[Chem. Pharm. Bull. 21(11)2396—2407(1973)]

UDC 547.496.3.04 : 546.14.04 : 547.79.057

Studies on Organic Sulfur Compounds. XIII.[1] The Oxidation Reaction of Alkoxycarbonylthioureas with Bromine

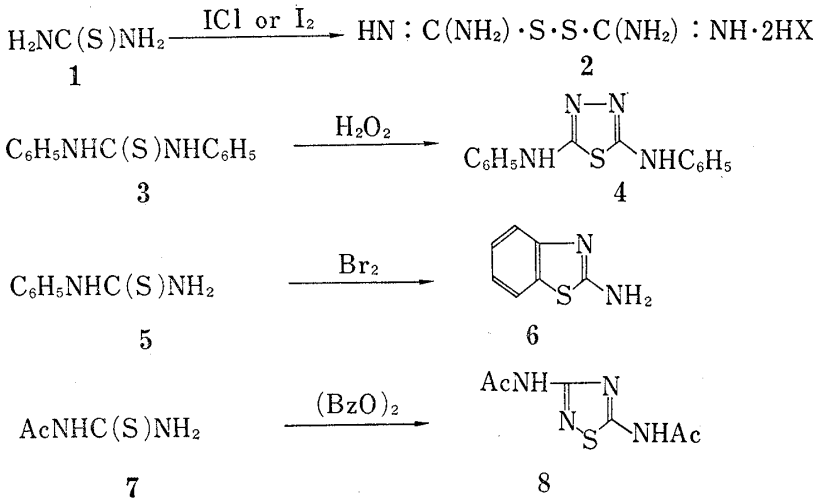
Mitsuo Nagano, Michiko Oshige,[2a] Takashi Matsui, Junzo Tobitsuka, and Kozo Oyamada[2b]

Central Research Laboratories[2a] and Agricultural Chemical Research Laboratories, Sankyo Co., Ltd.[2b]

(Received January 31, 1973)

N-Alkoxycarbonylthioureas (A) were reacted with bromine in $CHCl_3$ to afford sulfur, alkoxycarbonylureas (B), 3,5-bis(alkoxycarbonylimino)-1,2,4-dithiazolidines (C), 3,5-bis-(alkoxycarbonylamino)-1,2,4-thiadiazoles (D), 2-alkoxycarbonyl-5-alkoxycarbonylamino-3-imino-1,2,4-thiadiazolines (E) and 3-amino-5-alkoxycarbonylamino-1,2,4-thiadiazoles (F). This paper describes in detail on the confirmation of the structures of these reaction products.

Since G. McGowan[3] synthesized formamidine disulfide (**2**) by the reaction of thiourea (**1**) with chlorine iodine or iodine, various studies concerning the oxidation reaction of thioureas have been reported. For example, Suresh[4] has reported that N,N'-diphenylthiourea (**3**) was oxidized with hydrogen peroxide to give 2,5-bis(phenylamino)-1,3,4-thiadiazole (**4**).



Hunter[5] prepared 2-aminobenzothiazole (**6**) by the treatment of N-phenylthiourea (**5**) with bromine. Kinoshita, *et al.*[6] studied in detail the mass spectrum of 3,5-bis(acylamino)-1,2,4-thiadiazole (**8**) which was obtained by oxidation of N-acyl-thiourea (**7**) with benzoyl peroxide (BPO). However, there are no reports concerning the oxidation of alkoxycarbonylthioureas. The present paper describes the reaction of some alkoxycarbonylthioureas with bromine, and the confirmation of the structures of the reaction products is discussed.

To a solution of N-ethoxycarbonylthiourea (**9**; 14.8 g) in chloroform (300 ml), bromine (17.0 g) was added dropwise in an atmosphere of nitrogen under ice-cooling, and the reaction

1) Part XII: T. Matsui, M. Nagamo, J. Tobitsuka, and K. Oyamada *Yakugaku Zasshi*, **93**, 977 (1973).
2) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
3) G. McGowan, *J. Chem. Soc.*, **1886**, 190.
4) K.S. Suresh, *J. Indian Chem. Soc.*, **36**, 170 (1958).
5) R.F. Hunter, *J. Chem. Soc.*, **1925**, 2023 (1973).
6) T. Kinoshita and C. Tamura, *Tetrahedron Letters*, **1969**, 4963.

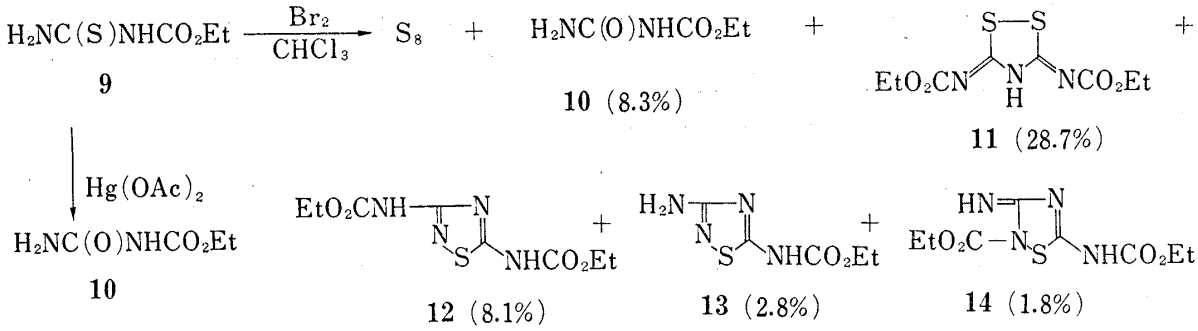


Chart 1

solution was refluxed for 2 hours and neutralized with ammonia. The reaction mixtures were chromatographed on silica gel to afford sulfur and five other products (**10**, **11**, **12**, **13** and **14**). The empirical formula of compound (**10**) was $C_4H_8O_3N_2$, and the infrared (IR) spectrum showed two absorption bands for two carbonyl groups at 1705 and 1742 cm^{-1}, and the nuclear magnetic resonance (NMR) spectrum consisted of a triplet due to three methyl protons ($C\underline{H}_3$-CH_2-, J=7.0 Hz) at 8.82 τ, a quartet due to two methylene protons ($CH_3C\underline{H}_2$-, J=7.0 Hz) at 5.85 τ and three amide protons approximately at 2.80 τ (2H) and 0.25 τ (1H). Furthermore, this compound was also obtained by oxidation of **9** with mercuric acetate. From these data, **10** was confirmed to be ethoxycarbonylurea which was prepared by treatment of nitrilotricarboxylate with ammonia.[7] The molecular formula of the compound (**11**) was expressed as $C_8H_{11}O_4N_3S_2$ by the elemental analysis and mass spectrum: M^+=277, and the IR spectrum showed two carbonyl bands at 1725 and 1640 cm^{-1}, and the NMR spectrum consisted of a triplet at 8.68 τ (methyl protons, J=7.0 Hz), a quartet at 5.68 τ (methylene protons, J=7.0 Hz) and a signal approximately at 1.95 τ (>NH, broad). This compound was hydrolyzed with 1N hydrochloric acid to give 1-ethoxycarbonyl-3-(N-ethoxycarbonylcarbamoyl)thiourea (**15**) in a good yield. This compound (**15**) was also obtained by the treatment of 1-ethoxycarbonyl-2-benzyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (**18**), which was prepared by the addition reaction of S-benzyl-N-ethoxycarbonylisothiourea (**16**) and ethoxycarbonyl isothiocyanate (**17**), with 1N hydrochloric acid. Compound (**11**) could be

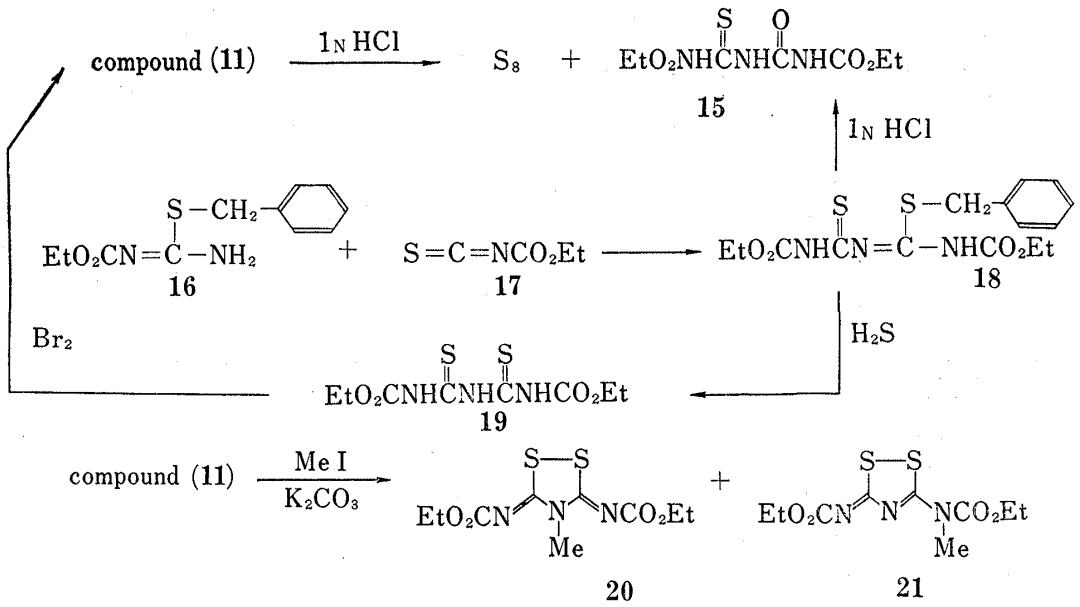
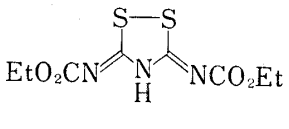


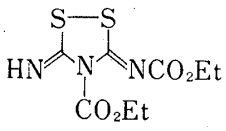
Chart 2

7) O. Diels, *Ber.*, **36**, 736 (1903).

