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Studies on Isoxazoles. XIII.[1] Synthesis and Chemical Properties of 3-Mercaptoisoxazoles

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3-Mercaptoisoxazoles (XI) were synthesized from 3-allylsulfinylisoxazoles (II). The reaction of II with triphenylphosphine in the presence of acetic anhydride gave the corresponding 3-acetylthioisoxazoles (VII). The thioacetates (VII) were converted into 3-mercaptoisoxazoles (XI) by reaction with silver nitrate and subsequent treatment of the resulting silver salts (X) with hydrogen sulfide. The thiols (XI) were oxidized in air to give the corresponding disulfides (XIV). In alkaline solution, 3-mercapto-5-phenylisoxazole (XIb) was decomposed into benzoylacetonitrile (IX) and sulfur.

Keywords——3-allylsulfinylisoxazoles; 3-acetylthioisoxazoles; silver 3-isaxazolylthiolates; 3-mercaptoisoxazoles; base-catalyzed ring opening; air oxidation

The synthesis and biological activities of 3-mercaptoisoxazoles have been one of our major interests.[3] In our studies on the synthesis of 3-mercaptoisoxazoles, 3-hydroxyisoxazoles were chosen as starting materials and converted into 3-allylthioisoxazoles in four steps.[3,4] In the present paper, we describe the transformation of 3-allylthioisoxazoles into 3-mercaptoisoxazoles.

Evance[5] first described the nucleophilic cleavage of allyl sulfenates to produce thiolate ions. The reaction of allyl *p*-tolylsulfenate (IIIa), which is prepared by the rearrangement[6] of an allyl sulfoxide (IIa), with trimethyl phosphite proceeds *via* the Michaelis–Arbuzov cleavage[7] of the phosphonium salt (IVa) to afford *p*-tolyl sulfides (Ia, Va) and a phosphate

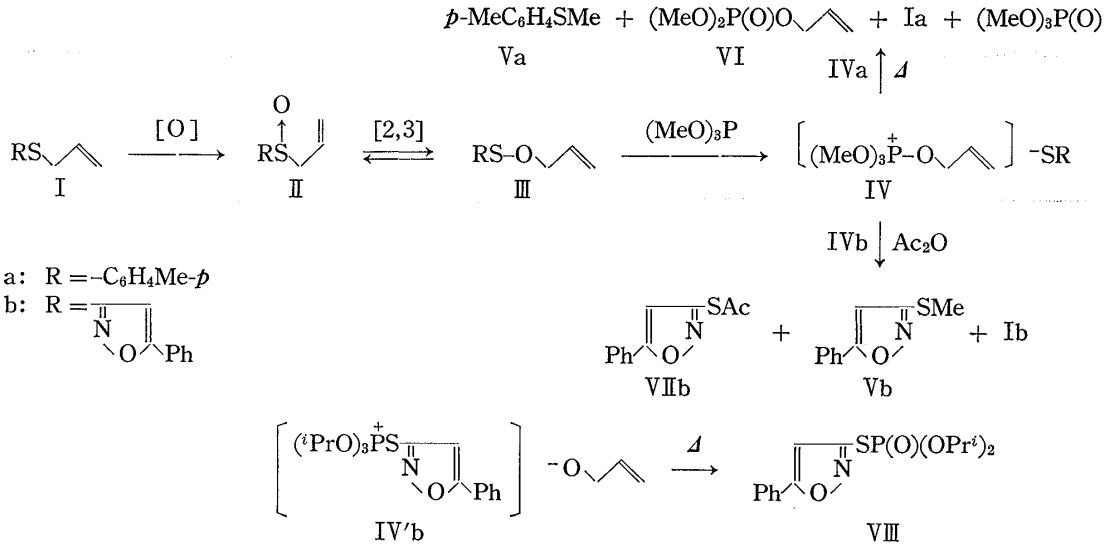
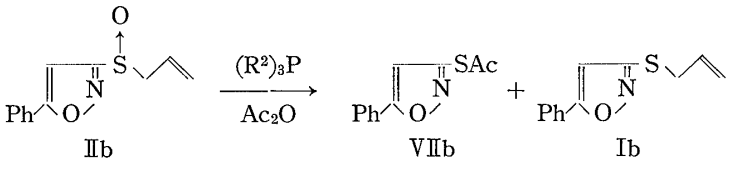


Chart 1

1) Part XII: S. Sugai and K. Tomita, *Chem. Pharm. Bull.*, **28**, 487 (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).
4) K. Tomita, S. Sugai, and M. Saito, *Chem. Pharm. Bull.*, **27**, 2415 (1979).
5) D.A. Evance and G.C. Andrews, *J. Am. Chem. Soc.*, **94**, 3672 (1972).
6) P. Bickart, F.W. Carson, J. Jacobus, E.G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4846 (1968).
7) R.G. Harrey and E.R. Desombre, *Top. Phosphorus Chem.*, **1**, 57 (1964).

