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Studies on Isoxazoles. IX.[1] Syntheses of 3-Phenoxy-, 3-Phenylthio- and 3-Alkylthioisoxazoles[2]

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The reaction of 3-chloro-2-methylisoxazolium chlorides with phenols or thiophenols in the presence of triethylamine or sodium methoxide gave 2-methyl-3-phenoxy- or 2-methyl-3-phenylthioisoxazolium chlorides, which were converted to 3-phenoxy- or 3-phenylthioisoxazoles in moderate yields by heating in an appropriate solvent. On pyrolysis of the 3-alkylthioisoxazolium salts prepared from 4-isoxazolin-3-thiones and alkyl halides, the yields of 3-alkylthioisoxazoles depended on the nature of the 2-substituent of the onium salts. 2-Benzyl-3-alkylthioisoxazolium salts gave the best yields. Mixtures of a 2-benzyl-4-isoxazolin-3-thione and a large excess of alkyl halide gave 3-alkylthioisoxazoles in good yields on heating.

Keywords——3-phenoxyisoxazoles; 3-phenylthioisoxazoles; 3-alkylthioisoxazoles; pyrolyses; competitive thermal bond cleavage reactions; addition-elimination reactions; 3-chloroisoxazolium salts; 3-alkylthioisoxazolium salts

In the course of studies on the chemical properties of 3-chloroisoxazolium chlorides, we found that the chlorine at the 3-position was easily displaced by the attack of suitable nucleophiles, and that 3-chloro-2-methylisoxazolium chlorides were transformed to 3-chloroisoxazoles on heating.[1] On the basis of these two findings, we planned syntheses of the previously unknown compounds, 3-phenoxy-, 3-phenylthio- and 3-alkylthioisoxazoles by utilizing the substitution reaction of 3-chloroisoxazolium chlorides with nucleophiles such as phenols, thiophenols and alkanethiols, followed by heating in an appropriate solvent. The only known compound of this type is 5-methyl-3-methylthio-4-(1-oximinoethyl)isoxazole.[4]

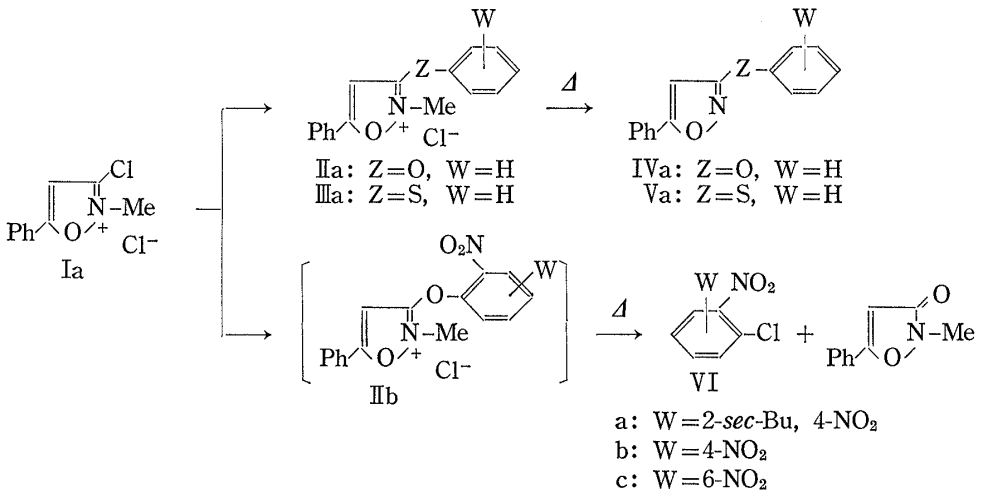
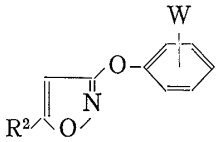


Chart 1

1) Part VIII: K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.* (Tokyo), **27**, 2398 (1979).
2) A part of this work was presented at the 11th Congress of Heterocyclic Chemistry, Kanazawa, October 1978.
3) Location: *2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo, 140, Japan.*
4) A. Dornow and K. Dehmer, *Chem. Ber.*, **100**, 2577 (1967).

