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Studies on Isoxazoles. XII.[1] Novel Syntheses of 4-Isothiazolin-3-thiones and Bis(3-isoxazolyl) Disulfides from 4-Isoxazolin-3-thiones

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Heating of 2,5-dimethyl-4-isoxazolin-3-thione (IIa) in acidic media gave 2,5-dimethyl-4-isothiazolin-3-thione (IIIa) and bis(5-methyl-3-isoxazolyl) disulfide (IVa) in poor yields. On the other hand, 2-methyl-5-phenyl-4-isoxazolin-3-thione (IIe) afforded only bis(5-phenyl-3-isoxazolyl) disulfide (IVb). The reactions of 4-isoxazolin-3-thiones (IIa—d) with hydrogen sulfide or thioacetic acid in 48% hydrobromic acid gave 4-isothiazolin-3-thiones (IIIa—d) in moderate yields, while 5-phenyl-4-isoxazolin-3-thiones (IIe, f) afforded 3-imino-5-phenyl-1,2-dithiols (VIe, f) in addition to 5-phenyl-4-isothiazolin-3-thiones (IIIe, f). A reaction mechanism is proposed. The thiol (VIe) was treated with base to give IIIe. An improved synthesis of the disulfides (IVa, b) was developed by the reaction of 2-methyl-4-isoxazolin-3-thiones (IIa, b) or 2-benzyl-4-isoxazolin-3-thiones (IIg, h) with bromine.

Keywords—— ring transformation; 4-isoxazolin-3-thiones; 4-isothiazolin-3-thiones; 3-imino-1,2-dithiols; hydrogen sulfide; bis(3-isoxazolyl) disulfides; thermal oxidation

We are interested in the biological activities of 3-mercaptoisoxazoles,[3] and we therefore developed a synthetic strategy for these compounds starting from 3-hydroxyisoxazoles. The initial conversion of 3-hydroxyisoxazoles into 2-substituted-4-isoxazolin-3-thiones was described in the previous paper.[3] During the course of studies on the subsequent extrusion of the 2-substituents, novel syntheses of 4-isothiazolin-3-thiones and bis(3-isoxazolyl) disulfides were discovered. The present paper describes the scope of these syntheses and discusses the reaction mechanism.