Table I. Products (%) isolated from the Reactions of 3-Allylsulfinyl-5-phenylisoxazole (IIb) with Phosphites or Triphenylphosphine in the Presence of Acetic Anhydride



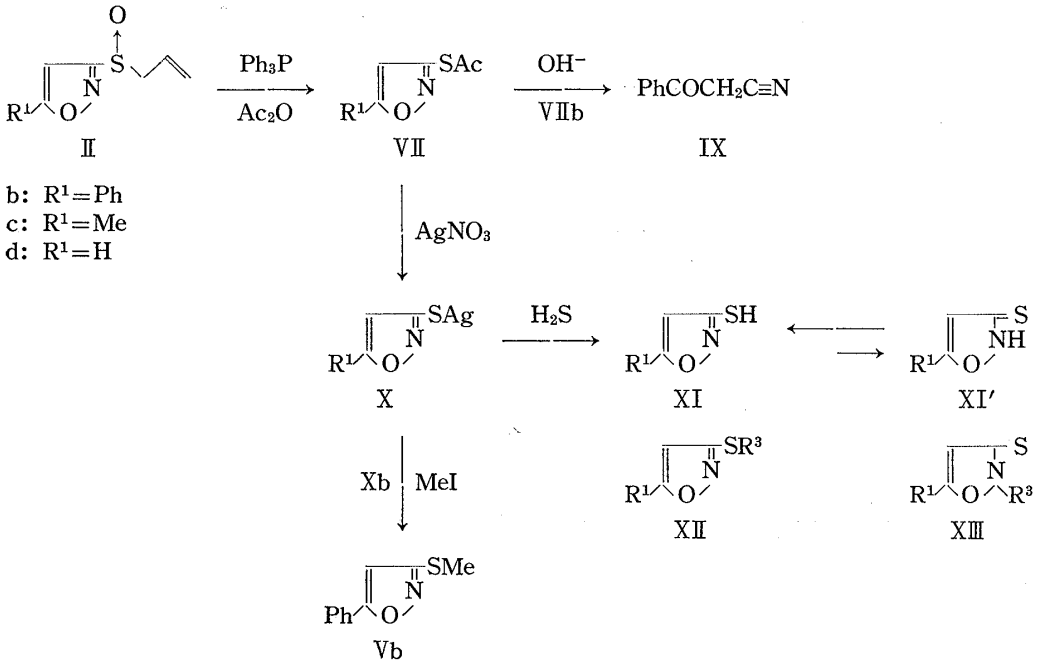
IIb VIIb Ib

$(R^2)_3P$ R^2	VIIb	Ib
OMe[a]	68.3	18.9
OEt[b]	59.8	14.7
O iso-Pr[c]	34.3	5.9
OPh	67.0	5.8
Ph	98.0	0

a) 3-Methylthio-5-phenylisoxazole (Vb) (2.7%) was isolated.
b) 3-Ethylthio-5-phenylisoxazole (XIIb, R^3=Et) (1.1%) was isolated.
c) S-(5-Phenyl-3-isoxazolyl) diisopropylphosphorothiolate (VIII) (43.2 %) was isolated.

(VI) (Chart 1). Therefore, it should be possible to trap the thiolate ion (RS^-) from the intermediate (IV) by using a suitable electrophile.