When 3-chloro-2-methyl-5-phenylisoxazolium chloride (Ia) was heated with phenol in tetrachloroethane, 3-chloro-5-phenylisoxazole was isolated as a sole product; it could also be obtained by heating Ia without solvent.[1] On the other hand, the salt (Ia) was initially converted to a 3-phenoxyisoxazolium chloride (IIa) by treatment with phenol and triethylamine, and subsequent heating in xylene afforded 3-phenoxy-5-phenylisoxazole (IVa) in 69.5% yield (Chart 1). Using this method, various 3-phenoxyisoxazoles (IV) were synthesized without isolation of the intermediate 3-phenoxyisoxazolium chlorides (II) (Table I). However, treatment of the salt (Ia) with phenols having two nitro substituents did not give a similar reaction, but produced 2-methyl-5-phenyl-4-isoxazolin-3-one and the corresponding dinitrochlorobenzenes (VI) (Chart 1). This could be explained in terms of the involvement of the salt (IIb), similar to IIa. Because of the strong electrophilicity at the 1-position on the dinitrobenzene ring, the chloride might have predominantly attacked the phenoxy group rather than the methyl group.

Table I. 3-Phenoxyisoxazoles (IV)

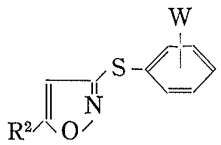


IV	R^2	W	Yield (%)	mp (°C) (n_D)	Formula	Analyses (%) Calcd. C ; H ; N	Found C ; H ; N
a	Ph	H	69.5[a]	54.5— 55.5	$C_{15}H_{11}NO_2$	75.94; 4.67; 5.90	76.10; 4.55; 6.06
b	Ph	2-Me	38.8	46 — 47	$C_{16}H_{13}NO_2$	76.47; 5.22; 5.57	76.64; 5.12; 5.54
c	Ph	3-Me	73.1	50 — 51	$C_{16}H_{13}NO_2$	76.47; 5.22; 5.57	76.77; 5.26; 5.61
d	Ph	4-Me	44.0	97 — 98	$C_{16}H_{13}NO_2$	76.47; 5.22; 5.57	76.06; 5.20; 5.36
e	Ph	2-F	55.8	57 — 58	$C_{15}H_{10}FNO_2$	70.58; 3.95; 5.49	70.78; 3.91; 5.29
f	Ph	3-Br	35.9	59 — 60	$C_{15}H_{10}BrNO_2$	56.99; 3.19; 4.43	57.50; 3.45; 4.83
g	Ph	4-Cl	42.1	110.5—111.5	$C_{15}H_{10}ClNO_2$	66.31; 3.71; 5.16	66.28; 3.43; 4.93
h	Ph	2-CO_2Me	66.1	78.5— 79	$C_{17}H_{13}NO_4$	69.15; 4.44; 4.74	69.20; 4.41; 4.93
i	Ph	4-NO_2	47.5	132.5—134	$C_{15}H_{10}N_2O_4$	63.83; 3.57; 9.93	64.11; 3.60; 9.95
j	Ph	3-NO_2	53.2	118.5—120.5	$C_{15}H_{10}N_2O_4$	63.83; 3.57; 9.93	63.28; 3.65;10.07
k	Ph	3-NMe_2	42.9	88 — 89	$C_{17}H_{16}N_2O_2$	72.84; 5.75; 9.99	72.77; 5.74;10.01
l	Ph	4-OMe	44.8	76 — 77	$C_{16}H_{13}NO_3$	71.90; 4.90; 5.24	71.86; 4.76; 5.15
m	Ph	2-Allyl	74.3	(n_D^{28} 1.5946)	$C_{18}H_{15}NO_2$	77.96; 5.45; 5.05	78.10; 5.57; 4.78
n	Me	H	56.4	(n_D^{30} 1.5290)	$C_{10}H_9NO_2$	68.56; 5.18; 8.00	68.52; 5.21; 8.11
o	Me	2-Me	32.9	(n_D^{25} 1.5277)	$C_{11}H_{11}NO_2$	69.83; 5.86; 7.40	69.05; 5.83; 7.80
p	Me	3-Me	32.9	(n_D^{25} 1.5290)	$C_{11}H_{11}NO_2$	69.83; 5.86; 7.40	69.89; 6.02; 7.46
q	Me	4-Me	36.8	($n_D^{21.5}$ 1.5964)	$C_{11}H_{11}NO_2$	69.83; 5.86; 7.40	69.69; 6.13; 7.66
r	Me	2-F	33.3	($n_D^{22.5}$ 1.5623)	$C_{10}H_8FNO_2$	62.18; 4.17; 7.25	62.26; 4.35; 7.37
s	Me	3-Pr, 4-Me	48.3	(n_D^{18} 1.5625)	$C_{14}H_{17}NO_2S$	63.85; 6.51; 5.32	64.22; 6.74; 5.49
t	Me	3-Me, 4-NO_2	53.2	($n_D^{22.5}$ 1.5623)	$C_{11}H_{10}N_2O_4$	56.42; 4.30;11.96	56.30; 4.53;11.82
u	Me	2-Et, 2-Allyl	32.5	(n_D^{22} 1.5276)	$C_{15}H_{17}NO_2$	74.05; 7.05; 5.76	73.56; 7.06; 5.46

a) From IIa.