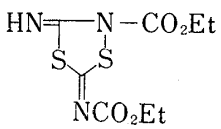
also synthesized by oxidation of 1-ethoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)-thiourea (**19**), which was easily prepared by the elimination of benzyl mercaptan from **18** with hydrogen sulfide according to the method of Dixit.[8] Furthermore, 11 was transformed to two methylated compounds (**20** and **21**) by treatment with methyliodide in the presence



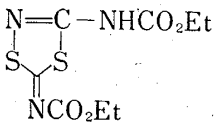
11



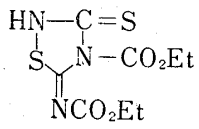
22



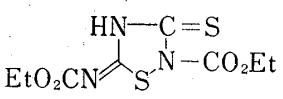
23



24



25



26

of potassium carbonate. These three experiments suggest that the possible structure of **11** is **11** or **26** among the postulated six cyclic compounds (**11**, **22**, **23**, **24**, **25** and **26**). To confirm the structure of **11** as being either of these two structural isomers (**11** and **26**), we tried to oxidize 1-ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)thiourea (**30**), which was prepared by the treatment of 2-benzyl-1-methoxycarbonylthiocarbamoyl)isothiourea (**28**) with hydrogen sulfide, with bromine. However, in the oxidation reaction of **30**, supposedly there are three reaction pathways (a, b-1 and b-2) for the formation of three five membered cyclic compound (**31**, **32** and **33**). Course a involves attack by one thiocarbonyl sulfur in **30** on the other sulfur to form **31**, and course b-1 or course b-2 proceeds *via* bond formation of the sulfur at the position **4** (or **2**) to the nitrogen at the position **1** (or **5**) to form **32** or **33**. Compound (**30**) was reacted with bromine under similar reaction conditions to those of **19** and bromine to give only one product. If the oxidation product of **30** is **32** or **33**, **32** would be hydrized to form 3-(N-ethoxycarbonylcarbamoyl)-1-methoxycarbonylthiourea (**34**), and **33** to give 1-ethoxycarbonylcarbamoyl-3-(N-methoxycarbonylcarbamoyl)thiourea (**29**). However, the oxidation compound was treated with 1N hydrochloric acid to afford sulfur and a mixture of **29** and **34**. The compounds (**29** and **34**) were prepared by the hydrolysis of 2-benzyl-1-methoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (**28**) and 2-benzyl-3-(N-methoxycarbonylthiocarbamoyl)-1-ethoxycarbonylisothiourea (**36**) with 1N hydrochloric acid, respectively. From this fact, the oxidation product in the reaction of **30** with bromine was regarded as 5-ethoxycarbonylimino-3-methoxycarbonylimino-1,2,4-dithiazolidine (**31**). Consequently, the structure of the compound (**11**) obtained in the reaction of **19** with bromine was confirmed as 3,5-bis(ethoxycarbonylimino)-1,2,4-dithiazolidine (**11**). The molecular formula of compound (**12**) was expressed as $C_8H_{12}O_4N_4S$ by the elemental analysis and mass spectrum: $M^+=260$, and the IR spectrum showed at the absorption bands for nitrogen-hydrogen bond (>NH) at 3220 and 3120 cm^{-1}, and for two carbonyl groups at 1727 and 1703 cm^{-1}, respectively; the NMR spectrum consisted of a triplet due to methyl protons at 8.62 τ, a quartet due to methylene protons at 5,55 τ and two broad peaks for amide protons at approximately -0.55 and 1.22 τ. From these data and the above mentioned references,[4-6] the structure of **12** may be presumably a five membered cyclic compound, namely 1,2,4-thiadiazole derivative or 1,3,4-thiadiazole derivative (**37**). 3,5-Diamino-1,2,4-thiadiazole (**40**), which was prepared by the oxidation of amidinothiourea (**39**) with 30% hydrogen peroxide,[9] was

8) S.N. Dixit, *J. Indian Chem. Soc.*, **39**, 407 (1962).
9) F. Kurzer, *J. Chem. Soc.*, **1955**, 1.

treated with ethyl chloroformate (**41**) in the presence of triethylamine to give **12**. The structure of compound (**12**) was consequently determined as 3,5-bis(ethoxycarbonylamino)-1,2,4-thiadiazole. The molecular formula of compound (**13**) was expressed as $C_5H_8O_2N_4S$, and the

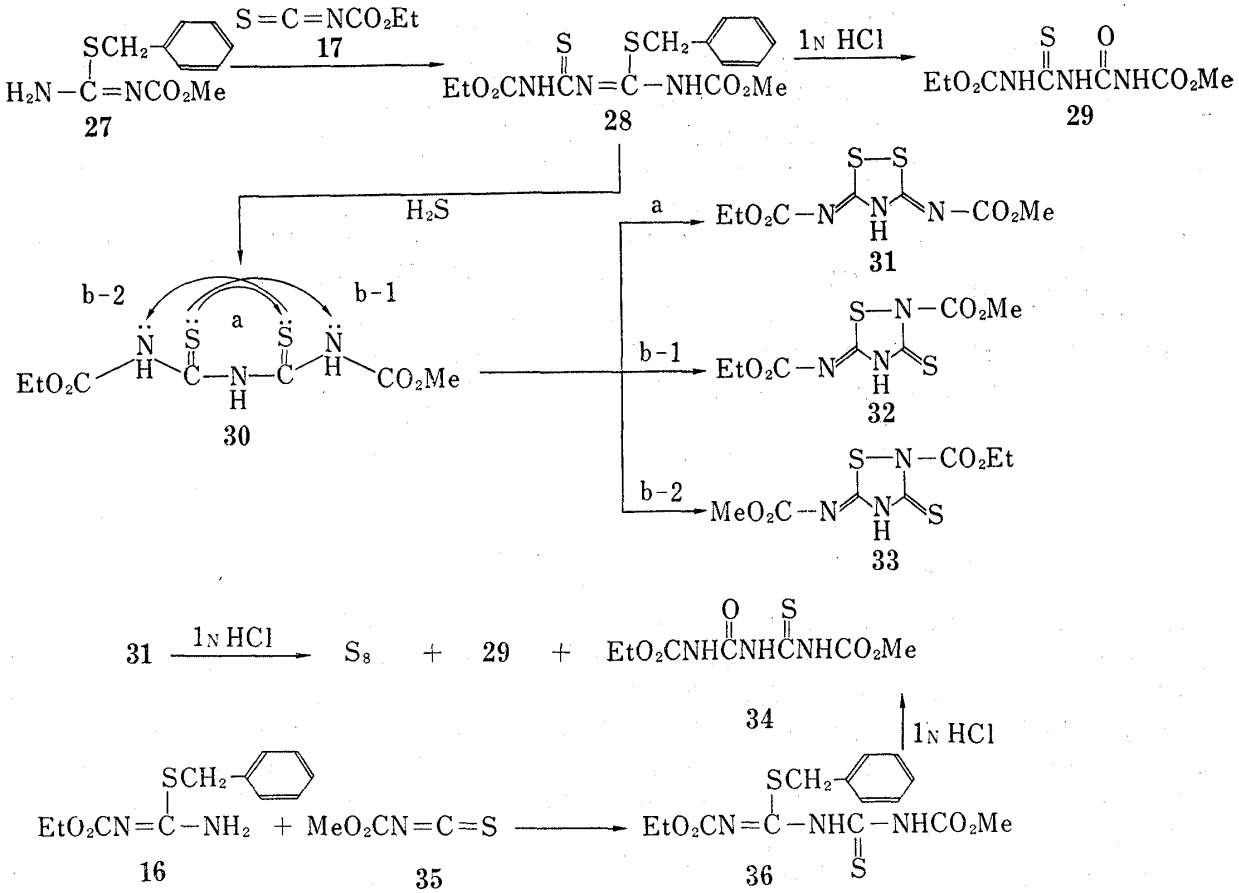


Chart 3

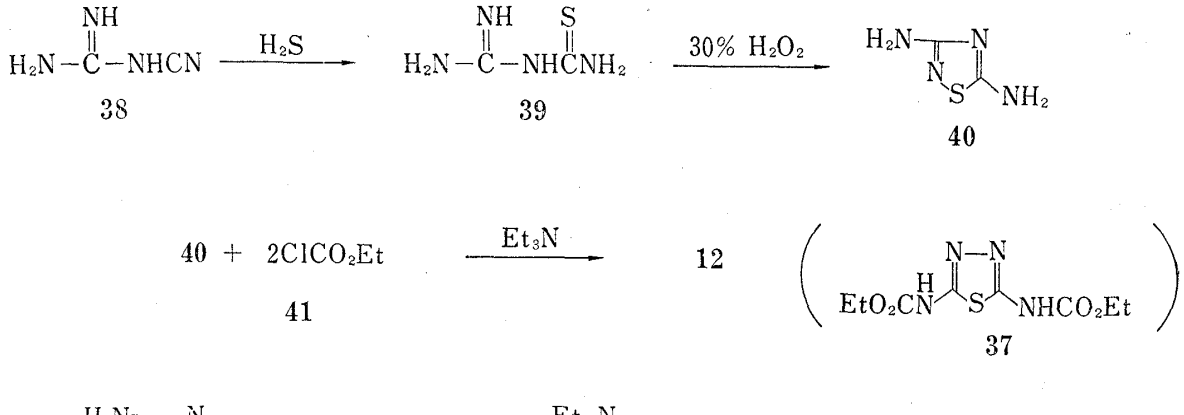
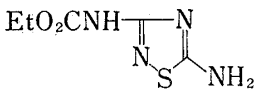


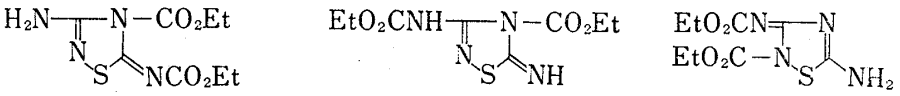
Chart 4

IR spectrum showed a carbonyl at 1730 cm^{-1}, the NMR spectrum consisted of a triplet due to three methyl protons at 8.72 τ, a quartet due to two methylene protons, a broad peak due to two amine protons approximately at 3.86 τ and one amide proton at approximately −2.10 τ (-NHCO-). Furthermore, **13** was treated with ethyl chloroformate (**41**) in the presence of triethyl amine to afford (**12**). From these data, it became clear that **13** was a 3,5-diamino-1,2,4-thiadiazole derivative. Thus the most likely structure of **13** was regarded as 5-amino-3-ethoxycarbonylamino-1,2,4-thiadiazole or 3-amino-5-ethoxycarbonyl-1,2,4-thiadiazole (**42**). However, there remained the problem of solving which of the two structural isomers corresponding to **13**.



