.24 g of 2-iso-propoxy-carbonylimino-thiazolo[3,2-*b*]thiadiazoline (**38**), colorless needles from benzene, mp 156—158° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N_3S_2$: C, 39.49; H, 3.73; N, 17.27; S, 26.36. Found: C, 39.42; H, 3.91; N, 17.12; S, 26.11. IR ν_{max}^{Nujol} cm^{-1}: 1580 and 1300 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 251 (2900), 308 (23000). NMR [$(CD_3)_2CO$] δ (*J*=Hz): 1.32 (6H, d, *J*=6.6), 5.08 (1H, q, q, $J_1=J_2=6.6$), 7.48 (1H, d, *J*=4.8), 8.05 (1H, d, *J*=4.8).

Reaction of N-*n*-Butoxycarbonyl-N′-(2-thiazolyl)thiourea (39) with Bromine——2.59 g of **39** was reacted with 1.70 g of bromine by the general method to give 2.36 g of 2-*n*-butoxycarbonylimino-thiazolo[3,2-*b*]-thiadiazoline (**40**), colorless needles from isopropyl ether, mp 120—122.° *Anal.* Calcd. for $C_9H_{11}O_2N_3S_2$: C, 42.00; H, 4.31; N, 16.33; S, 24.92. Found: C, 41.68; H, 4.19; N, 16.43; S, 25.15. IR ν_{max}^{Nujol} cm^{-1}: 1580 and 1290 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 252 (2900), 308 (22900). NMR ($CDCl_3$) δ (*J*=Hz): 0.96 (3H, t, *J*=6.5), 1.12—2.22 (4H, m), 4.35 (2H, t, *J*=6.5), 7.18 (1H, d, *J*=4.8), 7.72 (1H, d, *J*=4.8).

Reaction of N-iso-Butoxycarbonyl-N′-(2-thiazolyl)thiourea (41) with Bromine——2.59 g of **41** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) to give 2.40 g of 2-iso-butoxycarbonylimino-thiazolo[3,2-*b*]thia-diazoline (**42**), pale yellow needles from isopropylether, mp 125—126°. *Anal.* Calcd. for $C_9H_{11}O_2N_3S_2$: C, 42.00; H, 4.31; N, 16.33; S, 24.92. Found: C, 41.82; H, 4.54; N, 16.14; S, 24.73. IR ν_{max}^{Nujol} cm^{-1}: 1590 and 1290 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 251 (2900), 308 (22400). NMR [$(CD_3)_2CO$] δ (*J*=Hz): 0.99 (6H, d, *J*=6.5), 2.09 (1H, q, q, t, $J_1=J_2=J_3=6.5$), 4.07 (2H, d, *J*=6.5), 7.53 (1H, d, *J*=4.5), 8.09 (1H, d, *J*=4.5).

Reaction of N-Ethoxycarbonyl-N′-(5-methylthiazol-2-yl)thiourea (43) with Bromine——2.45 g of **43** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) to give 2.22 g of 2-ethoxycarbonylimino-5-methyl-thiazolo[3,2-*b*]thiadiazoline (**44**), colorless needles from benzene, mp 181—183° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N_2S_2$: C, 39.49; H, 3.73; N, 17.27; S, 26.36. Found: C, 39.91; H, 3.66; N, 17.27; S, 26.32. IR ν_{max}^{Nujol} cm^{-1}: 1592 and 1270 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 251 (3300), 312 (22600). NMR (DMF) δ (*J*=Hz): 1.32 (3H, t, *J*=7.0), 2.55 (3H, d, *J*=2.0), 4.31 (2H, q, *J*=7.0), 1.98 (1H, q, *J*=2.0).

Reaction of N-Ethoxycarbonyl-N′-(5-ethylthiazol-2-yl)thiourea (45) with Bromine——2.59 g of **45** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to afford 2.37 g of 2-ethoxycarbonyl-imino-5-ethyl-thiazolo[3,2-*b*]thiadiazoline (**46**), colorless needles from benzene, mp 175—177° (decomp.). *Anal.* Calcd. for $C_9H_{11}O_2N_3S_2$: C, 42.00; H, 4.31; N, 16.33; S, 24.92. Found: C, 41.92; H, 4.58; N, 16.38; S, 24.90. IR ν_{max}^{Nujol} cm^{-1}: 1590 and 1280 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 251 (3300), 312.3 (23000). NMR ($CDCl_3$) δ (*J*=Hz): 1.15 (3H, t, *J*=7.0), 1.18 (3H, t, *J*=7.0), 2.84 (2H, q, d, $J_1=7.0$, $J_2=2.0$), 4.38 (2H, q, *J*=7.0), 7.35 (1H, t, *J*=2.0).

Reaction of N-Ethoxycarbonyl-N′-(5-*n*-propylthiazol-2-yl)thiourea (47) with Bromine——2.73 g of **47** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) to give 2.46 g of 2-ethoxycarbonylimino-5-*n*-propyl-thiazolo[3,2-*b*]thiadiazoline (**48**), colorless needles from benzene, mp 172—174°. *Anal.* Calcd. for $C_{10}H_{13}O_2N_3S_2$: C, 44.26; H, 4.83; N, 15.49; S, 23.63. Found: C, 44.62; H, 4.81; N, 15.67; S, 23.53. IR ν_{max}^{Nujol} cm^{-1}: 1590 and 1285 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 251 (3500), 312.3 (23900). NMR ($CDCl_3$) δ (*J*=Hz): 1.03 (3H, t, *J*=7.0), 1.38 (3H, t, *J*=7.0), 1.75 (2H, q, t, $J_1=J_2=7.0$), 2.78 (2H, t, d, $J_1=7.0$, $J_2=1.0$), 4.39 (2H, q, *J*=7.0), 7.35 (1H, t, *J*=1.0).