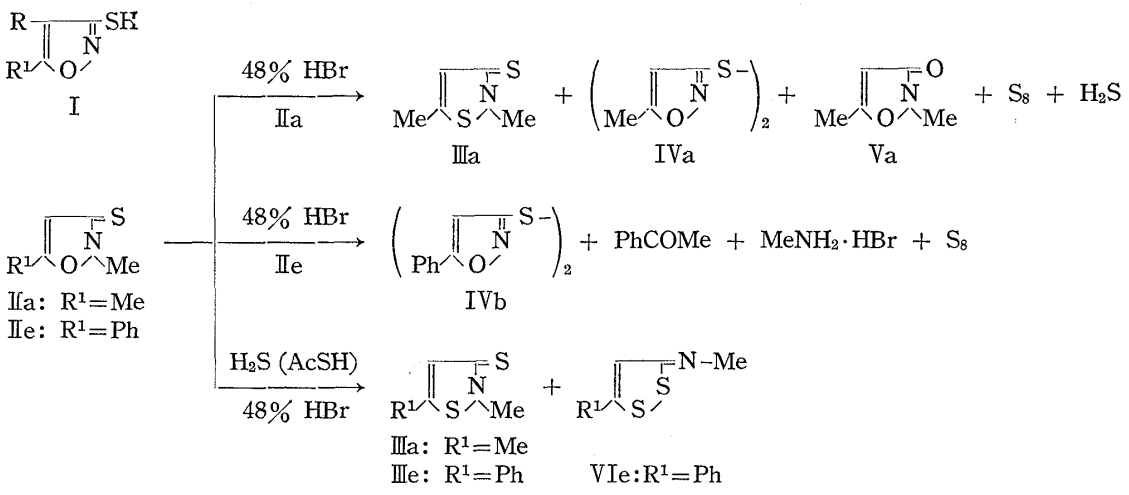


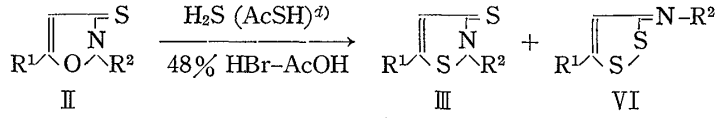
Chart 1

1) Part XI: S. Sugai and K. Tomita, *Chem. Parm. Bull.*, **28**, 103 (1980).
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140, Japan.*
3) K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.*, **27**, 2398 (1979).

The reaction of 2,5-dimethyl-4-isoxazolin-3-thione (IIa) with 48% hydrobromic acid (HBr) in boiling acetic acid (AcOH) did not give the expected 3-mercapto-5-methylisoxazole (I; R=H, R^1=CH_3), but afforded 2,5-dimethyl-4-isothiazolin-3-thione (IIIa), bis(5-methyl-3-isoxazolyl) disulfide (IVa), 3-isoxazolone (Va) and sulfur in poor yields (Chart 1, Table I). Such one-step isomerization of isoxazoles into isothiazoles has not previously been reported. Therefore, it seemed of interest to elucidate the pathway of transformation of IIa to IIIa.

On the other hand, the reaction of the 5-phenyl isomer (IIe, Chart 1) under the same conditions gave a disulfide (IVb) and various fragmentation products, including sulfur, acetophenone and monomethylamine hydrobromide. This suggested that a special factor was involved in the former reaction. As a result of careful examination, the generation of hydrogen sulfide (H_2S) was observed. Hydrogen sulfide would be formed by the degradation of IIa under acidic conditions. The introduction of H_2S during the reaction of IIa improved the yield of IIIa (Table I), and it was found to participate in the isomerization. The treatment of IIe with H_2S in acidic media gave a 3-imino-1,2-dithiol (VIe) in addition to a 4-isothiazolin-3-thione (IIIe). Moreover, VIe was quantitatively converted into IIIe by treatment with base.

Table I. Reactions of 4-Isoxazolin-3-thiones with H_2S (AcSH)[d] in 48% HBr and AcOH



II III VI

	II		III		VI		Recovery
	R^1	R^2	Yield (%)	mp (°C)	Yield (%)	mp (°C)	of II (%)
			3.0[a]		0[a]		38.4[a]
a	Me	Me	40.0	87—89	0		40.0
			15.5[b]		0[b]		44.4[b]
b	Me	Et	30.0	Oil	0		45.0
c	H	Me	42.0	111—112	0		20.0
d	^{n}Pr	Me	24.1	Oil	0		41.7
			0[c]		0[c]		0[c]
e	Ph	Me	29.2	155—157[e]	36.3	89—92	19.9
			29.2[d]		21.4[d]		0[d]
f	Ph	Et	38.9	92—95[f]	54.6	21—31	0

a) Without H_2S. The disulfide (IVa) (0.9%) was obtained.
b) Without 48% HBr.
c) Without H_2S. The disulfide (IVb) (1.5%) was obtained.
d) AcSH was used in place of H_2S.
e) Lit.[12] mp 153°.
f) Lit.[12] mp 93°.

It was reported[4] that isoxazoles (VII) are converted stepwise into the corresponding isothiazoles (IX) by reductive ring opening and subsequent treatment of the resulting enaminoketone (VIII) with phosphorus pentasulfide and chloranil (Chart 2). On the basis of the pathway of VII to IX, the reaction of II to III and VI was tentatively assumed to proceed as follows. A thermal cleavage[1] of the N–O bond in II would give an acylthioacetamide (X) similar to VIII. This would undergo acid-catalyzed transformation[5] of the carbonyl function to give a thiocarbonyl group with H_2S, followed by cyclization to give III or VI.