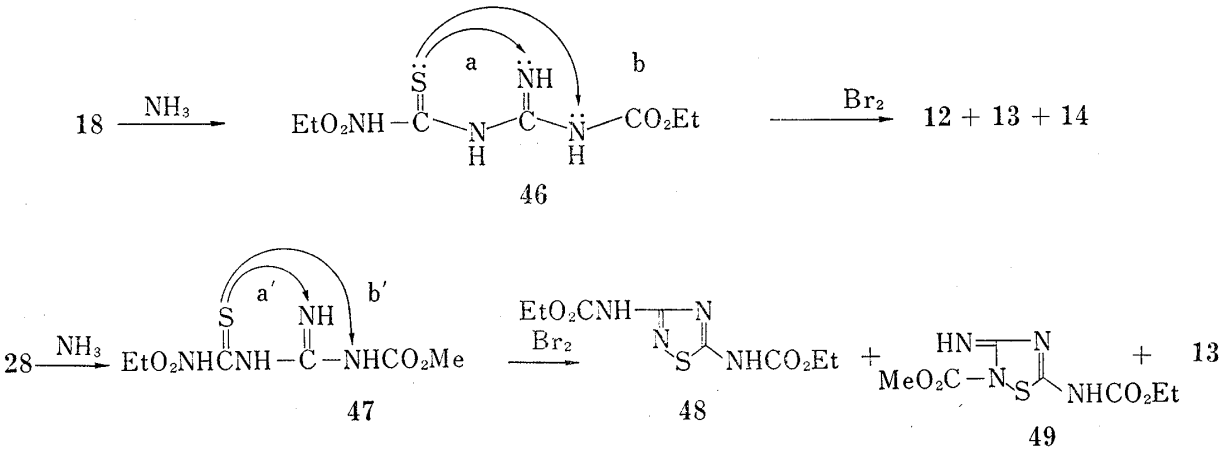
42

The molecular formula of compound (**14**) was expressed as $C_8H_{12}O_4N_4S$ by the elemental analysis and mass spectrum (M^+=260), and the IR spectrum showed a signal at 1735 cm^{-1} wherein two carbonyl bands overlapped each other, and the band of a carbon-nitrogen double bond at 1655 cm^{-1}; the NMR spectrum consisted of two triplets due to methyl protons at 8.76 and 8.66 τ, two quartets due to methylene protons at 5.80 and 5.63 τ. Compound (**14**)



43 44 45

was transformed to **13** by thermal treatment in 1N hydrochloric acid solution. On the basis of the above mentioned data, four possible structures for compound (**14**) were regarded as the 1,2,4-thiadiazoline structures (**14**, **43**, **44** and **45**). 1-Ethoxycarbonyl-3-(N-ethoxycarbonylamidino)thiourea (**46**), which was obtained by the treatment of **18** with ammonia gas, was reacted with bromine to afford three compounds, namely **12**, **13** and **14**. In the case of the oxidation reaction of 1-ethoxycarbonyl-3-(N-methoxycarbonylamidino)thiourea (**47**) with bromine by the above manner, three products, namely 5-ethoxycarbonylamino-3-methoxycarbonylamino-1,2,4-thiadiazole (**48**), 5-ethoxycarbonylamino-3-imino-2-methoxycarbonyl-1,2,4-thiazoline (**49**) and **13**, were also obtained. From these experiments, the structures of **14** and **13** were consequently determined as being 2-ethoxycarbonyl-5-ethoxycarbonylamino-3-imino-1,2,4-thiadiazolidine and 3-amino-5-ethoxycarbonylamino-1,2,4-thiadiazole, respectively.



46 47 48 49

Chart 5

N-Ethoxycarbonyl-N′-phenylthiourea (**77**) was oxidized with bromine under same reaction conditions as those in the case of **9**, and the reaction mixtures were treated with water to afford only sulfur and N-ethoxycarbonyl-N′-phenylurea (**78**) in good yields. On the

other hand, in the case of N-ethoxycarbonyl-N′-methylthiourea (**79**) five compounds, namely sulfur, **20**, 3,5-bis(ethoxycarbonylimino)-2,4-dimethyl-1,2,4-thiadiazolidine (**80**), 5-ethoxycarbonylimino-4-methyl-3-methylamino-1,2,4-thiadiazoline (**81**) and N-ethoxycarbonyl-N′-methylurea (**82**) were obtained, but the product corresponding to 2-alkoxycarbonyl-5-alkoxycarbonylimino-4-alkyl-3-alkylimino-1,2,4-thiadiazolidines (E) could not be isolated. These reaction products were confirmed on the basis of the elemental analyses and the spectral data. The yields of these products of alkoxycarbonylthioureas (A) with bromine are summarized in Table I.

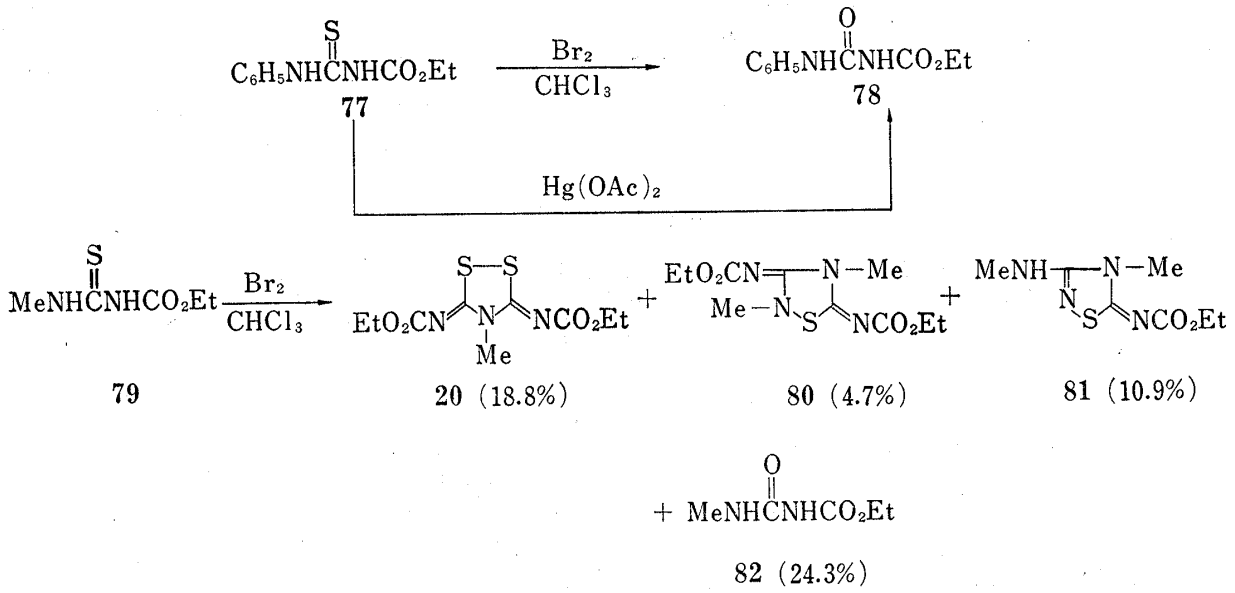


Chart 6

TABLE I. Yields of the Products in the Reaction of Alkoxycarbonylthioureas (A) with Bromine

A: $R_1NHCSNHCO_2R_2$			S_8	B	C	D	E	F
R_1	R_2	Compd. No.						
H	Me	**50**	17.2(%)	53(8.3%)	51(30.4%)	52(6.6%)	not isolated	not isolated
H	Et	**9**	18.2(%)	10(8.3%)	11(28.7%)	12(8.1%)	14(1.8%)	13(2.8%)
H	*n*-Pr	**54**	19.6(%)	59(9.6%)	55(26.3%)	56(9.8%)	57(2.8%)	58(2.2%)
H	iso-Pr	**60**	19.8(%)	65(9.4%)	61(27.1%)	62(9.2%)	63(2.8%)	64(0.6%)
H	*n*-Bu	**66**	20.1(%)	71(9.7%)	67(25.8%)	68(9.8%)	69(3.4%)	70(1.8%)
H	iso-Bu	**72**	22.6(%)	76(10.2%)	73(26.0%)	74(10.3%)	75(3.5%)	not isolated
C_6H_5	Et	**77**	82.5(%)	78(92.5%)	not isolated	not isolated	not isolated	not isolated
Me	Et	**79**	26.7(%)	82(24.3%)	20(18.8%)	80(4.7%)	not isolated	81(10.9%)

The mechanism of the formation of the products in the reaction of alkoxycarbonylthioureas (A) with bromine remains equivocal, but supposedly A may be transformed to formamidine salts (G) which could intramolecularly cyclize to dithiazolidines (C) by the elimination of ammonia, or A may form dithiobiurets (H), which would be formed by the elimination of ammonia from two molecules of A, with subsequent oxidation to form C by bromine. On the other hand, hydrogen sulfide may be eliminated from two molecules of A to form amidino thioureas (**1**) which could be oxidized to produce three cyclic compounds (D, E and F). The pathways for the transformation of A to C, D, E and F are shown schematically in Chart 7.