The reaction of Ia with thiophenol in the presence of triethylamine in benzene gave an unexpected product, which had a structure derived by cleavage of the N–O bond; this reaction will be discussed in a separate paper. In place of triethylamine, treatment with sodium methoxide in methanol afforded 2-methyl-5-phenyl-3-phenylthioisoxazolium chloride (IIIa) in good yield, and on heating in toluene, 5-phenyl-3-phenylthioisoxazole (Va) was obtained in 75.5% yield (Chart 1). Various 3-phenylthioisoxazoles (V) were prepared by this method without purification of the 3-phenylthioisoxazolium salts (III) (Table II).

Table II. 3-Phenylthioisaxazoles (V)

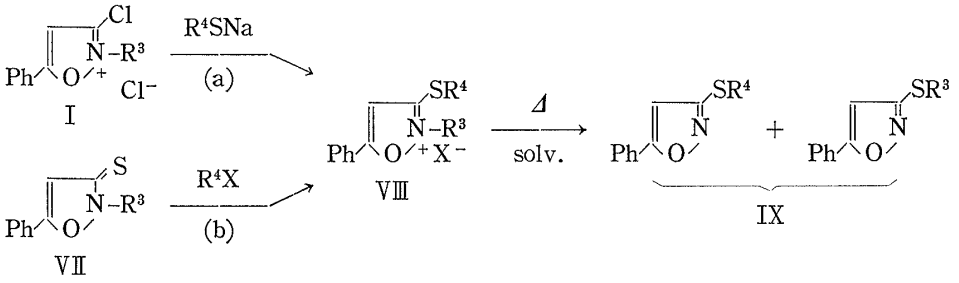


V	R^2	W	Yield (%)	mp (°C) (n_D)	Formula	Analyses (%) Calcd. C ; H ; N	Found C ; H ; N
a	Ph	H	75.5[a]	66—67	$C_{15}H_{11}NOS$	71.12; 4.38; 5.53	70.81; 4.37; 5.41
b	Ph	4-Me	49.6	72	$C_{16}H_{13}NOS$	71.88; 4.90; 5.24	72.02; 4.88; 5.18
c	Ph	4-Cl	58.9	66—67	$C_{15}H_{10}ClNOS$	62.61; 3.50; 4.87	62.55; 3.42; 4.93
d	Me	H	34.7	($n_D^{26.5}$ 1.5816)	$C_{10}H_9NOS$	62.80; 4.74; 7.32	62.83; 4.71; 7.14
e	Me	4-Me	48.8	($n_D^{20.1}$ 1.5776)	$C_{11}H_{11}NOS$	64.36; 5.40; 6.82	64.64; 5.86; 6.73
f	Me	4-Cl	42.9	(n_D^{23} 1.5921)	$C_{10}H_8ClNOS$	53.22; 3.57; 6.21	53.28; 3.78; 6.33

a) From IIIa.

We next attempted to synthesize 3-alkylthioisoxazoles (IX). Neither the substitution reaction of 3-chloroisoxazoles with sodium alkylthiolates according to the synthetic method for 5-ethylthioisoxazoles,[5] nor the diethyldithiophosphate method[6] employing 3-hydroxyisoxazoles gave IX. However, we found a general and versatile reaction based on the synthesis of 3-phenylthioisoxazoles (V). First, the reaction of 3-chloro-2-methyl-5-phenylisoxazolium chloride (Ia) with methyl thioglycolate in the presence of sodium methoxide gave 3-methoxycarbonylmethylthio-2-methyl-5-phenylisoxazolium chloride (VIIIa) in good yield (Method a in Table III). However, the thermal reaction of VIIIa in toluene afforded methyl (5-phenyl-3-isoxazolylthio)acetate (IXa) in poor yield. The yield of the ethyl ester (IXi) was not