In order to examine this hypothetical pathway, the ring cleavage product of IIe, N-methylbenzoylthioacetamide (Xa)[1] (Chart 2) was treated with H_2S under acidic conditions to give

4) D.N. McGregor, U. Corbin, J.E. Swigor, and L.C. Cheney, *Tetrahedron*, **25**, 389 (1969).
5) E. Campaigne and B.E. Edwards, *J. Org. Chem.*, **27**, 3760 (1960).

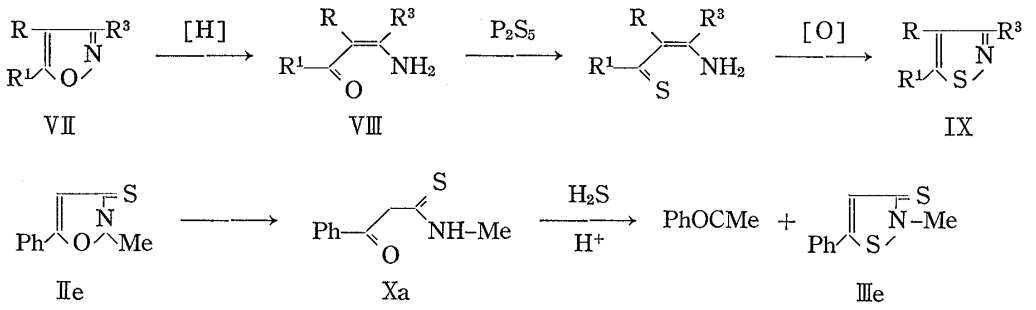


Chart 2

acetophenone as a major product, and IIIe in only 2% yield. This result excluded the possibility of X as an intermediate, and suggested that reaction occurred between II and H_2S before the ring opening. An alternative pathway was therefore proposed, as shown in Chart 3.