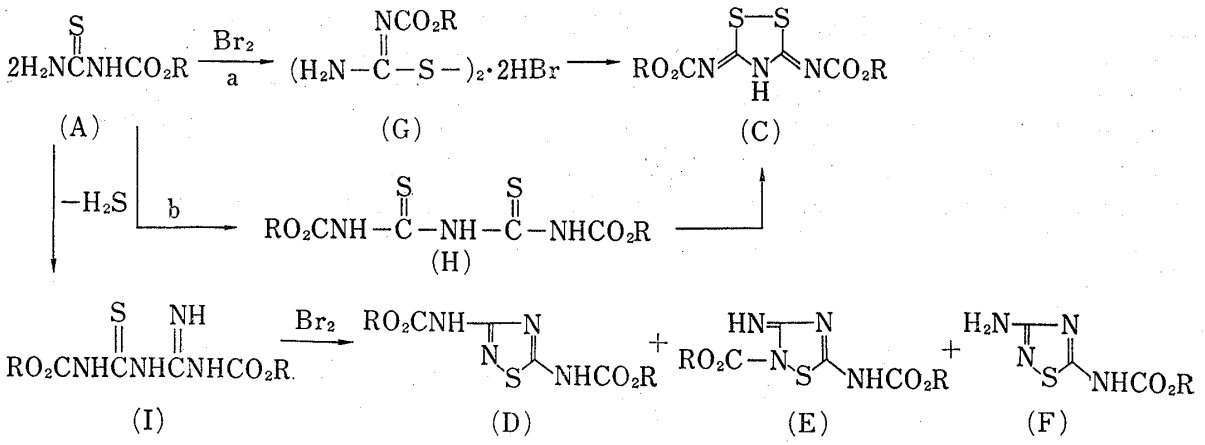


Chart 7

Experimental[10]

General Method for the Reaction of N-Alkoxycarbonylthioureas (A) with Bromine——To a solution of A (0.10 mole) in $CHCl_3$ (250 ml), bromine (0.105 mole) in $CHCl_3$ (50 ml) was added dropwise at temperatures of 0° to 10° in an atmosphere of nitrogen, and the reaction mixture was stirred at room temperature for 1 hr and was refluxed for 2 hr. After removal of $CHCl_3$, the residue was poured into cold water (300 ml) and neutralized with 28% ammonia, and subsequently was extracted with $CHCl_3$ (250 ml×2). The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and after evaporation of the solvent the resulting residue was eluted with benzeneethyl acetate on silica gel, and the isolated products were refined by recrystallization.

Reaction of N-Ethoxycarbonylthiourea (9) with Bromine——**9** (14.8 g) and bromine (17.0 g) was reacted in $CHCl_3$ (300 ml) by the general method to give sulfur (0.42 g), **10**, **11**, **12**, **13**, and **14**. N-Ethoxycarbonylurea (**10**), 1.15 g, colorless needles from AcOEt, mp 198—199°. *Anal.* Calcd. for $C_4H_8O_3N_2$: C, 36.36; H, 6.10; N, 21.20. Found: C, 36.00; H, 6.14; N, 20.85. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3250, 3150, and 1600 (>NH and $-NH_2$), 1742 and 1235 (–C(O)O–), 1705 (–NH–CO–NH–). NMR (DMSO-d_6) τ (J=Hz): 8.82 (3H, t, J=7.0), 5.85 (2H, q, J=7.0), *ca.* 2.80 (2H, broad), *ca.* 0.25 (1H, broad). This compound (**10**; 0.86 g) was also obtained by the oxidation of **9** (1.5 g) with mercuric acetate (3.5 g) in $CHCl_3$ (200 ml) and AcOH (30 ml). 3,5-Bis(ethoxycarbonylimino)-1,2,4-dithiazolidine (**11**), 7.95 g, colorless needles from benzene, mp>300°. *Anal.* Calcd. for $C_8H_{11}O_4N_3S_2$: C, 34.66; H, 4.00; N, 15.16; S, 23.09. Found: C, 34.89; H, 3.91; N, 15.15; S, 23.05. Mass Spectrum: M^+=277. IR ν_{max}^{Nujol} cm^{-1}: 3150 (>NH), 1725 (>C=O), 1640 (>C=O or –N=C<), 1627 (–N=C<– or >C=O). UV λ_{max}^{EtOH} mμ (ε): 269 (14700), 302 (9400), 320 (8500, sh.). NMR (DMF) τ (J=Hz): 8.68 (6H, t, J=7.0), 5.68 (4H, q, J=7.0), *ca.* 4.12 (1H, broad). 3,5-Bis(ethoxycarbonylamino)-1,2,4-thiadiazole (**12**), 2.11 g, colorless needles from benzene, mp 230—232°. *Anal.* Calcd. for $C_8H_{12}O_4N_4S$: C, 36.93; H, 4.65; N, 21.53; S, 12.29. Found: C, 36.72; H, 4.34; N, 21.55; S, 12.11. Mass Spectrum: M^+=260. IR ν_{max}^{Nujol} cm^{-1}: 3220 and 3120 (>NH), 1727 (>C=O), 1703 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 256.5 (4000). NMR ($CDCl_3$) τ (J=Hz): 8.62 (6H, t, J=7.0), 5.55 (4H, q, J=7.0), *ca.* −0.55 (1H, broad), *ca.* −1.22 (1H, broad). 3-Amino-5-ethoxycarbonylamino-1,2,4-thiadiazole (**13**), 0.52 g, colorless needles from AcOEt, mp>300°. *Anal.* Calcd. for $C_5H_8O_2N_4S$: C, 31.25; H, 4.29; N, 29.78; S, 17.31. Found: C, 31.82; H, 4.18; N, 29.71; S, 17.03. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3300, and 1634 ($-NH_2$), 3200 (>NH), 1730 and 1255 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 272 (3100). NMR (DMSO-d_6) τ (J=Hz): 8.72 (3H, t, J=7.0), 5.72 (2H, q, J=7.0), *ca.* 3.86 (2H, broad), *ca.* −2.10 (1H, broad). 2-Ethoxycarbonyl-5-ethoxycarbonylamino-3-imino-1,2,4-thiadiazoline (**14**), 0.46 g, colorless needles from AcOEt, 0.46 g, mp 210—213° (decomp.). *Anal.* Calcd. for $C_8H_{12}O_4N_4S$: C, 36.91; H, 4.64; N, 21.52; S, 12.31. Found: C, 37.14; H, 4.46; N, 21.72; S, 12.41. Mass Spectrum; M^+=260. IR ν_{max}^{Nujol} cm^{-1}: 3420 and 3120 (>NH), 1655 (–N=C<), 1735 and 1250 (–C(O)–O–). UV λ_{max}^{EtOH} mμ (ε): 262 (15100), 271 (15100). NMR (DMSO-d_6) τ (J=Hz): 8.76 (3H, t, J=7.0), 8.66 (3H, t, J=7.0), 5.80 (2H, q, J=7.0), 5.63 (2H, q, J=7.0), *ca.* 1.84 (1H, broad), 0.68 (1H, broad).

Hydrolysis Reaction of 3,5-Bis(ethoxycarbonylimino)-1,2,4-dithiazolidine (11)——To a solution of **11** (2.77 g) in acetone (50 ml), 1N HCl (20 ml) was added and stirred for 4 hr at room temperature. After removal of acetone, the residue was poured into cold water (50 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (200 ml×2). The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4. $CHCl_3$ was removed under reduced pressure and the resulting residue was eluted with AcOEt–benzene on silica gel to give sulfur (0.28 g) and **15**. 1-Ethoxycarbonyl-3-(N-ethoxycarbonylcarbamoyl)thiourea (**15**), 2.26 g,

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

colorless needles from AcOEt, mp 141—143°. *Anal.* Calcd. for $C_8H_{13}O_5N_3S$: C, 36.50; H, 4.98; N, 15.97; S, 12.15. Found: C, 36.74; H, 5.12; N, 15.64; S, 11.83. IR ν_{max}^{Nujol} cm^{-1}: 3200 and 3120 (>NH), 1770 (>C=O), 1738 (>C=O), 1705 (>C=O). UV λ_{max}^{EtOH} $m\mu$ (ε): 222 (2600), 281 (1700). NMR ($CDCl_3$) τ (J=Hz): 8.66 (6H, t, J=7.0), 5.68 (4H, q, J=7.0), *ca.* 1.24 (1H, broad), *ca.* −0.90 (1H, broad), *ca.* −1.60 (1H, broad).

Synthesis of 1-Ethoxycarbonyl-3-(N-ethoxycarbonylcarbamoyl)thiourea (15)——1) N-Ethoxycarbonylthiourea (9; 18.8 g) in acetone (300 ml) was treated with benzyl bromide (26.2 g) for 6 hr at room temperature in the presence of K_2CO_3 (21.1 g) and the insolved salt was filtered off and the solvent of the filtrate was removed under reduced pressure. Ethyl ether (500 ml) was added to the resulting residue, and the ethereal layer was washed with H_2O and dried over anhyd. Na_2SO_4. After the removal of ether, the residual solid was recrystallized from ligroin to give colorless needles of **16**. N-Ethoxycarbonyl-S-benzyl-isothiourea (**16**), 19.7 g, mp 56—58°. *Anal.* Calcd. for $C_{11}H_{14}O_2N_2S$: C, 55.44; H, 5.92; N, 11.75; S, 13.46. Found: C, 55.50; H, 5.79; N, 12.14; S, 13.58. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3170, and 1615 (-NH_2), 1660 and 1260 (-C(O)-O-). NMR ($CDCl_3$) τ (J=Hz): 8.70 (3H, t, J=7.0), 5.80 (2H, q, J=7.0), 5.65 (2H, s), 2.82—2.46 (5H, m), *ca.* 2.33 (2H, broad). 2) To a solution of **16** (2.38 g) in AcOEt (200 ml), ethoxycarbonyl isothiocyanate (**17**; 14.4 g) was added and stirred for 24 hr at room temperature, and after removal of AcOEt, the residue was eluted with benzene on silica gel to give 9.8 g of 1-ethoxycarbonyl-2-benzyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (**18**) as yellow needles of mp 85—86°. *Anal.* Calcd. for $C_{15}H_{19}O_4N_3S_2$: C, 48.78; H, 5.19; N, 11.38; S, 17.33. Found: C, 48.67; H, 5.15; N, 11.30; S, 17.28. IR ν_{max}^{Nujol} cm^{-1}: 3260 and 3170 (>NH), 1750 (>C=O), 1705 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.70 (6H, t, J=7.0), 5.74 (2H, q, J=7.0), 5.70 (2H, q, J=7.0), 5.58 (2H, s), 2.88—2.42 (5H, m), *ca.* 1.64 (1H, broad), *ca.* −2.64 (1H, broad). 3) To a solution of **18** (3.37 g) in acetone (100 ml), 1N HCl (60 ml) was added and stirred for 2 days at room temperature. After removal of acetone, the residual aqueous solution was neutralized with $NaHCO_3$, and the reaction product was extracted with $CHCl_3$ (100 ml) from the solution, $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4. $CHCl_3$ was removed under reduced pressure, and the resulting residue was eluted with benzene on silica gel, and the isolated product was recrystallized with *n*-hexane–benzene to give 2.18 g of **15**.