Table III. Pyrolyses of Isoxazolium Salts (VIII)



VIII	R^3	R^4	X	Method	Yield (%)	mp (°C)	Solv.[a]	IX Yield (%)		Yield (%)
a	Me	CH_2CO_2Me	Cl	a	79.6	146—147	T	IXa	4.0	0
b	Me	CH_2CO_2Et	Br	b	87.2	139—140	T	IXi	6.3	0
							A	IXi	28.9	0
c	Et	CH_2CO_2Et	Br	b	83.5	115—117	A	IXi	8.1	0
d	Allyl	CH_2CO_2Et	Br	b	86.7	117—118	A	IXi	59.1	IXe 7.3
e	CH_2Ph	CH_2CO_2Et	Br	b	85.5	110—111	A	IXi	68.8	IXf 14.9

a) T, toluene; A, acetonitrile.

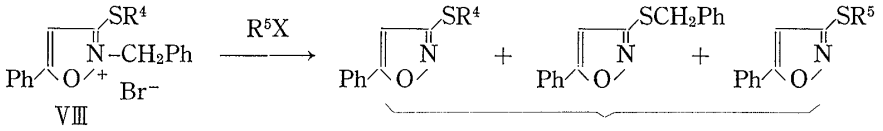
5) G. Adembri and R. Nesi, *J. Heterocycl. Chem.*, **9**, 695 (1972).
6) *a*) A. Nakanishi and S. Oae, *Tetrahedron*, **29**, 2023 (1973); *b*) J. Perregaard, B.S. Pedersen, and S.O. Lawesson, *Acta Chem. Scand. B*, **31**, 460 (1977).

affected by employing the onium bromide (VIIIb) prepared from 2-methyl-5-phenyl-4-isoxazolin-3-thione (VIIa)[1] and ethyl bromoacetate (Method b), but a considerable improvement of the yield was observed on using acetonitrile in place of toluene. Heating of the 2-ethyl derivative (VIIIc) in acetonitrile gave a lower yield of IXi than was obtained from VIIIb. The results obtained suggest that the yields of the 3-alkylthioisoxazoles (IX) may depend on the feasibility of bond cleavage between the nitrogen atom and the 2-substituent in the salts (VIII). Therefore, the following isoxazolium salts substituted at the 2-position with good leaving groups were chosen. The first candidate, the 2-benzhydryl-3-ethoxycarbonylmethylthio-5-phenylisoxazolium salt, could not be obtained, because the attempted synthesis of 2-benzhydryl-3-chloro-5-phenylisoxazolium chloride by our method[1] from the corresponding 3-isoxazolone and phosgene failed, resulting in the formation of 3-chloro-5-phenylisoxazole and benzhydryl chloride. Second, 2-benzyl-3-ethoxycarbonylmethylthio-5-phenylisoxazolium bromide (VIIIe) afforded 68.8% yield of IXi, together with 3-benzylthio-5-phenylisoxazole (IXf) and benzyl bromide (Table III). The third compound, the 2-allyl derivative (VIIId) gave the sulfide (IXi) in 59.1% yield. Consequently, the 2-benzyl derivative (VIIIe) appeared to be the best starting material.

No interconversion between IXi and IXf was observed. Therefore, the reaction of VIIIe was carried out under various conditions in order to examine the formation of the by-product (IXf), which could reduce the yield of IXi. When VIIIe was heated with benzyl bromide, the yield of the desired ester (IXi) decreased with increasing amount of the bromide, while that of IXf increased (Table IV). The employment of an equimolar amount of α-bromo-*p*-xylene reduced the yield of IXf, but a new sulfide (IXv) was obtained. The production of IXf could be avoided by using a large excess of α-bromo-*p*-xylene or methyl iodide, but other sulfides (IXb, v) were produced. The ratio of the products varied, depending on the amounts and the kinds of halides employed. The reaction mechanism for the formation of IXf from VIIIe may be as shown in Chart 2.