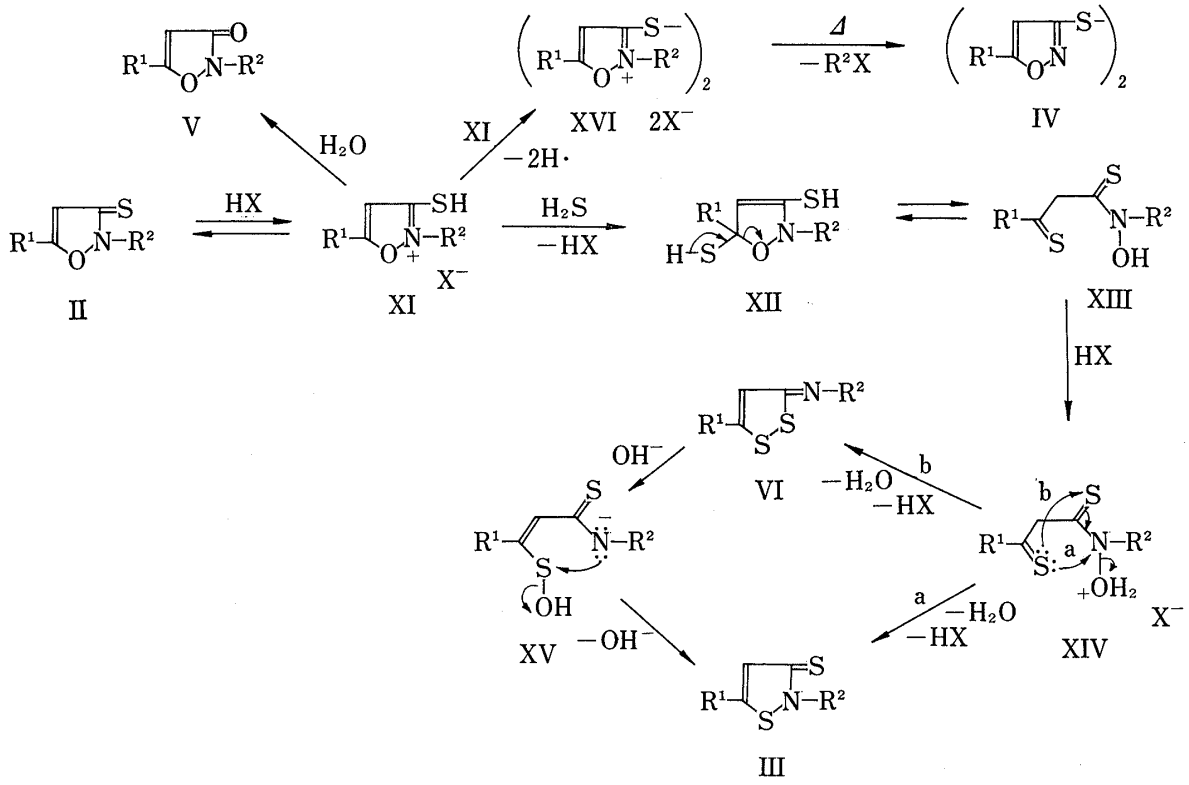


Chart 3

The thione (II) may be quaternized by acid to give a salt (XI). The nucleophilic attack of H_2S on XI at the 5-position would give a hemiketal (XII), which may then isomerize into a thiohydroxamic acid (XIII). In acidic media, two cyclization reactions, one leading to III with the formation of an S–N bond and the other leading to VI with an S–S bond, may compete. Base-catalyzed isomerization of VI to III would proceed *via* a sulfenic acid (XV). Hydrolysis of the intermediate salt (XI) would give 3-isoxazolone (V).

The treatment of IIa with H_2S in AcOH alone reduced the yield of IIIa (Table I). On the other hand, the reaction of IIa with H_2S in benzene did not give the isomerized product (IIIa), but afforded 1,4-dithiins.[1] Strong acid was found to give the key intermediate (XI)

in the initial step of the reaction (Chart 3). Some papers[6] have reported C^5–O bond fission reactions similar to the proposed pathway from XI to XIII. Generally speaking, hydroxylamines[7] undergo acid-catalyzed S_{N2} type reaction on the nitrogen atom. It seems reasonable, therefore, that the cyclization of the thiohydroxamic acid (XIII) to III or VI would be catalyzed by acid. The S–S bond fission in the isomerization of VI into III is equivalent to that observed in the reaction[8] of disulfides with base. On the other hand, 3-imino-1, 2-benzodithiols similar to VI were described[9] to be in equilibrium with the corresponding benzisothiazolin-3-thiones.

The synthesis of III was generalized by heating II with H_2S or thioacetic acid in a strong acid. Various 4-isothiazolin-3-thiones (IIIb—d, f) (Table I) were obtained in moderate yields with recovery of the starting materials.

Bis(3-isoxazolyl) disulfides (IVa, b) also attracted our attention, because the disulfides were considered to be potentially useful synthetic intermediates for 3-mercaptoisoxazoles (I). A plausible reaction pathway from II to IV is shown in Chart 3. Oxidative dimerization of XI would give a bisonium salt (XVI), which would afford IV with the elimination of alkyl halide (R^2X). A proposed bisonium salt (XVIa) was prepared by the oxidation of IIa with half-equimolar bromine (Chart 4). Subsequent pyrolysis of XVIa gave IVa in moderate yield. The same reaction of IIe gave XVIb, which was converted to IVb. The thermal reaction of 3-alkylthio-2-benzylisoxazolium halides was reported[10] to afford 3-alkylthioisoxazoles with the facile elimination of benzyl halides. Therefore, 2-benzyl-4-isoxazolin-3-thiones (IIg, h) were heated with half-equimolar bromine to give the corresponding disulfides (IVa, b) in better yields.