Synthesis of 1-Ethoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)thiourea (19)——A solution of (18; 3.69 g) in EtOH (50 ml) was saturated with H_2S below room temperature and allowed to stand over night at room temperature, and after removal of EtOH under reduced pressure, the residue was eluted with benzene on silica gel and the isolated product was recrystallized from benzene–*n*-hexane to give 2.50 g of **19**, mp 137—138°. *Anal.* Calcd. for $C_8H_{13}O_4N_3S_2$: C, 34.41; H, 4.09; N, 15.09; S, 22.92. Found: C, 34.17; H, 4.66; N, 15.23; S, 22.79. IR ν_{max}^{Nujol} cm^{-1}: 3200 and 3130 (>NH), 1778 (>C=O), 1730 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.65 (6H, t, J=7.0), 5.68 (4H, q, J=7.0), *ca.* −0.80 (2H, broad), *ca.* −2.80 (1H, broad).

Reaction of 1-Ethoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)thiourea (19) with Bromine——To a solution of **19** (2.77 g) in $CHCl_3$ (250 ml), bromine (1.70 g) in $CHCl_3$ (50 ml) was added dropwise below room temperature and stirred for 1 hr at room temperature. After removal of $CHCl_3$ under reduced pressure, the residue was poured into ice water (200 ml) and neutralized with $NaHCO_3$, and the reaction product was extracted with $CHCl_3$ (300 ml), and the $CHCl_3$ layer was washed with H_2O and dried over Na_2SO_4. $CHCl_3$ was evaporated under reduced pressure and the resulting solid was recrystallized from AcOEt to give 2.45 g of **11**.

Reaction of 2,5-Bis(ethoxycarbonylimino)-1,2,4-dithiazoline (11) with Methyl Iodide——The mixture of **11** (2.63 g), methyl iodide (2.0 g), acetone (100 ml) and K_2CO_3 (1.4 g) was stirred for 2 days at room temperature, and an insoluble salt was filtered off and the solvent was evaporated under reduced pressure, and the resulting residue was poured into ice water (200 ml) and neutralized with 1N HCl, and the reaction products were extracted with benzene (300 ml), and the benzene layer was washed with H_2O and dried over anhyd. Na_2SO_4. After removal of benzene, the residue was eluted with AcOEt–benzene on silica gel to afford two products (**20** and **21**). 3,5-Bis(ethoxycarbonylimino)-4-methyl-1,2,4-dithiazolidine (**20**), 0.45 g, colorless needles from AcOEt, mp 188—189°. *Anal.* Calcd. for $C_9H_{13}O_4N_3S_2$: C, 37.12; H, 4.50; N, 14.43; S, 21.97. Found: C, 37.56; H, 4.52; N, 14.40; S, 21.93. Mass Spectrum: M^+=291. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.61 (6H, t, J=7.0), 6.15 (3H, s), 5.68 (4H, q, J=7.0). 3-(N-Ethoxycarbonyl-N-methylamino)-5-ethoxycarbonylimino-1,2,4-dithiazoline (**21**), 1.85 g, colorless needles from benzene, mp 115—117°. *Anal.* Calcd. for $C_9H_{13}O_4N_3S_2$: C, 37.12; H, 4.50; N, 14.43; S, 21.97. Found: C, 36.84; H, 4.58; N, 14.28; S, 21.97.

Synthesis of 2-Benzyl-1-methoxycarbonylisothiourea (27)——The mixture of N-methoxycarbonylthiourea (5.5 g), benzyl bromide, K_2CO_3 (9.0 g) and acetone (150 ml) was stirred for 2 days at room temperature. An insoluble salt was filtered off, and the acetone of the filtrate was evaporated under reduced pressure, and the residue was poured into ice water (300 ml) and neutralized with 1N HCl, and the reaction product was extracted with ether (500 ml), The ethereal layer was washed with H_2O and dried over anhyd. Na_2SO_4, and the solvent was evaporated, and the residual solid was recrystallized from ligroin to give 5.6 g of 2-benzyl-1-ethoxycarbonylisothiourea (**27**) ,colorless needles, mp 70—72°. *Anal.* Calcd. for $C_{10}H_{12}O_2N_2S$: C, 53.57; H, 5.39; N, 12.50; S, 14.27. Found: C, 54.08; H, 5.49; N, 12.44; S, 14.55. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3230, and 1602 (>NH_2), 1667 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 6.06 (3H, s), 5.63 (2H, s), 2.81—2.52 (5H, m), 2.72—2.17 (2H, broad).

Synthesis of 2-Benzyl-1-methoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (28)——To a solution of **27** (2.24 g) in AcOEt (50 ml), ethoxycarbonyl isothiocyanate (**17**; 1.5 g) was added, and the reaction mixture was stirred for 24 hr at room temperature, and after removal of AcOEt, the yellow resulting solid was recrystallized from isopropyl ether to afford 2.6 g of 2-benzyl-1-methoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (**28**), colorless needles, mp 91—92°. *Anal.* Calcd. for $C_{14}H_{17}O_4N_3S_2$: C, 47.32; H, 4.82; N, 11.83; S, 18.01. Found: C, 47.16; H, 4.75; N, 11.49; S, 18.44. IR ν_{max}^{Nujol} cm^{-1}: 3250 and 3150 (>NH), 1740 (>C=O), 1645 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 8.77 (3H, t, J=7.0), 6.30 (3H, s), 5.87 (2H, q, J=7.0), 5.56 (2H, s), 2.79—2.40 (5H, m), *ca.* −0.26 (2H, broad).

Synthesis of 1-Ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)thiourea (30)——A solution of **28** (4.3 g) in EtOH (200 ml) was saturated with H_2S and allowed to stand overnight, and EtOH was evaporated under reduced pressure, and the residue was eluted with benzene on silica gel to afford 3.4 g of **30**. 1-Ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)thiourea (**30**), colorless needles from *n*-hexane–benzene, mp 142—144°. *Anal.* Calcd. for $C_7H_{11}O_4N_3S_2$; C, 31.70: H, 4.18; N, 15.95; S, 24.13. Found: C, 31.55; H, 4.12; N, 16.18; S, 24.08. IR ν_{max}^{Nujol} cm^{-1}: 3300 (>NH), 1748 (>C=O), 1722 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.65 (3H, t, J=7.0), 6.10 (3H, s), 5.63 (2H, q, J=7.0), *ca.* −0.10 (2H, broad), *ca.* −2.82 (1H, broad).

Reaction of 1-Ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)thiourea (30) with Bromine——To a solution of **30** (2.75 g) in $CHCl_3$ (250 ml), bromine (1.70 g) was added dropwise below room temperature, and the reaction solution was stirred for 1 hr at room temperature, and the solvent was removed under reduced pressure, and then the resulting residue was poured into ice water (200 ml) and neutralized with $NaHCO_3$, and the reaction product was extracted with $CHCl_3$ (100 ml×3). The $CHCl_3$ layer was washed with H_2O and after removal of $CHCl_3$, the resulting solid was recrystallized from AcOEt to afford 2.45 g of **31**. 5-Ethoxycarbonylimino-3-methoxycarbonylimino-1,2,4-dithiazolidine (**31**), colorless needles, mp 194—195°. *Anal.* Calcd. for $C_7H_9O_4N_3S_2$: C, 31.95; H, 3.45; N, 15.97; S, 24.32. Found: C, 31.96; H, 3.58; N, 15.98; S, 24.01. IR ν_{max}^{Nujol} cm^{-1}: 3120 (>NH), 1722 (>C=O), 1640 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 8.72 (3H, t, J=7.0), 6.20 (3H, s), 5.76 (2H, q, J=7.0), *ca.* 3.15 (1H, broad).

Hydrolysis Reaction of 5-Ethoxycarbonylimino-3-methoxycarbonylimino-1,2,4-dithiazolidine (31)——The mixture of **31** (0.60 g) in acetone (50 ml) and 1N HCl (15 ml) was allowed to stand overnight at room temperature, and after removal of acetone, the resulting aqueous solution was neutralized with $NaHCO_3$, and the reaction products were extracted with $CHCl_3$ (100 ml). The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated under reduced pressure, and then the resulting residue was eluted with benzene on silica gel to afford 0.48 g of sulfur (0.07 g) and 0.20 g of the mixture of **29** and **34**.

Synthesis of 1-Ethoxycarbonyl-3-(N-methoxycarbonylcarbamoyl)thiourea (29)——After the mixture of 2-benzyl-1-methoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (**28**; 2.8 g) in acetone (100 ml) and 1N HCl (60 ml) was stirred for 24 hr at room temperature, acetone was removed under reduced pressure and the resulting aqueous solution was neutralized with $NaHCO_3$, and the reaction product was extracted with $CHCl_3$ (200 ml), the $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4. After removal of $CHCl_3$, the residue was eluted with benzene to give 1.39 g of 1-ethoxycarbonyl-3-(N-methoxycarbonylcarbamoyl)thiourea (**29**), pale yellow needles from AcOEt, mp 168—169°. *Anal.* Calcd. for $C_7H_{11}O_5N_3S$: C, 33.73; H, 4.44; N, 16.85; S, 12.86. Found: C, 33.80; H, 4.41; N, 16.98; S, 12.99. IR ν_{max}^{Nujol} cm^{-1}: 3200 and 3130 (>NH), 1778 (>C=O), 1742 (>C=O), 1700 (>C=O). NMR ($CDCl_3$) τ (J=Hz): 8.75 (3H, t, J=7.0), 6.27 (3H, s), 5.80 (2H, q, J=7.0), −0.86—0.20 (3H, broad).