3-Allylsulfinyl-5-phenylisoxazole (IIb) was prepared by the oxidation of a sulfide (Ib)[4] with *m*-chloroperbenzoic acid (Chart 1). The reaction of IIb with trimethyl phosphite in the presence of acetic anhydride as an electrophile afforded 3-acetylthio-5-phenylisoxazole (VIIb) and sulfides (Ib, Vb). These products appear to be produced by the nucleophilic attack of the thiolate ion on acetic anhydride and the phosphonium cation in the intermediate salt (IVb). The reactions of IIb with various phosphites gave VIIb, together with Ib. A phosphorothiolate (VIII) was also obtained in moderate yield, when triisopropyl phosphite was used (Table I). The phosphorothiolate (VIII) could be formed from another phosphonium salt (IV'b) (Chart 1). Treatment of IIb with triphenylphosphine, however, afforded exclu-



II VII IX X XI XI' XII XIII Vb

Chart 2

sively VIIb in excellent yield. Similarly, sulfoxides (IIc, d) were converted into 3-acetylthioisoxazoles (VIIc, d) (Chart 2).

Base-catalyzed deacetylation of VIIb gave benzoylacetonitrile (IX) in place of the expected 3-mercapto-5-phenylisoxazole (XIb) (Chart 2). On the other hand, the reaction of VII with silver nitrate in methanol gave silver 3-isoxazolylthiolates (X) in high yields. The structure of the silver salt Xb was confirmed by reaction with methyl iodide to give 3-methylthio-5-phenylisoxazole (Vb).[4] The treatment of X with hydrogen sulfide gave 3-mercaptoisoxazoles (XI), which would be in equilibrium with the thioxo isomer (XI′). The ultraviolet (UV) spectra of XIb and XIc resembled those of the corresponding 3-alkylthioisoxazoles (XII)[4] rather than those of 4-isoxazolin-3-thiones (XIII)[3] (Fig. 1). The nuclear magnetic resonance (NMR) and infrared (IR) spectra of each compound (XI) showed a peak assignable to the mercapto group.

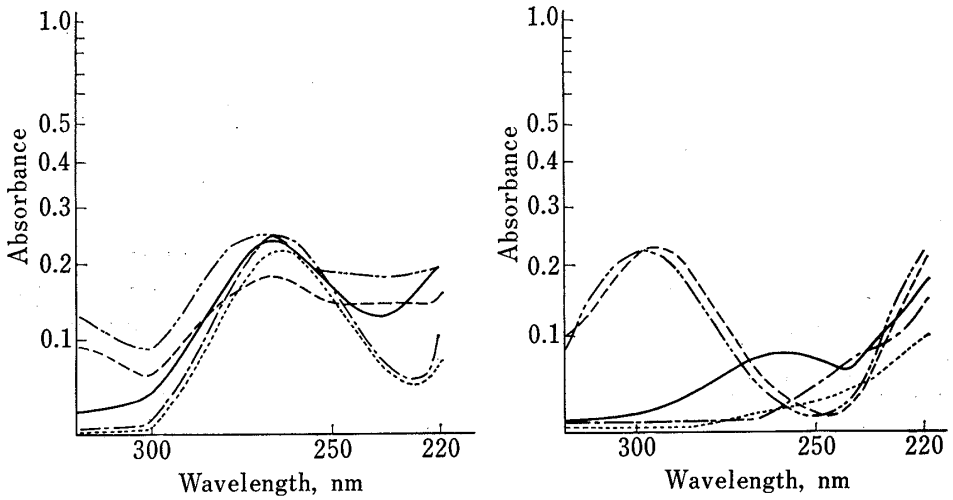


Fig. 1. UV Spectra of 3-Alkylthioisoxazoles (XIIb, c) and 4-Isoxazoline-3-thiones (XIIIb, c) in Ethanol

The chemical properries of 3-mercaptoisoxazoles (XI) were investigated. On standing in ethanol, 3-mercaptoisoxazoles (XI) were oxidized to give bis(3-isoxazolyl) disulfides (XIV). The stability of the thiols is in the order XIb>XIc>XId; XIb is most insensitive to auto-oxidation. In an alkaline solution, XIb was transformed into benzoylacetonitrile (IX), with loss of sulfur. The reaction sequence can be outlined as shown in Chart 3. A thiolate (XV) might undergo fragmentation by both or either of the following routes. One involves a 3-isoxazolyl carbanion (XVI) (path a), and the other involves an initial S–N interaction to afford a thiazirin intermediate (XVII). Subsequently, the intermediate (XVII) might isomerize into IX *via* a nitrile sulfide (XVIII) (path b). The reaction of nitrile sulfides with acetylenes has been reported[8] to yield isothiazoles. An attempt to trap the intermediate (XVIII) with dimethyl acetylenedicarboxylate was unsuccessful. An isoxazolyl carbanion similar to XVI has been proposed as an intermediate in the ring-opening reactions induced

8) R.K. Howe, T.A. Gruner, L.G. Carter, L.L. Black, and J.E. Franz, *J. Org. Chem.*, **43**, 3736 (1978).

by base-catalyzed proton abstraction[9] from 3-unsubstituted isoxazoles, by treatment[10] of 3-acetylisoxazoles with sodium ethoxide, and by base-catalyzed decarboxylation[11] of 3-isoxazolylcarboxylic acids.