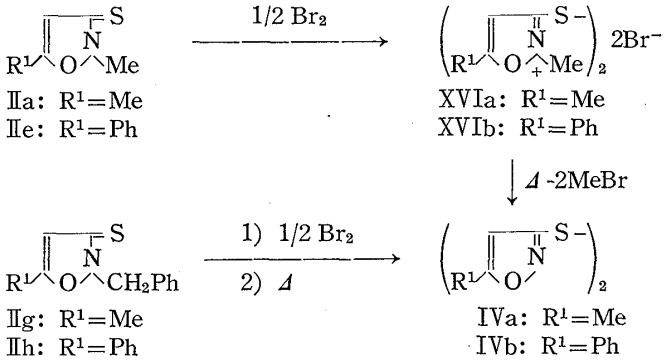


Chart 4

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi G_3 spectrometer and MS spectra on a JEOL JMS-01SG mass spectrometer. NMR spectra were taken on Varian EM-360A and Varian A-60 spectrometers using tetramethylsilane as an internal standard. The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Preparative TLC was carried out on Merck TLC plates, Silica Gel $60F_{254}$ (layer thickness 2 mm), and spots were visualized by ultraviolet irradiation or by exposure to iodine. Columns for chromatography were prepared with Wakogel C-200 (100—200 mesh) (Wako Pure Chemical Co., Inc.).

6) *a*) I. Adachi, *Chem. Pharm. Bull.*, **17**, 2209 (1969); *b*) E.C. Taylar and J. Bartulin, *Tetrahedron Lett.*, **1967**, 2337.
7) *a*) T. Okamoto, K. Shudo, and T. Ohta, *J. Am. Chem. Soc.*, **97**, 7184 (1975); *b*) T. Ohta, K. Shudo, and T. Okamoto, *Tetrahedron Lett.*, **1978**, 1983.
8) A.J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071 (1960).
9) E.W. McClelland and C.E. Salkeld, *J. Chem. Soc.*, **1936**, 1143.
10) K. Tomita, S. Sugai, and M. Saito, *Chem. Pharm. Bull.*, **27**, 2415 (1979).

Reaction of 2,5-Dimethyl-4-isoxazolin-3-thione (IIa) with 48% HBr——A solution of IIa (500 mg) in 48% HBr (4 ml) and AcOH (8 ml) was heated at 100—110° for 6 hr. After cooling, H_2O (30 ml) and CH_2Cl_2 (30 ml) were added to the mixture. The organic layer was separated, and concentrated. The residue was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give sulfur (14 mg), bis(5-methyl-3-isoxazolyl) disulfide (IVa) (4 mg, 1%), mp 37—38°, and IIa (192 mg). The aq. layer was made basic with 10% NaOH, and extracted with CH_2Cl_2 (30 ml×3). After removing the solvent, the residue was separated by preparative TLC (*n*-hexane–acetone=2: 1) to afford 2,5-dimethyl-4-isothiazolin-3-thione (IIIa) (17 mg, 3%) and 2,5-dimethyl-4-isoxazolin-3-one[11] (Va) (43 mg, 10%). IIIa: *Anal.* Calcd for $C_5H_7NS_2$: C, 41.35; H, 4.86; N, 9.64; S, 44.15. Found: C, 41.38; H, 4.76; N, 9.87; S, 43.76. NMR (CCl_4) δ: 2.46 (3H, d, J=1.4 Hz, 5-C$\underline{H}_3$), 3.59 (3H, s, N–C$\underline{H}_3$), 6.57 (1H, q, J=1.4 Hz, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 3060, 1535, 1460. MS *m/e*: 145 (M^+), 116, 83, 71, 59. IVa: *Anal.* Calcd for $C_8H_8N_2O_2S_2$: C, 42.09; H, 3.53; N, 12.27; S, 28.09. Found: C, 41.77; H, 3.77; N, 12.03; S, 28.26. NMR ($CDCl_3$) δ: 2.38 (6H, d, J=0.8 Hz, 2×C$\underline{H}_3$), 6.25 (2H, q, J=0.8 Hz, 2×4-H). MS *m/e*: 228 (M^+), 196.