Synthesis of 2-Benzyl-1-ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)isothiourea (36)——After the mixture of S-benzyl-N-ethoxycarbonylisothiourea (**16**; 2.36 g) in AcOEt (50 ml) and methoxycarbonyl isothiocyanate (**35**; 1.5 g) was stirred for 24 hr at room temperature, the solvent was evaporated under reduced pressure and the resulting solid was recrystallized from isopropyl ether to afford 3.23 g of 2-benzyl-1-ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)isothiourea (**36**), yellow needles, mp 88—90°. *Anal.* Calcd. for $C_{14}H_{17}O_4N_3S_4$: C, 47.32; H, 4.82; N, 11.83; S, 18.01. Found: C, 47.33; H, 4.71; N, 11.59; S, 18.08. IR ν_{max}^{Nujol} cm^{-1}: 3230 and 3160 (>NH), 1748 (>C=O), 1710 (>C=O. NMR ($CDCl_3$) τ (J=Hz): 8.70 (3H, t, J=7.0), 6.24 (3H, s), 5.70 (2H, q, J=7.0), 5.56 (2H, s), 2.80—2.42 (5H, m), *ca.* 5.82 (1H, broad), *ca.* −2.70 (1H, broad).

Hydrolysis Reaction of 2-Benzyl-1-ethoxycarbonyl-3-(N-methoxycarbonylthiocarbamoyl)isothiourea (36)—The mixture of **36** (2.8 g) in acetone (60 ml) and 1N HCl (60 ml) was stirred for 24 hr at room temperature, and after removal of acetone, the resulting aqueous solution was neutralized with $NaHCO_3$, and then the reaction product was extracted with $CHCl_3$ (300 ml), and the $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4. $CHCl_3$ was removed under reduced pressure and the resulting residue was eluted with benzene on silica gel to afford 2.16 g of 3-(N-ethoxycarbonylcarbamoyl)-1-methoxycarbonylthiourea (**34**), pale yellow needles from benzene, mp 167—169°. *Anal.* Calcd. for $C_7H_{11}O_5N_3S$: C, 33.73; H, 4.44; N, 16.85; S, 12.86. Found: C, 33.78; H, 4.49; N, 16.85; S, 12.97. IR ν_{max}^{Nujol} cm^{-1}: 3180 and 3120 (>NH), 1780 (>C=O), 1742 (>C=O), 1700 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 8.75 (3H, t, J=7.0), 6.27 (3H, s), 5.80 (2H, q, J=7.0), −0.86—2.20 (3H, broad).

Reaction of 3,5-Diamino-1,2,4-thiadiazole (40) and Ethyl Chloroformate (41)——To a solution of 2,5-diamino-1,2,4-thiadiazole (**40**; 0.88 g)[9] dissolved in EtOH (50 ml) in the presence of triethylamine (2.50 g), ethyl chloroformate (2.20 g) was added dropwise under ice water, and the reaction solution was refluxed

for 2 hr, and after removal of EtOH, the residue was poured into water (100 ml) and the deposit was collected on the glass filter and recrystallized from AcOEt to give 1.39 g of 3,5-bis(ethoxycarbonylamino)-1,2,4-thiadiazole (**12**).

Reaction of 3-Amino-5-ethoxycarbonylamino-1,2,4-thiadiazole (13) and Ethyl Chloroformate (41)——To the suspension of **13** (0.19 g) in EtOH (50 ml) in the presence of triethylamine (1.20 g), **41** (0.12 g) was added at room temperature and the reaction solution was refluxed for 2 hr, and after removal of EtOH the resulting residue was eluted with AcOEt on silica gel to afford 0.11 g of 3,5-bis(ethoxycarbonylamino)-1,2,4-thiadiazole (**12**).

Thermal Decomposition of 2-Ethoxycarbonyl-5-ethoxycarbonylamino-3-imino-1,2,4-thiadiazoline (14) with 1N HCl——The suspension of **14** (0.27 g) in 1N HCl (30 ml) was refluxed for 4 hr and neutralized with $NaHCO_3$, and the deposit was collected on the glass filter and washed with H_2O and benzene to give 0.05 g of 3-amino-5-ethoxycarbonylamino-1,2,4-thiadiazole (**13**).

Synthesis of 1-Ethoxycarbonyl-3-(N-ethoxycarbonylamidino)thiourea (46)——In a solution of 2-benzyl-1-ethoxycarbonyl-3-(N-ethoxycarbonylthiocarbamoyl)isothiourea (**18**; 13.50 g) in ether (300 ml), ammonia gas was saturated at a range of 0° to 10° and was stirred for 2 hr, and the solvent and excess ammonia were removed, and the residual solid was recrystallized from *n*-hexane–EtOH to afford 8.40 g of **46**. 1-Ethoxycarbonyl-3-(N-ethoxycarbonylamidino)thiourea (**46**), a colorless powder, mp>300°. *Anal.* Calcd. for $C_8H_{14}O_4N_4S$: C, 36.64; H, 5.38; N, 21.37; S, 12.20. Found: C, 37.13; H, 5.42; N, 21.40; S, 12.32. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3220 and 1630 (>NH and $-NH_2$). NMR ($CDCl_3$) τ (J=Hz): 8.72 (3H, t, J=7.0), 8.68 (3H, t, J=7.0), 5.78 (2H, q, J=7.0), 5.74 (2H, q, J=7.0), *ca.* 1.74—0.30 (3H, broad), *ca.* −2.70 (1H, broad).

Reaction of 1-Ethoxycarbonyl-3-(N-ethoxycarbonylamidino)thiourea (46) with Bromine——To a solution of **46** (2.62 g) in $CHCl_3$ (250 ml), bromine (1.80 g) in $CHCl_3$ (50 ml) was added dropwise under ice cooling in an atmosphere of nitrogen, and after the reaction solution was stirred for 2 hr, $CHCl_3$ was evaporated under reduced pressure, and then ice water (200 ml) was added to the residue, and the reaction product was extracted with $CHCl_3$ (300 ml), and $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4. $CHCl_3$ was evaporated under reduced pressure, and the resulting residue was eluted with AcOEt on silica gel to give 0.42 g of 3,5-bis(ethoxycarbonylamino)-1,2,4-thiadiazole (**12**), 0.43 g of 2-ethoxycarbonyl-5-ethoxycarbonylamino-3-imino-1,2,4-thiadiazoline (**13**) and 0.25 g of 5-ethoxycarbonylamino-3-amino-1,2,4-thiadiazole (**14**).

Synthesis of 1-Ethoxycarbonyl-3-(N-methoxycarbonylamidino)thiourea (47)——3.55 g of **28** was treated with ammonia at the same reaction conditions as those in the synthesis of (**46**) to afford 2.17 g of 1-ethoxycarbonyl-3-(N-methoxycarbonylamidino)thiourea (**47**), a colorless powder (*n*-hexane–EtOH), mp> 300°. *Anal.* Calcd. for $C_7H_{12}O_4N_4S$: C, 38.87; H, 4.87; N, 22.58; S, 12.89. Found: C, 33.84; H, 4.71; N, 22.72; S, 12.50. IR ν_{max}^{Nujol} cm^{-1}: 3550, 3470, 3300, 3230 and 1642 (>NH and $-NH_2$), 1737 (>C=O), 1722 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 9.08 (3H, t, J=7.0), 6.23 (3H, s), 5.86 (2H, q, J=7.0), 0.40—1.20 (3H, broad), *ca.* −2.34 (1H, broad).

Reaction of 1-Ethoxycarbonyl-3-(N-methoxycarbonylamidino)thiourea (47) with Bromine——**47** (2.48 g) was treated with bromine (1.80 g) in $CHCl_3$ (300 ml) under same reaction conditions as the case of **46** to afford 0.23 g of **13**, 0.38 g of **48** and 0.39 g of **49**. 5-Ethoxycarbonylamino-3-methoxycarbonylamino-1,2,4-thiadiazole (**48**), colorless needles (AcOEt), mp 141—142°. *Anal.* Calcd. for $C_7H_{10}O_4N_4S$: C, 34.15; H, 4.09; N, 22.76; S, 13.00. Found: C, 34.21; H, 4.34; N, 22.64; S, 13.13. IR ν_{max}^{Nujol} cm^{-1}: 3230 and 3120 (>NH), 1720 (>C=O), 1710 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 8.74 (3H, t, J=7.0), 6.37 (3H, s), 5.70 (2H, q, J=7.0), *ca.* −0.48 (1H, broad). 5-Ethoxycarbonylamino-3-imino-2-methoxycarbonyl-1,2,4-thiadiazoline (**49**), colorless needles from AcOEt, mp 169—171°. *Anal.* Calcd. for $C_7H_{10}O_4N_4S$: C, 34.15; H, 4.09; N, 22.76; S, 13.00. Found: C, 34.34; H, 4.16; N, 22.04; S, 12.97. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3280 and 3110 (>NH), 1738 and 1232 (>C(O)–O–). NMR (DMSO-d_6) τ (J=Hz): 8.72 (3H, t, J=7.0), 6.01 (3H, s), 5.82 (2H, q, J=7.0), *ca.* 1.80 (1H, broad), *ca.* 0.70 (1H, broad).

Reaction of N-Methoxycarbonylthiourea (50) with Bromine——**50** (13.4 g) was reacted with Bromine in $CHCl_3$ (300 ml) by the general method to give 0.46 g of sulfur, **51**, **52**, and **53**. N-Methxycarbonylurea (**53**), colorless needles from EtOH, mp 210—212°; 0.98 g. *Anal.* Calcd. for $C_3H_6O_3N_2$: C, 30.51; H, 5.12; N, 23.72. Found: C, 30.38; H, 4.90; N, 23.45. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3380, 3150 and 1665 (>NH and $-NH_2$), 1750 (>C=O), 1705 (>C=O). 2,5-Bis(methoxycarbonylimino)-1,2,4-dithiazolidine (**51**), colorless needles from AcOEt, mp>300°, 7.55 g. *Anal.* Calcd. for $C_6H_7O_4N_3S_2$: C, 28.92; H, 2.38; N, 16.87; S, 25.69. Found: C, 29.15; H, 2.58; N, 16.96; S, 25.50. IR ν_{max}^{Nujol} cm^{-1}: 3140 (>NH), 1733 (>C=O), 1646 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 225 (8400), 268.5 (16400), 302 (11200), 320 (9500, sh.). NMR (DMSO-d_6) τ (J=Hz): 6.29 (6H, s), *ca.* 3.32 (1H, broad). 3,5-Bis(methoxycarbonylamino)-1,2,4-thiadiazole (**52**), colorless needles from AcOEt, mp>300°, 1.53 g. *Anal.* Calcd. for $C_6H_8O_4N_4S$: C, 31.04; H, 4.47; N, 24.14; S, 13.78. Found: C, 31.41; H, 4.19; N, 24.17; S, 13.49. IR ν_{max}^{Nujol} cm^{-1}: 3180 (>NH), 1735 (>C=O), 1720 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 257 (4000). NMR (DMSO-d_6) τ: 6.30 (3H, s), 6.16 (3H, s), *ca.* −0.52 (1H, broad), *ca.* −2.54 (1H, broad).

