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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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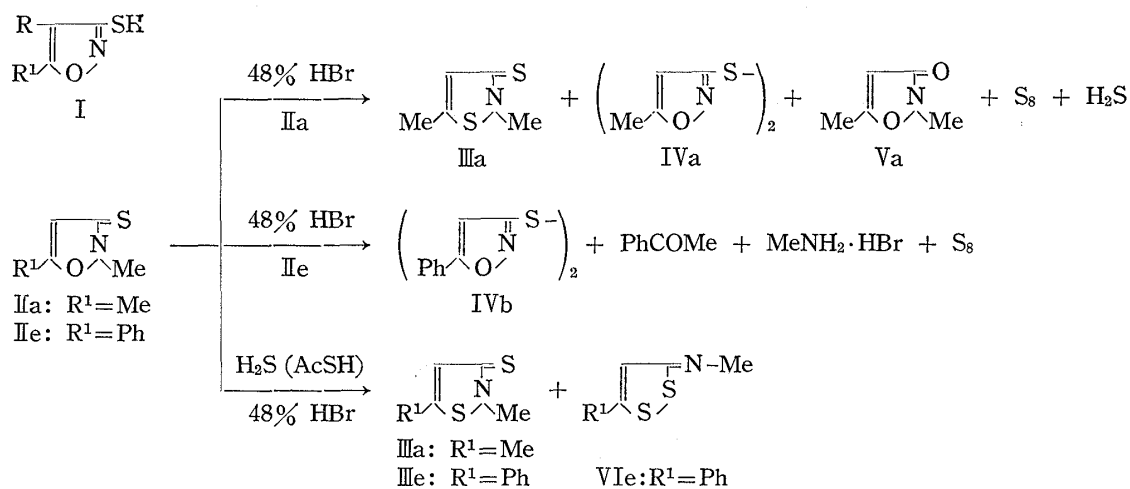
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Heating of 2,5-dimethyl-4-isoxazolin-3-thione (IIa) in acidic media gave 2,5-dimethyl-4-isothiazolin-3-thione (IIIa) and bis(5-methyl-3-isoxazolyl) disulfide (IVa) in poor yields. On the other hand, 2-methyl-5-phenyl-4-isoxazolin-3-thione (IIe) afforded 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.



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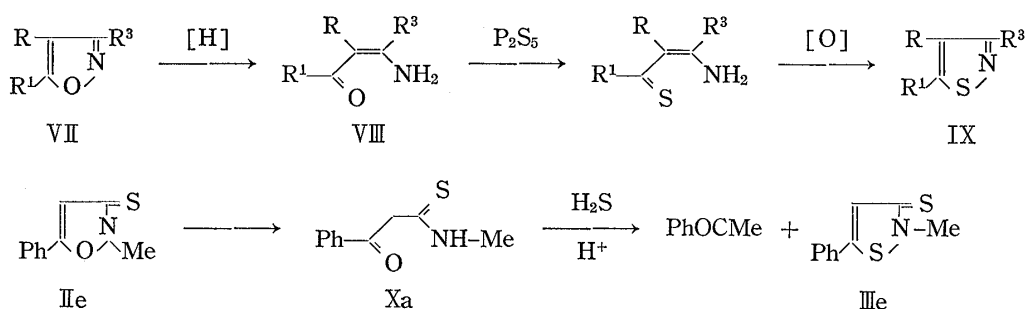


Chart 2

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.