Reaction of N-Ethoxycarbonyl-N′-(5-*n*-butylthiazol-2-yl)thiourea (49) with Bromine——2.87 g of **49** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to give 2.62 g of 2-ethoxycar-bonylimino-5-*n*-butyl-thiazolo[3,2-*b*]thiadiazoline (**50**), colorless plates from benzene–*n*-hexane, mp 168—

170°. *Anal.* Calcd. for $C_{11}H_{15}O_2N_3S_2$: C, 46.29; H, 5.30; N, 14.73; S, 22.47. Found: C, 45.86; H, 5.40; N, 14.78; S, 22.55. IR ν_{max}^{Nujol} cm^{-1}: 1590 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 251 (4200), 314 (23400). NMR ($CDCl_3$) δ (*J*=Hz): 0.97 (3H, t, *J*=6.0), 1.38 (3H, t, *J*=7.0), 1.11—2.02 (4H, m), 2.80 (2H, t, d, J_1=7.0, J_2=1.0), 4.39 (2H, q, *J*=7.0), 7.33 (1H, t, *J*=1.0).

Reaction of N-Ethoxycarbonyl-N′-(5-bromothiazol-2-yl)thiourea (51) with Bromine——3.10 g of **51** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to give 2.72 g of 2-ethoxycarbonylimino-5-bromo-thiazolo[3,2-*b*]thiadiazoline (**52**), colorless needles from acetone, mp 194—196°. *Anal.* Calcd. for $C_7H_6O_2N_3S_2Br$: C, 27.28; H, 1.96; N, 13.64; S, 20.81; Br, 25.93. Found: C, 27.29; H, 1.81; N, 13.81; S, 20.64; Br, 25.70. IR ν_{max}^{Nujol} cm^{-1}: 1582 and 1275 (-C(O)-O-). UV λ_{max}^{EtOH} mμ (ε): 250 (4000), 316 (24700). NMR ($CDCl_3$) δ (*J*=Hz): 1.40 (3H, t, *J*=7.0), 4.42 (2H, q, *J*=7.0), 7.64 (1H, s).

Reaction of N-Ethoxycarbonyl-N′-(4-methylthiazol-2-yl)thiourea (53) with Bromine——2.45 g of **53** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to give 2.15 g of 2-ethoxycarbonyl-6-methyl-thiazolo[3,2-*b*]thiadiazoline (**54**), colorless needles from benzene, mp 187° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N_3S_2$: C, 39.49; H, 3.73; N, 17.27; S, 26.36. Found: C, 39.45; H, 3.86; N, 17.18; S, 26.13. IR ν_{max}^{Nujol} cm^{-1}: 1590 and 1285 (-C(O)-O-). UV λ_{max}^{EtOH} mμ (ε): 254 (2500), 311 (22400). NMR ($CDCl_3$) δ (*J*=Hz): 1.39 (3H, t, *J*=7.0), 2.48 (3H, d, *J*=1.0), 4.39 (2H, q, *J*=7.0), 6.69 (1H, q, *J*=1.0).

Reaction of N-Ethoxycarbonyl-N′-(4-phenylthiazol-2-yl)thiourea (55) with Bromine——3.07 g of **55** was reacted with 1.70 g of bromine in $CHCl_3$ (300 ml) by the general method to afford 2.04 g of 2-ethoxycarbonyl-6-phenyl-thiazolo[3,2-*b*]thiadiazoline (**56**), colorless needles from AcOEt, mp 210—212° (decomp.). *Anal.* Calcd. for $C_{13}H_{11}O_2N_3S_2$: C, 51.15; H, 3.63; N, 13.77; S, 20.96. Found: C, 51.05; H, 3.51; N, 13.77; S, 20.93. IR ν_{max}^{Nujol} cm^{-1}: 1580 and 1300 (-C(O)-O-). UV λ_{max}^{EtOH} mμ (ε): 258 (10200), 316 (20300).

Reaction of N-Ethoxycarbonyl-N′-(2-benzothiazolyl)thiourea (57) with Bromine——3.87 g of **57** was reacted with 1.70 g of bromine by the general method to give 2.44 g of 2-ethoxycarbonylimino-benzothiazolo-[3,2-*b*]thiadiazoline (**58**), colorless plates from acetone, mp 205—207° (decomp.). *Anal.* Calcd. for $C_{11}H_9O_2N_3S_2$: C, 47.32; H, 3.25; N, 15.05; S, 22.92. Found: C, 46.72; H, 2.87; N, 14.94; S, 22.52. IR ν_{max}^{Nujol} cm^{-1}: 1590 and 1285 (-C(O)-O). UV λ_{max}^{EtOH} mμ (ε): 252 (7000, sh.), 261.5 (12500), 280 (3600, sh,). 290 (5100, sh.), 322 (26900). NMR ($CDCl_3$) δ (*J*=Hz): 1.42 (3H, t, *J*=7.0), 4.43 (2H, q, *J*=7.0), 7.24—8.02 (4H, m).