Reaction of N-*n*-Propoxycarbonylthiourea (54) with Bromine——**54** (16.2 g) was reacted with Bromine (17.0 g) in $CHCl_3$ (300 ml) by the general method to afford 0.41 g of sulfur, **55**, **56**, **57**, **58**, and **59**. 3,5-Bis-(*n*-propoxycarbonylimino)-1,2,4-dithiazolidine (**55**), colorless needles from benzene, mp>300°, 8.05 g. *Anal.* Calcd. for $C_{10}H_{15}O_4N_3S_2$: C, 39.35; H, 4.95; N, 13.77; S, 20.96. Found: C, 39.34; H, 5.01; N, 13.86; S, 20.81. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1728 (>C=O), 1642 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 223 (11100), 268.5 (18300),

310 (10400). NMR (DMSO-d_6) τ (J=Hz): 9.06 (6H, t, J=7.0), 8.28 (4H, q, t, J_1=J_2=7.0), 5.82 (4H, t, J=7.0), 4.22 (1H, broad). 3,5-Bis(*n*-propoxycarbonylamino)-1,2,4-thiadiazole (**56**), colorless needles from benzene, mp 196—197°, 2.82 g. *Anal.* Calcd. for $C_{10}H_{16}O_4N_4S$: C, 41.66; H, 5.59; N, 19.44; S, 11.10. Found: C, 41.52; H, 5.51; N, 19.24; S, 11.36. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1738 (>C=O), 1700 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 258 (4100). NMR ($CDCl_3$) τ (J=Hz): 8.90 (6H, t, J=7.0), 8.16 (4H, q, t, J_1=J_2=7.0), 5.65 (4H, t, J=7.0), *ca.* −0.58 (1H, broad), *ca.* −1.28 (1H, broad). 3-Imino-2-*n*-propoxycarbonyl-5-*n*-propoxycarbonylamino-1,2,4-thiadiazole (**57**), colorless needles from benzene, mp 172—173°, 0.81 g. *Anal.* Calcd. for $C_{10}H_{16}O_4N_4S$: C, 41.66; H, 5.59; N, 19.44; S, 11.10. Found: C, 41.41; H, 5.59; N, 19.66.; S, 11.26. IR ν_{max}^{Nujol} cm^{-1}: 3420 and 3140 (-NH), 1732 (>C=O), 1652 (>C=N-). UV λ_{max}^{EtOH} mμ (ε): 261 (20800), 272 (21000). NMR (DMSO-d_6) τ (J=Hz): 9.08 (3H, t, IJ=6.5), 9.05 (3H, t, J=6.5), 8.37 (2H, q, t, J_1=J_2=6.5), 8.22 (2H, q, t, J_1=J_2=6.5), 5.90 (2H, t, J=6.5), 5.70 (2H, t, J=6.5), *ca.* 1.75 (1H, broad), *ca.* 0.62 (1H, broad). 3-Amino-5-*n*-propoxycarbonylamino-1,2,4-thiadiazole (**58**), colorless needles from AcOEt, mp >300°, 0.44 g. *Anal.* Calcd. for $C_6H_{10}O_2N_3S$: C, 35.36; H, 4.99; N, 27.72; S, 15.83. Found: C, 35.84; H, 4.68; N, 27.64; S, 15.72. IR ν_{max}^{Nujol} cm^{-1}: 3480, 3350, 3230, 3120 and 1650 (>NH and -NH_2). UV λ_{max}^{EtOH} mμ (ε): 272 (3100). NMR (DMSO-d_6) τ (J=Hz): 9.08 (3H, t, J=6.5), 8.32 (2H, q, t, J_1=J_2=6.5), 5.83 (2H, t, J=6.5), *ca.* 3.82 (2H, broad), *ca.* −2.10 (1H, broad). *n*-Propoxycarbonylurea (**59**), colorless needles from benzene, mp 179—180°, 1.40 g. *Anal.* Calcd. for $C_5H_{10}O_3N_2$: C, 41.09; H, 6.90; N, 19.19. Found: C, 41.14; H, 6.87; N, 19.00. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3230, 3150 and 1680 (>NH and -NH_2), 1748 and 1235 (>C(O)-O-), 1712 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 9.10 (3H, t, J=6.5), 8.38 (2H, q, t, J_1=J_2=6.5), 5.96 (2H, t, J=6.5), *ca.* 2.84 (2H, broad), *ca.* 0.23 (1H, broad).

Reaction of N-Isopropoxycarbonylthiourea (60) with Bromide——**60** (16.2 g) was treated with bromine (17.0 g) in $CHCl_3$ (300 ml) by the general method to afford 0.41 g of sulfur, **61**, **62**, **63**, **64**, and **65**. 3,5-Bis(isopropoxycarbonylimino)-1,2,4-dithiazolidine (**61**), colorless needles from AcOEt, mp>300°, 8.27 g. *Anal.* Calcd. for $C_{10}H_{16}O_4N_3S_2$: C, 39.35; H, 4.95; N, 13.77; S, 20.96. Found: C, 39.72; H, 5.15; N, 13.78; S, 20.78. IR ν_{max}^{Nujol} cm^{-1}: 3170 (>NH), 1725 (>C=O), 1648 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 223 (11400), 269 (17400), 304 (12500), 324 (9400, sh.). NMR (DMSO-d_6) τ (J=Hz): 8.72 (12H, d, J=6.8), 4.97 (2H, q, q, J_1=J_2=6.8), *ca.* 4.08 (1H, broad). 3,5-Bis(isopropoxycarbonylamino)-1,2,4-thiadiazole (**62**), colorless needles from benzene, mp 213—214°, 21.67 g. *Anal.* Calcd. for $C_{10}H_{16}O_4N_4S$: C, 41.66; H, 5.59; N, 19.44; S, 11.10. Found: C, 41.86; H, 5.47; N, 19.93; S, 11.16. IR ν_{max}^{Nujol} cm^{-1}: 3250 and 3160 (>NH), 1735 (>C=O), 1698 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 257.5 (4100). NMR ($CDCl_3$) τ (J=Hz): 8.58 (12H, d, J=7.0), 4.76 (2H, q, q, J_1=J_2=7.0), *ca.* 0.06 (1H, broad), *ca.* −1.02 (1H, broad). 2-Isopropoxycarbonyl-5-isopropoxycarbonylamino-3-imino-1,2,4-thiadiazoline (**63**), colorless needles from benzene, mp 185—186°, 0.81 g. *Anal.* Calcd. for $C_{10}H_{16}O_4N_4S$: C, 41.66; H, 5.59; N, 19.44; S, 11.10. Found: C, 41.84; H, 5.83; N, 18.98; S, 10.60. IR ν_{max}^{Nujol} cm^{-1}: 3440 and 3140 (>NH), 1732 (>C=O), 1652 (>C=N-). UV λ_{max}^{EtOH} mμ (ε): 261 (19600), 273 (19700). 3-Amino-5-isopropoxycarbonylamino-1,2,4-thiadiazole (**64**), colorless needles from AcOEt, mp>300°, 0.12 g. *Anal.* Calcd. for $C_6H_{10}O_2N_4S$: C, 35.64; H, 4.99; N, 27.27; S, 15.83. Found: C, 3572; H, 4.74; N, 27.58; S, 15.62. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3280, 3170 and 1635 (>NH and -NH_2), 1715 and 1248 (>C(O)-O-). N-Isopropoxycarbonylurea (**65**), colorless needles from benzene, mp 192—193°, 1.41 g. *Anal.* Calcd. for $C_5H_{10}O_3N_2$: C, 41.09; H, 6.90; N, 19.17. Found: C, 41.46; H, 6.92; N, 18.83. IR ν_{max}^{Nujol} cm^{-1}: 3390, 3330, 3240 and 1630 (>NH and -NH_2), 1715 and 1243 (>C(O)-O-), 1670 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 8.77 (6H, d, J=6.5), 5.15 (1H, q, q, J_1=J_2=6.5), *ca.* 2.86 (2H, broad), *ca.* 0.34 (1H, broad).