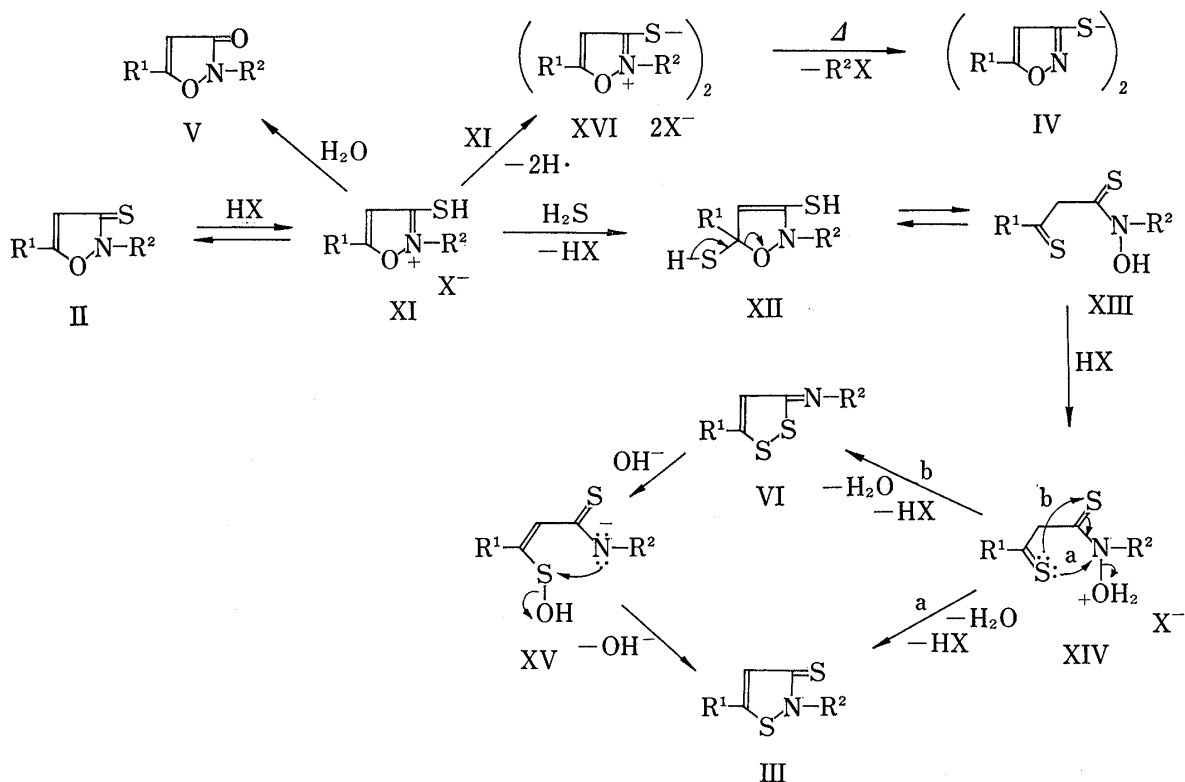


Chart 3

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-isoxazalone (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 papers⁶⁾ have reported C⁵-O bond fission reactions similar to the proposed pathway from XI to XIII. Generally speaking, hydroxylamines⁷⁾ 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 reaction⁸⁾ of disulfides with base. On the other hand, 3-imino-1,2-benzodithiols similar to VI were described⁹⁾ to be in equilibrium with the corresponding benzisothiazolin-3-thiones.

The synthesis of III was generalized by heating II with H₂S 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 (R²X). 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 reported¹⁰⁾ 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.

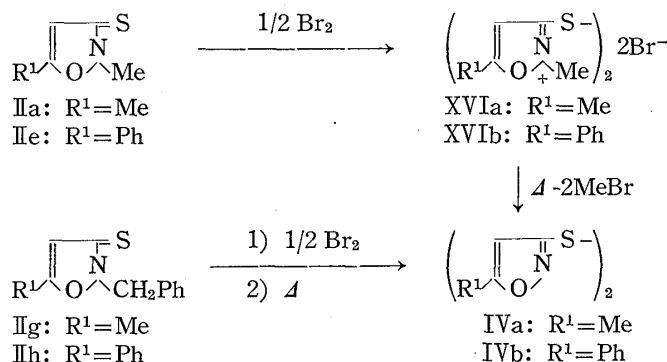


Chart 4

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi G₃ 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 60F₂₅₄ (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.).