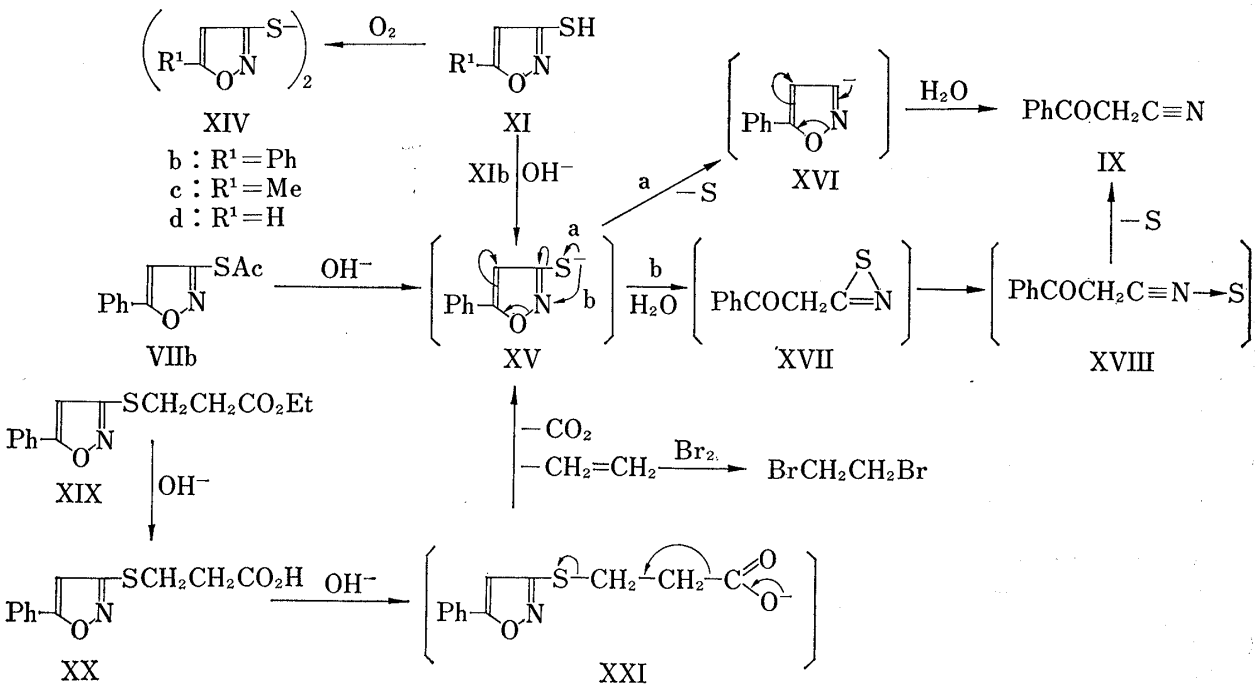


Chart 3

The transformation of 3-acetylthio-5-phenylisoxazole (VIIb) into benzoylacetonitrile (IX) presumably proceeds *via* the same intermediate (XV) (Chart 3). In the previous paper,[4] the alkaline hydrolysis of ethyl *β*-(5-phenyl-3-isoxazolylthio)propionate (XIX) was reported to give IX as a major product. The reaction mixture was examined by gas chromatography to detect ethylene, which was brominated to give ethylene dibromide. The treatment of *β*-(5-phenyl-3-isoxazolylthio)propionic acid (XX) with base also gave IX. In a basic medium, therefore, the resulting carboxylate ion (XXI) would undergo heterolytic fragmentation[12] to give the intermediate (XV).

Experimental

Melting points are uncorrected. IR spectra were recorded on a Hitachi G_3 spectrometer, UV spectra on a Beckmann DB spectrophotometer and MS spectra on a JEOL JMS-01SG mass spectrometer. NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The abbreviations used are as follows: s(singlet); d (doublet); q (quartet) and m (multiplet). Gas chromatography was performed with a Hitachi 163 gas chromatograph. Preparative TLC was carried out on Silica Gel 60 F_{254} (E. Merck). Columns for chromatography were prepared with Wakogel C-200 (Wako Pure Chemical Industries, Ltd.).