Competitive thermal bond cleavage reactions of the salt (VIIIe), one leading to the ester (IXi) with the elimination of benzyl bromide and the other leading to the thione (VIIe)

Table IV. Reactions[a] of Isoxazolium Salts (VIII) with Alkyl Halides (R^5X)



VIII IX

VIII			IX					
R^4	R^5X	(eq.)	Yield (%)		Yield (%)		Yield (%)	
CH_2CO_2Et VIIIe	None		IXi	68.8	IXf	14.9		0
	$PhCH_2Br$	(1.0)	IXi	64.6			IXf	31.8
	$PhCH_2Br$	(10.0)	IXi	51.0			IXf	40.8
	(*p*)$MeC_6H_4CH_2Br$	(1.0)	IXi	63.9	IXf	10.1[b]	IXv	15.7[b]
	(*p*)$MeC_6H_4CH_2Br$	(10.0)	IXi	51.3		0	IXv	34.5
	MeI	(10.0)	IXi	35.7		0	IXb	51.8
CH_2Ph VIIIf	None				IXf	82.8		0
	$PhCH_2Br$	(1.0)			IXf	98.9		0
	$BrCH_2CO_2Et$	(10.0)			IXf	21.3	IXi	76.7

a) In CH_3CN at 70—80° for 4.5 hr.
b) The contents were calculated from NMR data.

together with ethyl bromoacetate, were presumed to occur. The thione (VIIe) could react with benzyl bromide or ethyl bromoacetate to give the corresponding onium salt (VIIIf) or (VIIIe), respectively. The former salt might afford IXf by the elimination of benzyl bromide. Of course, the reactions between VIIIe and VIIe, and VIIe and VIIIf could represent a kind of equilibrium.

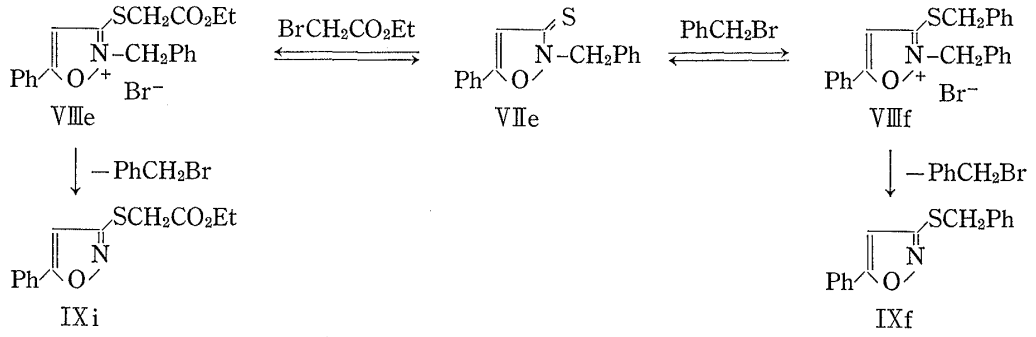


Chart 2

The proposed mechanism was supported by the detection of the dissociated thione (VIIe) by TLC during the reaction and by the isolation of the generated ethyl bromoacetate. On pyrolysis of 2-benzyl-3-phenylthio-5-phenylisoxazolium chloride (IIIb), which cannot be susceptible to bond cleavage between the sulfur atom and phenyl group, no 3-benzylthio-5-phenylisoxazole (IXf) was produced. This also appears to support the present mechanism. Furthermore, the 3-benzylthioisoxazolium bromide (VIIIf) prepared from VIIe and benzyl bromide gave only the sulfide (IXf) on heating, whereas treatment with a 10-fold molar excess of ethyl bromoacetate afforded IXi (76.7%) and IXf (21.3%) (Table IV). A reversible process may exist between VIIe and VIIIf, and the elimination of the benzyl group from the sulfur atom in VIIIf seems more feasible than that from the nitrogen atom.

According to the above mechanism, the undesired formation of IXf could be avoided by employing a large amount of ethyl bromoacetate. Consequently, a versatile synthetic method for 3-alkylthioisoxazoles (IX) by heating 2-benzyl-4-isoxazolin-3-thiones (VII) with a large excess of the corresponding alkyl halides (R^4X) seemed feasible. In fact, VIIe was heated with a 10-fold molar excess of ethyl bromoacetate to give the ester (IXi) in 92.8% yield. Various 3-alkylthioisoxazoles (IX) prepared by this method are listed in Table V; it is clear that these reactions were affected by the nature of R^4X. The reactions with inert alkyl halides, such as chloroacetonitrile and chloroacetamide, required activation by potassium iodide. An active halide as ethyl bromoacetate gave a good result without the activation reagent, but acetates with α-methyl or α-phenyl group reduced the yield of the sulfides