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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, H₂O (30 ml) and CH₂Cl₂ (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 CH₂Cl₂ (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-one¹¹ (Va) (43 mg, 10%). IIIa: *Anal.* Calcd for C₅H₇NS₂: 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 (CCl₄) δ : 2.46 (3H, d, J =1.4 Hz, 5-CH₃), 3.59 (3H, s, N-CH₃), 6.57 (1H, q, J =1.4 Hz, 4-H). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3060, 1535, 1460. MS m/e : 145 (M⁺), 116, 83, 71, 59. IVa: *Anal.* Calcd for C₈H₈N₂O₂S₂: 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 (CDCl₃) δ : 2.38 (6H, d, J =0.8 Hz, 2 × CH₃), 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 CHCl₃ with acetone to give monomethylamine hydrobromide (185 mg, 63%), mp 245–255°. IVb: *Anal.* Calcd for C₁₈H₁₂N₂O₂S₂: 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 (CDCl₃) δ : 7.94 (2H, s, 2 × 4-H), 7.42–8.06 (10H, m, 2 × C₆H₅). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1610. Monomethylamine hydrobromide: *Anal.* Calcd for CH₅BrN: 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 $\nu_{\text{max}}^{\text{Nujol}}$ 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 H₂S at 100–110° for 3–5 hr. After cooling, the mixture was extracted with CH₂Cl₂. The extract was concentrated to recover II. The aq. layer was made basic with 10% NaOH, and extracted with CH₂Cl₂. 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 C₆H₉NS₂: 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 (CCl₄) δ : 1.33 (3H, t, J =7 Hz, CH₂CH₃), 2.45 (3H, d, J =1 Hz, 5-CH₃), 4.15 (2H, q, J =7 Hz, CH₂), 6.52 (1H, q, J =1 Hz, 4-H). IR $\nu_{\text{max}}^{\text{Liquid}}$ 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 C₄H₅NS₂: 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 (CDCl₃) δ : 3.73 (3H, s, CH₃), 6.90 (1H, d, J =6 Hz, 4-H), 8.25 (1H, d, J =6 Hz, 5-H). IR $\nu_{\text{max}}^{\text{Nujol}}$ 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 C₇H₁₁NS₂: 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 (CDCl₃) δ : 1.02 (3H, t, J =7 Hz, CH₂CH₃), 1.67 (2H, m, CH₂CH₃), 2.73 (2H, t of d, J =7, 1 Hz, 5-CH₂), 3.67 (3H, s, N-CH₃), 6.68 (1H, t, J =1, 4-H). IR $\nu_{\text{max}}^{\text{Liquid}}$ 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 C₁₀H₉NS₂: 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 (CDCl₃) δ : 3.77 (3H, s, CH₃), 7.13 (1H, s, 4-H), 7.52 (5H, s, C₆H₅). IR $\nu_{\text{max}}^{\text{Liquid}}$ 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 C₁₁H₁₁NS₂: 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 (CCl₄) δ : 1.48 (3H, t, J =7 Hz, CH₂CH₃), 4.29 (2H, q, J =7 Hz, CH₂), 7.08 (1H, s, 4-H), 7.46 (5H, s, C₆H₅). IR $\nu_{\text{max}}^{\text{Nujol}}$ 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 C₁₀H₉NS₂: 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 (CCl₄) δ : 3.13 (3H, s, CH₃), 6.78 (1H, s, 4-H), 7.3–7.7 (5H, m, C₆H₅). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3050, 1605. MS m/e : 207 (M⁺), 178, 166, 143, 121, 102.

3-Ethylimino-5-phenyl-1,2-dithiol (VIIf): *Anal.* Calcd for C₁₁H₁₁NS₂: 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 (CCl₄) δ : 1.31 (3H, t, J =7 Hz, CH₂CH₃), 3.18 (2H, q, J =7 Hz, CH₂), 6.77 (1H, s, 4-H), 7.3–8.2 (5H, m, C₆H₅). IR $\nu_{\text{max}}^{\text{Nujol}}$ 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 H₂O (50 ml), the precipitated sulfur (35 mg) was collected by filtration. The filtrate was made basic with 10% NaOH, and extracted with CH₂Cl₂ (20 ml × 3). The solvent was evaporated off to leave a residue, which

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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-one¹³⁾ (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 H₂O (10 ml), and extracted with CH₂Cl₂ (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 H₂S—A solution of Xa (500 mg) in 48% HBr (4 ml) and AcOH (8 ml) was bubbled through with H₂S 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 CH₂Cl₂ (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 CHCl₃ (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 CH₂Cl₂ 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-CH₃), 4.41 (6H, s, 2 × N-CH₃), 7.67 (2H, q, *J*=0.8 Hz, 2 × 4-H). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1570, 1510.

Bis(2-methyl-5-phenylisoxazolium) Dibromide 3,3'-Disulfide (XVIb)—53%, mp 125—130°. *Anal.* Calcd for C₂₀H₁₈Br₂N₂O₂S₂ · H₂O: 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 (CD₃OD) δ: 4.10 (6H, s, 2 × CH₃), 7.18 (2H, s, 2 × 4-H), 7.5—8.2 (10H, m, 2 × C₆H₅). IR $\nu_{\text{max}}^{\text{Nujol}}$ 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 CHCl₃ (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 CHCl₃ (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-phenylisoxazole¹⁰⁾ (20 mg) and IVb (215 mg, 61%).

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