3-Allylsulfinylisoxazoles (II)——General Procedure: *m*-Chloroperbenzoic acid (0.011 mol) was added to a solution of 3-allylthioisoxazole (I)[4] (0.01 mol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 1 hr, and washed with aq. sat. $NaHCO_3$ solution. The solvent was evaporated off, and the residue was chromatographed on a column (*n*-hexane–acetone=20: 1) to give II.

9) N.K. Kochetkov and E.D. Khomutova, *Zhur. Obshchei Khim.*, **29**, 535 (1959).
10) A. Quilico and M. Smonetta, *Gazz. Chim. Ital.*, **76**, 200 (1946).
11) S. Cusmano and S. Giambrone, *Gazz. Chim. Ital.*, **80**, 702 (1950).
12) C.A. Grob and P.W. Schiess, *Angew. Chem. Int. Ed. Engl.*, **6**, 1 (1967).

3-Allylsulfinyl-5-phenylisoxazole (IIb)——91.6%, $n_D^{25.5}$ 1.6105. *Anal.* Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00; S, 13.74. Found: C, 61.63; H, 4.87; N, 5.85; S, 13.33. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3140, 1610, 1590, 1563, 1050, 760.

3-Allylsulfinyl-5-methylisoxazole (IIc)——100%, mp 46—48°. *Anal.* Calcd for $C_7H_9NO_2S$: C, 49.11; H, 5.30; N, 8.18; S, 18.73. Found: C, 49.26; H, 5.09; N, 8.09; S, 18.58. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1590, 1050, 925.

3-Allylsulfinylisoxazoles (IId)——88.8%, n_D^{21} 1.5325. *Anal.* Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.91; S, 20.40. Found: C, 46.04; H, 4.64; N, 9.09; S, 20.04. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3100, 1635, 1530, 1050, 930.

Reactions of IIb with Phosphites——General procedure: A mixture of IIb (0.001 mol) and a phosphite (0.002 mol) in acetic anhydride (5 ml) was stirred at room temperature for 48 hr. The mixture was diluted with ether (20 ml), washed with H_2O (100 ml), and concentrated. The residue was separated by preparative TLC (*n*-hexane–acetone=3: 1). Products isolated and their yields are listed in Table I.

S-(5-Phenyl-3-isoxazolyl) Diisopropylphosphorothiolate (VIII)——n_D^{21} 1.5226. *Anal.* Calcd for $C_{15}H_{20}NO_4PS$: C, 52.78; H, 5.91; N, 4.10; P, 9.07; S, 9.39. Found: C, 52.69; H, 6.19; N, 4.03; P, 8.81. S, 9.78; IR $\nu_{max}^{Liq.}$ cm^{-1}: 3100, 1610, 1590, 1570, 1263, 990, 760.

3-Acetylthioisoxazoles (VII)——General Procedure: A mixture of 3-allylsulfinylisoxazole (II) (0.01 mol) and triphenyl phosphine (0.02 mol) in acetic anhydride (20 ml) was stirred at room temperature for 20—48 hr. The resulting mixture was diluted with ether (30 ml), washed with H_2O (100 ml), and concentrated. The residue was chromatographed on a column (*n*-hexane–acetone=10: 1) to give VII.

3-Acetylthio-5-phenylisoxazole (VIIb)——98.0%, mp 69.5—70.5°. *Anal.* Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 60.48; H, 4.14; N, 6.13; S, 14.85. NMR ($CDCl_3$) δ: 2.47 (3H, s, C$\underline{H}_3$), 6.82 (1H, s, 4-H), 7.3—7.9 (5H, m, C$_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 3125, 1715, 1610, 1590.

3-Acetylthio-5-methylisoxazole (VIIc)——80.9%, n_D^{19} 1.5191. *Anal.* Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.72; H, 4.60; N, 8.85; S, 20.57. NMR ($CDCl_3$) δ: 2.42 (6H, s, 2×C$\underline{H}_3$), 6.35 (1H, s, 4-H). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3140, 1730, 1595.