Reaction of 2-Methyl-5-phenyl-4-isoxazolin-3-thione (IIe) with 48% HBr——A solution of IIe (500 mg) in 48% HBr (4 ml) and AcOH (8 ml) was heated for 7 hr. After cooling, the mixture was extracted with ether (20 ml×3). The extract was concentrated, and the residue was column chromatographed (*n*-hexane–acetone=50: 1) to give sulfur (19 mg), acetophenone (61 mg) and bis(5-phenyl-3-isoxazolyl) disulfide (IVb) (7 mg, 2%), mp 115—117°. The aq. layer was concentrated *in vacuo* to dryness, and the solid was precipitated from $CHCl_3$ with acetone to give monomethylamine hydrobromide (185 mg, 63%), mp 245—255°. IVb: *Anal.* Calcd for $C_{18}H_{12}N_2O_2S_2$: C, 61.34; H, 3.43; N, 7.95; S, 18.50. Found: C, 61.50; H, 3.39; N, 8.19; S, 18.11. NMR ($CDCl_3$) δ: 7.94 (2H, s, 2×4-H), 7.42—8.06 (10H, m, 2×C_6H_5). IR ν_{max}^{Nujol} cm^{-1}: 1610. Monomethylamine hydrobromide: *Anal.* Calcd for CH_6BrN: C, 10.73; H, 5.40; Br, 71.36; N, 12.51. Found: C, 10.75; H, 5.67; Br, 70.96; N, 12.52. IR ν_{max}^{Nujol} cm^{-1}: 3300—3000.

Syntheses of 4-Isothiazolin-3-thiones (III)——General Procedure: A solution of a 4-isoxazolin-3-thione (II) (0.01 mol) in 48% HBr (5 ml) and AcOH (10 ml) was bubbled through with H_2S at 100—110° for 3—5 hr. After cooling, the mixture was extracted with CH_2Cl_2. The extract was concentrated to recover II. The aq. layer was made basic with 10% NaOH, and extracted with CH_2Cl_2. The solvent was evaporated off to leave a residue, which was separated by column chromatography or preparative TLC to give III and a 3-imino-1,2-dithiol (VI) (Table I).

2-Ethyl-5-methyl-4-isothiazolin-3-thione (IIIb): *Anal.* Calcd for $C_6H_9NS_2$: C, 45.25; H, 5.70; N, 8.79; S, 40.26. Found: C, 45.30; H, 5.79; N, 8.84; S, 39.76. NMR (CCl_4) δ: 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.45 (3H, d, J=1 Hz, 5-C$\underline{H}_3$), 4.15 (2H, q, J=7 Hz, C$\underline{H}_2$), 6.52 (1H, q, J=1 Hz, 4-H). IR ν_{max}^{Liquid} cm^{-1}: 3075, 1540, 1360. MS *m/e*: 159 (M^+), 131, 117, 116, 83, 71, 59.

2-Methyl-4-isothiazolin-3-thione (IIIc): *Anal.* Calcd for $C_4H_5NS_2$: C, 36.31; H, 3.84; N, 10.67; S, 48.87. Found: C, 36.48; H, 3.76; N, 10.39; S, 48.88. NMR ($CDCl_3$) δ: 3.73 (3H, s, C$\underline{H}_3$), 6.90 (1H, d, J=6 Hz, 4-H), 8.25 (1H, d, J=6 Hz, 5-H). IR ν_{max}^{Nujol} cm^{-1}: 3050, 1480, 1350. MS *m/e*: 131 (M^+), 102, 69, 57, 45.