Reaction of N-*n*-Butoxycarbonylthiourea (66) with Bromine——**66** (17.6 g) was treated with bromine (17.0 g) in $CHCl_3$ (300 ml) by the general method to afford 0.38 g of sulfur, **67**, **68**, **69**, **70**, and **71**. 3,5-Bis-(*n*-butoxycarbonylimino)-1,2,4-dithiazolidine (**67**), colorless needles from benzene, mp 207—209°, 8.60 g. *Anal.* Calcd. for $C_{12}H_{19}O_4N_3S_2$: C, 43.24; H, 5.75; N, 12.61; S, 19.20. Found: C, 43.68; H, 5.48; N, 13.18; S, 19.35. IR ν_{max}^{Nujol} cm^{-1}: 3150 (>NH), 1725 (>C=O), 1640 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 224 (11700), 268.5 (16700), 301 (16200), 324 (9000, sh.). NMR ($CDCl_3$) τ (J=Hz): 9.10 (6H, t, J=6.5), 8.92—8.02 (8H, m), 5.78 (4H, t, J=6.5), *ca.* −1.32 (1H, broad). 3,5-Bis(*n*-butoxycarbonylamino)-1,2,4-thiadiazole (**68**), colorless needles from benzene, mp 168—170°, 3.09 g. *Anal.* Calcd. for $C_{12}H_{20}O_4N_4S$: C, 45.56; H, 6.37; N, 17.71; S, 10.11. Found: C, 45.81; H, 6.24; N, 18.05; S, 10.20. IR ν_{max}^{Nujol} cm^{-1}: 3180 and 3130 (>NH), 1732 (>C=O), 1695 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 258 (4000). NMR ($CDCl_3$) τ (J=Hz): 9.02 (6H, t, J=6.0), 8.84—7.86 (8H, m), 5.62 (4H, t, J=6.0), *ca.* −0.72 (1H, broad), *ca.* −1.28 (1H, broad). 2-*n*-Butoxycarbonyl-5-*n*-butoxycarbonylamino-3-imino-1,2,4-thiadiazoline (**69**), colorless needles from benzene, mp 119—121°, 1.75 g. *Anal.* Calcd. for $C_{12}H_{20}O_4N_4S$: C, 45.56; H, 6.37; N, 17.71; S, 10.11. Found: C, 45.57; H, 6.04; N, 18.12; S, 10.45. IR ν_{max}^{Nujol} cm^{-1}: 3400 and 3150 (>NH), 1735 (>C=O), 1650 (>C=N-). UV λ_{max}^{EtOH} mμ (ε): 261.5 (21000), 271 (21100). NMR ($CDCl_3$) τ (J=Hz): 9.05 (3H, t, J=6.5), 9.00 (3H, t, J=6.5), 8.86—7.94 (8H, m), 5.73 (2H, t, J=6.5), 5.62 (2H, t, J=6.5), *ca.* 1.85 (1H, broad), *ca.* 0.56 (1H, broad). 3-Amino-5-*n*-butoxycarbonylamino-1,2,4-thiadiazole (**70**), colorless needles from AcOEt, mp 215—216°, 0.73 g. *Anal.* Calcd. for $C_7H_{12}O_2N_4S$: C, 38.89; H, 5.59; N, 25.92; S, 14.80. Found: C, 38.43; H, 5.62; N, 25.49; S, 14.98. IR ν_{max}^{Nujol} cm^{-1}: 3490, 3350, 3220 and 1652 (>NH and -NH_2), 1730 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 272 (3200). NMR (DMSO-d_6) τ (J=Hz): 9.08 (3H, t, J=6.5), 8.90—8.02 (4H, m), 5.77 (2H, t, J=6.5), *ca.* 3.82 (2H, broad), *ca.* −2.12 (1H, broad). *n*-Butoxycarbonylurea (**71**), colorless needles from benzene, mp 153—154°, *Anal.* Calcd. for $C_6H_{12}O_3N_2$: C, 44.99; H, 7.55; N, 17.49. Found: C, 44.99; H, 7.59; N, 17.62. IR ν_{max}^{Nujol} cm^{-1}:

3380, 3320, 3180, 3120 and 1670 (>NH and $-NH_2$), 1738 and 1235 (>C(O)–O–), 1700 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 9.08 (3H, t, J=6.5), 8.94—8.07 (4H, m), 5.92 (2H, t, J=6.5), *ca.* 2.85 (2H, broad), *ca.* 0.30 1H, broad).

Reaction of N-Isobutoxycarbonylthiourea (72) with Bromine——**72** (17.6 g) was reacted with bromine (17.0 g) in $CHCl_3$ (300 ml) by the general method to afford 0.43 g of sulfur, **74**, **75**, and **76**. 3,5-Bis(isobutoxycarbonylimino)-1,2,4-dithiazolidine (**73**), colorless needles from AcOEt, mp>300°, 8.66 g. *Anal.* Calcd. for $C_{12}H_{19}O_4N_3S_2$: C, 43.24; H, 5.75; N, 12.61; S, 19.20. Found: C, 43.32; H, 5.77; N, 12.83; S, 19.27. IR ν_{max}^{Nujol} cm^{-1}: 3150 (>NH), 1730 (>C=O), 1635 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 224 (11800), 268.5 (17100), 301 (14600), 320 (10400, sh.). NMR (DMSO-d_6) τ (J=Hz): 9.06 (12H, d, J=7.0), 8.00 (2H, q, q, t, $J_1=J_2=J_3=$ 7.0), 5.96 (4H, d, J=7.0), *ca.* 3.80 (1H, broad). 3,5-Bis(isobutoxycarbonylamino)-1,2,4-thiadiazole (**74**), colorless needles from AcOEt, mp 189—190°, 3.26 g. *Anal.* Calcd. for $C_{12}H_{19}O_4N_4S$: C, 45.56; H, 6.37; N, 17.71; S, 10.11. Found: C, 45.48; H, 6.41; N, 17.74; S, 10.27. IR ν_{max}^{Nujol} cm^{-1}: 3180 and 3150 (>NH), 1729 (>C=O), 1695 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 258 (4200). NMR ($CDCl_3$) τ (J=Hz): 9.00 (12H, d, J=6.8), 7.88 (2H, q, q, t, $J_1=J_2=J_3=6.8$), 5.82 (4H, d, J=6.8), *ca.* −0.92 (1H, broad), *ca.* −1.28 (1H, broad). 2-Isobutoxycarbonyl-5-isobutoxycarbonylamino-3-imino-1,2,4-thiadiazoline (**75**), colorless needles from benzene mp 159—161°, 1.11 g. *Anal.* Calcd. for $C_{12}H_{20}O_4N_4S$: C, 45.56; H, 6.37; N, 17.71; S, 10.11. Found: C, 45.49; H, 6.31; N, 17.59; S, 10.17. IR ν_{max}^{Nujol} cm^{-1}: 3420 and 3120 (>NH), 1738 (>C=O broad), 1645 (>C=N-). UV λ_{max}^{EtOH} mμ (ε): 261 (21800), 271 (22100). NMR ($CDCl_3$) τ (J=Hz): 9.08 (6H, d, J=6.8), 8.98 (6H, d, J= 6.8), 1.70—2.48 (2H, m), *ca.* 0.48 (1H, broad). N-Isobutoxycarbonylurea (**76**), colorless needles from benzene, mp 184—185°, 1.63 g. *Anal.* Calcd. for $C_6H_{12}O_3N_2$: C, 44.99; H, 7.55; N, 17.49. Found: C, 44.98; H, 7.48; N, 17.42. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3340, 3240 and 1665 (>NH and $-NH_2$), 1720 and 1245 (>O(O)–O–), 1695 (>C=O). NMR (DMSO-d_6) τ (J=Hz): 9.10 (6H, t, J=6.8), 8.05 (1H, q, q, t, $J_1=J_2=J_3=6.8$), 6.20 (2H, d, J=6.8), *ca.* 2.84 (2H, broad), *ca.* 0.30 (1H, broad).

Reaction of N-Ethoxycarbonyl-N′-phenylthiourea (77) with Bromine——**77** (22.4 g) was reacted with Bromine (17.0 g) in $CHCl_3$ (300 ml) by the general method to give 19.3 g of (**78**). N-Ethoxycarbonyl-N′-phenylurea (**78**), colorless needles from AcOEt, mp 101—107°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.63; H, 5.81; N, 13.46. Found: C, 57.59; H, 5.68; N, 13.40. IR ν_{max}^{Nujol} cm^{-1}: 3230 and 3100 (>NH), 1730 and 1245 (>C(O)–O–), 1695 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 240.5 (16800). NMR (DMSO-d_6) τ (J=Hz): 8.74 (3H, t, J= 7.0), 5.75 (2H, q, J=7.0), 3.08—2.38 (5H, m), *ca.* 0.06 (1H, broad), *ca.* −0.30 (1H, broad).

Reaction of N-Ethoxycarbonyl-N′-methylthiourea (79) with Bromine ——**79**(16.1 g) was reacted with bromine (17.0 g) in $CHCl_3$ (300 ml) by the general method to afford 0.52 g of sulfur, 5.49 g of **20**, **80**, **81**, and **82**. 3,5-Bis(ethoxycarbonylimino)-2,4-dimethyl-1,2,4-thiadiazolidine (**80**), colorless needles from benzene, mp 83—84°, 1.35 g. *Anal.* Calcd. for $C_{10}H_{16}O_4N_4S$: C, 41.66; H, 5.59; N, 19.44; S, 11.10. Found: C, 41.40; H, 5.50; N, 19.30; S, 11.31. Mass Spectrum: M^+=288, IR ν_{max}^{Nujol} cm^{-1}: 1665 (>C=O), 1635 (>C=O). UV λ_{max}^{EtOH} mμ (ε): 247.5 (24100), 286 (3400). NMR ($CDCl_3$) τ (J=Hz): 8.68 (3H, t, J=7.0), 8.63 (3H, t, J=7.0), 6.70 (3H, s), 6.42 (3H, s), 5.78 (2H, q, J=7.0), 5.66 (2H, q, J=7.0). 5-Ethoxycarbonylimino-4-methyl-3-methylamino-1,2,4-thiadiazoline (**81**), colorless needles from benzene, mp 192.5—193.5°, 2.31 g. *Anal.* Calcd. for $C_7H_{12}O_2N_4S$: C, 38.89; H, 5.59; N, 25.92; S, 14.80. Found: C, 39.19; H, 5.55; N, 26.13; S, 14.92. Mass Spectrum: M^+=216. IR ν_{max}^{Nujol} cm^{-1}: 3320 (>NH), 1625 (>C=N– or >C=O), 1610 (>C=O or >C=N–). UV λ_{max}^{EtOH} mμ (ε): 287.5 (8200). NMR ($CDCl_3$) τ (J=Hz): 8.68 (3H, t, J=7.0), 6.98 (3H, d, J=4.0), 6.48 (3H, s), 5.73 (2H, q, J=7.0), *ca.* 4.84 (1H, broad). N-Ethoxycarbonyl-N′-methylurea (**82**), colorless needles from AcOEt, mp 135—136°, 3.55 g. *Anal.* Calcd. for $C_5H_{10}O_3N_2$: C, 41.09; H, 6.90; N, 19.17. Found: C, 41.34; H, 6.96; N, 19.30. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3200, 3120 and 1680 (>NH and $-NH_2$), 1765 and 1210 (>C(O)–O–), NMR ($CDCl_3$) τ (J=Hz): 8.70 (3H, t, J=7.0), 7.11 (3H, d, J=5.0), 5.78 (2H, q, J=7.0), *ca.* 2.18 (1H, broad), *ca.* 1.32 (1H, broad).