3-Acetylthioisoxazole (VIId)——85.2%, $n_D^{14.7}$ 1.5228. *Anal.* Calcd for $C_5H_5NO_2S$: C, 41.95; H, 3.52; N, 9.78; S, 22.40. Found: C, 41.94; H, 3.63; N, 9.59; S, 22.38. NMR ($CDCl_3$) δ: 2.49 (3H, s, C$\underline{H}_3$), 6.67 (1H, d, J=2 Hz, 4-H), 8.52 (1H, d, J=2 Hz, 5-H). MS *m/e*: 143 (M$^+$), 115, 101. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3140, 1715, 1535.

Reaction of VIIb with NaOH——NaOH (120 mg) in H_2O (3 ml) was added to a solution of VIIb (55 mg) in EtOH (10 ml). The mixture was stirred at room temperature for 48 hr. After addition of conc. HCl (2 ml) and H_2O (30 ml), an insoluble solid was filtered off. The filtrate was extracted with CH_2Cl_2 (10 ml×3). The extract was concentrated, and the residue was purified by preparative TLC (*n*-hexane–acetone=3: 1) to give benzoylacetonitrile (39 mg, 65.0%). The product was identical (by IR and NMR) with an authentic sample.[13]

Silver 3-Isoxazolylmercaptides (X)——General Procedure: A solution of 3-acetylthioisoxazole (VII) (0.01 mol) in MeOH (10 ml) was added to a solution of silver nitrate (0.04 mol) in MeOH (200 ml). The mixture was stirred at room temperature for 1 hr and then filtered. The collected solid was washed successively with H_2O, MeOH and acetone to give X.

Silver 5-Phenyl-3-isoxazolylmercaptide (Xb)——94.3%, mp 202—208° (dec.). *Anal.* Calcd for C_9H_6AgNOS: C, 38.05; H, 2.13; N, 4.93; S, 11.29. Found: C, 38.53; H, 1.83; N, 5.00; S, 10.84. IR ν_{max}^{Nujol} cm^{-1}: 3140, 1610, 1590, 1565.

Silver 5-Methyl-3-isoxazolylmercaptide (Xc)——96.7%, mp 168—176° (dec.). *Anal.* Calcd for C_4H_4AgNOS: C, 21.64; H, 1.82; N, 6.31; S, 14.44. Found: C, 21.29; H, 1.48; N, 6.15; S, 14.45. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1590.

Silver 3-Isoxazolylmercaptide (Xd)——91.0%, mp 173—177° (dec.). *Anal.* Calcd for C_3H_2AgNOS: C, 17.32; H, 0.97; N, 6.73; S, 15.42. Found: C, 17.43; H, 0.73; N, 6.48; S, 15.34. IR ν_{max}^{Nujol} cm^{-1}: 3150, 1537.

Reaction of Xb with Methyl Iodide——A suspension of Xb (341 mg) and methyl iodide (1.5 g) in CH_2Cl_2 (5 ml) was stirred at room temperature for 33 hr and filtered. After concentrating the filtrate, the residue was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give 3-methylthio-5-phenylisoxazole (Vb)[4] (170 mg, 73.9%), bis(5-phenyl-3-isoxazolyl) disulfide (XIb)[1] (9 mg, 4.3%) and 2-methyl-5-phenyl-4-isoxazolin-3-thione[3] (1 mg, 0.4%).

3-Mercaptoisoxazoles (XI)——General Procedure: Hydrogen sulfide was bubbled through an ice-cold suspension of X (0.01 mol) in CH_2Cl_2 (10 ml) for 0.5 hr. An insoluble solid (Ag_2S) was filtered off, and the filtrate was concentrated below 30° to give XI.

3-Mercapto-5-phenylisoxazole (XIb)——74.3%, mp 43—45°. *Anal.* Calcd for C_9H_7NOS: C, 61.00; H, 3.98; N, 7.40; S, 18.90. Found: C, 60.93; H, 4.14; N, 7.58; S, 18.92. NMR ($CDCl_3$) δ: 3.87 (1H, s, S$\underline{H}$), 6.38 (1H, s, 4-H), 7.3—7.8 (5H, m, C$_6\underline{H}_5$). MS *m/e*: 177 (M$^+$), 145, 130, 118, 105, 77, 69, 51. IR ν_{max}^{Nujol} cm^{-1}: 3130, 2530, 1610, 1590, 1570, 785, 755.

13) J.B. Dorsch and S.M. McElvain, *J. Am. Chem. Soc.*, **54**, 2960 (1932).