2-Methyl-5-*n*-propyl-4-isothiazolin-3-thione (IIId): *Anal.* Calcd for $C_7H_{11}NS_2$: C, 48.52; H, 6.40; N, 8.08; S, 37.00. Found: C, 48.44; H, 6.45; N, 8.28; S, 36.80. NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.67 (2H, m, $C\underline{H}_2CH_3$), 2.73 (2H, t of d, J=7, 1 Hz, 5-C$\underline{H}_2$), 3.67 (3H, s, N–C$\underline{H}_3$), 6.68 (1H, t, J=1, 4-H). IR ν_{max}^{Liquid} cm^{-1}: 2950, 1540, 1330. MS *m/e*: 173 (M^+), 145, 140, 111, 101, 87.

2-Methyl-5-phenyl-4-isothiazolin-3-thione (IIIe):[12] *Anal.* Calcd for $C_{10}H_9NS_2$: C, 57.94; H, 4.38; N, 6.76; S, 30.93. Found: C, 57.76; H, 4.37; N, 6.89; S, 30.90. NMR ($CDCl_3$) δ: 3.77 (3H, s, C$\underline{H}_3$), 7.13 (1H, s, 4-H), 7.52 (5H, s, $C_6\underline{H}_5$). IR ν_{max}^{Liquid} cm^{-1}: 3050, 1530, 1485, 1340. MS *m/e*: 207 (M^+), 178, 145, 121, 102, 77.

2-Ethyl-5-phenyl-4-isothiazolin-3-thione (IIIf):[12] *Anal.* Calcd for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.01; N, 6.03; S, 28.97. Found: C, 59.69; H, 5.03; N, 6.46; S, 29.19. NMR (CCl_4) δ: 1.48 (3H, t, J=7 Hz, C$\underline{H}_3$), 4.29 (2H, q, J=7 Hz, C$\underline{H}_2$), 7.08 (1H, s, 4-H), 7.46 (5H, s, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 3050, 1520, 1480, 1335. MS *m/e*: 221 (M^+), 178, 145, 135, 102, 77.

3-Methylimino-5-phenyl-1,2-dithiol (VIe): *Anal.* Calcd for $C_{10}H_9NS_2$: C, 57.92; H, 4.38; N, 6.76; S, 30.93. Found: C, 57.78; H, 4.15; N, 6.52; S, 31.05. NMR (CCl_4) δ: 3.13 (3H, s, C$\underline{H}_3$), 6.78 (1H, s, 4-H), 7.3—7.7 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 3050, 1605. MS *m/e*: 207 (M^+), 178, 166, 143, 121, 102.

3-Ethylimino-5-phenyl-1,2-dithiol (VIf): *Anal.* Calcd for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.01; N, 6.33; S, 28.97. Found: C, 59.55; H, 5.18; N, 6.07; S, 28.59. NMR (CCl_4) δ: 1.31 (3H, t, J=7 Hz, C$\underline{H}_3$), 3.18 (2H, q, J=7 Hz, C$\underline{H}_2$), 6.77 (1H, s, 4-H), 7.3—8.2 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Neat} cm^{-1}: 3050, 1600. MS *m/e*: 221 (M^+), 206, 192, 166, 157, 128, 121, 102, 77.

Reaction of IIe with Thioacetic Acid——A solution of IIe (500 mg) in 48% HBr (4 ml) and AcOH (8 ml) was treated with thioacetic acid (398 mg). The mixture was stirred at 80—90° for 4.5 hr. After addition of H_2O (50 ml), the precipitated sulfur (35 mg) was collected by filtration. The filtrate was made basic with 10% NaOH, and extracted with CH_2Cl_2 (20 ml×3). The solvent was evaporated off to leave a residue, which

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12) G.L. Coustumer and Y. Mollier, *Bull. Soc. Chim. Fr.*, **1970**, 3076.

was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give acetophenone (31 mg), IIIe (158 mg, 29%), VIe (116 mg, 21%) and 2-methyl-5-phenyl-4-isoxazolin-3-one[13] (9 mg).