3-Mercapto-5-methylisoxazole (XIc)——56.7%, n_D^{26} 1.5666. *Anal.* Calcd for C_4H_5NOS: C, 41.72; H, 4.38; N, 12.17; S, 27.84. Found: C, 41.67; H, 4.25; N, 11.90; S, 27.58. NMR ($CDCl_3$) δ: 2.37 (3H, d, J=1 Hz, C<u>H</u>$_3$), 3.73 (1H, s, S<u>H</u>), 5.93 (1H, q, J=1 Hz, 4-H). MS *m/e*: 115 (M^+), 100, 83, 72, 64, 43. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3120, 2550, 1600.

3-Mercaptoisoxazole (XId)——55.1%, oil. NMR (CCl_4) δ: 3.92 (1H, s, S<u>H</u>), 6.55 (1H, d, J=2 Hz, 4-H), 8.43 (1H, d, J=2 Hz, 5-H). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3150, 2550, 1535. UV λ_{max}^{EtOH} nm: 312, 268.

Bis(3-isoxazolyl) Disulfides (XIV)——General Procedure: A solution of 3-mercaptoisoxazole (XI) in EtOH was allowed to stand at room temperature, then concentrated. The residue was purified by preparative TLC (*n*-hexane–acetone=3: 1) to give XIV [reaction time, yield]: bis(5-phenyl-3-isoxazolyl) disulfide (XIVb)[1] [72 hr, 53.2%]; bis(5-methyl-3-isoxazolyl) disulfide (XIVc)[1] [24 hr, 53.2%]; bis(3-isoxazolyl) disulfide (XIVd) [12 hr, 64.8%]. XIVd: oil. *Anal.* Calcd for $C_6H_4N_2O_2S_2$: C, 35.99; H, 2.01; N, 13.99; S, 32.07. Found: C, 35.63; H, 2.03; N, 13.89; S, 32.07. NMR ($CDCl_3$) δ: 6.63 (2H, d, J=2 Hz, 2×4-H), 8.43 (2H, d, J=2 Hz, 2×5-H). MS *m/e*: 200 (M^+). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3150, 1530.

Reaction of XIb with NaOH——NaOH (90 mg) in H_2O (2 ml) was added to a solution of XIb (18 mg) in EtOH (2 ml). After stirring at room temperature for 48 hr, the mixture was acidified with 10% HCl, and extracted with $CHCl_3$ (10 ml×3). The extract was concentrated, and the residue was purified by preparative TLC (*n*-hexane–acetone=3: 1) to yield benzoylacetonitrile (IX)[13] (8 mg, 53.3%).

Reaction of Ethyl β-(5-Phenyl-3-isoxazolylthio)propionate (XIX)[4] with NaOH——A mixture of XIX (350 mg) and NaOH (210 mg) in 50% aq. EtOH (6 ml) was stirred at room temperature for 15 hr under a nitrogen atmosphere in a sealed tube. A part of the ambient nitrogen was subjected to gas chromatography on Porapak Q, detecting ethylene. The remaining nitrogen was absorbed in a solution of bromine (650 mg) in CH_2Cl_2 (7 ml). The resulting solution was washed with aq. $Na_2S_2O_3$ solution and concentrated below 30°. Gas chromatography of the residue on Porapak Q resulted in the detection of ethylene dibromide. Both ethylene and ethylene dibromide were identical with corresponding authentic samples. The remaining reaction mixture was acidified with 10% HCl and extracted with ether (10 ml×3). After removal of the solvent, the residue was separated by preparative TLC (*n*-hexane-acetone=3: 1) to give sulfur (8 mg), benzoylacetonitrile (IX)[13] (152 mg, 75.2%) and β-(5-phenyl-3-isoxazolylthio)propionic acid (XX)[3] (42 mg, 13.4%).

Reaction of β-(5-Phenyl-3-isoxazolylthio)propionic Acid[3] (XX) with NaOH——XX (498 mg) was added to a solution of NaOH (400 mg) in H_2O (5 ml). After stirring at room temperature for 15 hr, the solution was acidified with conc. HCl, and extracted with ether (20 ml×3). The extract was concentrated, and the residue was separated by preparative TLC (*n*-hexane–acetone=3: 1) to give benzoylacetonitrile (IX)[13] (239 mg, 82.5%) and XX (25 mg, 5.1%).

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