Isomerization of VIe into IIIe——A solution of VIe (70 mg) in MeOH (5 ml) was treated with 10% NaOH (5 ml). After stirring at room temperature for 17 hr, the mixture was diluted with H_2O (10 ml), and extracted with CH_2Cl_2 (10 ml×3). The solvent was evaporated off to give IIIe (48 mg, 96%), mp 155—157° (lit.[12] mp 153°).

Reaction of N-Methylbenzoylthioacetamide (Xa)[1] with H_2S——A solution of Xa (500 mg) in 48% HBr (4 ml) and AcOH (8 ml) was bubbled through with H_2S at 100—110° for 4 hr. After cooling, the precipitated crystals (Xa, 49 mg) were collected by filtration. The filtrate was made basic with 10% NaOH, and extracted with CH_2Cl_2 (20 ml×3). The extract was concentrated, and the residue was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give acetophenone (122 mg, 39%) and IIIe (10 mg, 2%).

Bis(2,5-dimethylisoxazolium) Dibromide 3,3′-Disulfide (XVIa)——A solution of IIa (615 mg) in $CHCl_3$ (10 ml) was treated with bromine (381 mg). The mixture was stirred at room temperature for 4 hr, then filtered. The collected product was precipitated from CH_2Cl_2 with ether to give XVIa (739 mg, 74.2%), mp 141—145°. NMR (DMSO-d_6). δ: 2.68 (6H, d, J=0.8 Hz, 2×5-C$\underline{H}_3$), 4.41 (6H, s, 2×N-C$\underline{H}_3$), 7.67 (2H, q, J=0.8 Hz, 2×4-H). IR ν_{max}^{Nujol} cm^{-1}: 1570, 1510.

Bis(2-methyl-5-phenylisoxazolium) Dibromide 3,3′-Disulfide (XVIb)——53%, mp 125—130°. *Anal.* Calcd for $C_{20}H_{18}Br_2N_2O_2S_2 \cdot H_2O$: C, 42.80; H, 3.24; Br, 28.52; N, 5.00; S, 11.44. Found: C, 42.76; H, 3.54; Br, 28.83; N, 5.04; S, 11.27. NMR (CD_3OD) δ: 4.10 (6H, s, 2×C$\underline{H}_3$), 7.18 (2H, s, 2×4-H), 7.5—8.2 (10H, m, 2×C$_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1590, 1550.

Bis(5-methyl-3-isoxazolyl) Disulfide (IVa)——a) A solution of XVIa (578 mg) in MeCN (5 ml) was refluxed for 3 hr, then concentrated. The residue was column chromatographed (*n*-hexane–acetone=30: 1) to give IVa (151 mg, 39%).

b) A solution of 2-benzyl-5-methyl-4-isoxazolin-3-thione (IIg) (615 mg) in $CHCl_3$ (10 ml) was treated with bromine (240 mg). The mixture was stirred at room temperature for 3 hr, and then at 60—70° for 3 hr. After removal of the solvent, the residue was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give IVa (258 mg, 75%) and benzyl bromide (220 mg).

Bis(5-phenyl-3-isoxazolyl) Disulfide (IVb)——a) A solution of XVIb (700 mg) in MeCN (20 ml) was refluxed for 5 hr, then concentrated. The residue was column chromatographed (*n*-hexane–acetone=20: 1) to give IVb (187 mg, 41%).

b) A solution of 2-benzyl-5-phenyl-4-isoxazolin-3-thione (IIh) (534 mg) in $CHCl_3$ (20 ml) was treated with bromine (176 mg). The mixture was stirred at room temperature for 15 hr, and then at 80° for 1 hr. After removing the solvent, the residue was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give benzyl bromide (158 mg), 3-benzylthio-5-phenylisoxazole[10] (20 mg) and IVb (215 mg, 61%).

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