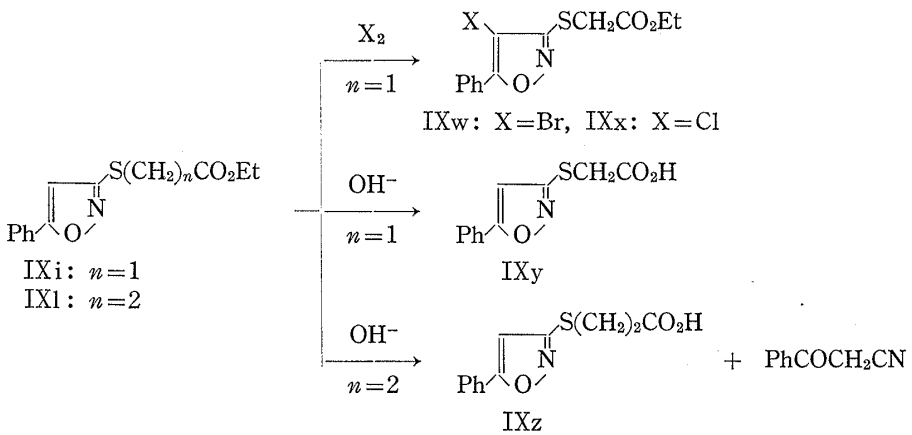
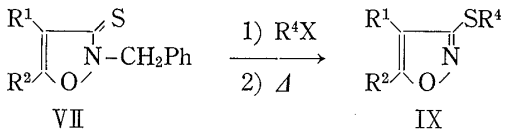


Chart 3

TABLE V. 3-Alkylthioisaxazoles (IX)



VII			IX				Analyses (%) Calcd. (Found)	NMR δ_{ppm}	
R^1	R^2	R^4X		Yield (%)	mp (°C) (n_D)	Formula	C ; H ; N ; S	Solv.[a]	4-H
H	Ph	MeI	b	84.9	56— 57	$C_{10}H_9NOS$	62.80; 4.74; 7.32; 16.77 (62.73; 4.84; 7.23; 16.69)	S	6.31
H	Ph	EtI	c	89.6	51— 52	$C_{11}H_{11}NOS$	64.36; 5.40; 6.82; 15.62 (64.56; 5.58; 6.77; 15.53)	S	6.25
H	Ph	PrI	d	84.1	41— 42	$C_{12}H_{13}NOS$	65.72; 5.98; 6.39; 14.62 (65.20; 5.96; 6.22; 14.40)	C	6.37
H	Ph	Allyl Br	e	77.3	38— 40	$C_{12}H_{11}NOS$	66.33; 5.10; 6.45; 14.76 (66.46; 5.12; 6.63; 14.97)	C	6.38
H	Ph	$PhCH_2Br$	f	98.9	115—116	$C_{16}H_{13}NOS$	71.88; 4.90; 5.24; 11.99 (72.14; 4.84; 5.51; 12.27)	C	6.37
H	Ph	$ClCH_2CN$	g	56.3[b]	86— 87	$C_{11}H_8N_2OS$	61.09; 3.73;12.95; 14.83 (61.17; 3.75;12.89; 15.14)	C	6.50
H	Ph	$ClCH_2CONH_2$	h	64.0[b]	198—199[d]	$C_{11}H_{10}N_2O_2S$	56.40; 4.30;11.96; 13.69 (56.42; 4.26;12.09; 14.82)	D	7.08
H	Ph	$BrCH_2CO_2Et$	i	92.8	77— 78	$C_{13}H_{13}NO_3S$	59.30; 4.98; 5.32; 12.18 (59.25; 4.93; 5.30; 12.45)	S	6.36
H	Ph	$BrCH(Me)CO_2Et$	j	46.7[b]	(n_D^{16} 1.5626)	$C_{14}H_{15}NO_3S$	60.63; 5.45; 5.05; 11.56 (60.31; 5.74; 4.81; 11.28)	—	—
H	Ph	$BrCH(Ph)CO_2Et$	k	52.6	101—102	$C_{19}H_{17}NO_3S$	67.24; 5.05; 4.13; 9.45 (67.05; 4.94; 4.13; 9.22)	—	—
H	Ph	$Br(CH_2)_2CO_2Et$	l	43.6[b]	53— 54	$C_{14}H_{15}NO_3S$	60.63; 5.45; 5.05; 11.56 (60.89; 5.47; 5.14; 11.87)	C	6.38
H	Ph	$BrCH_2CO_2H$	m	69.6	145—146[e]	$C_{11}H_9NO_3S$	56.16; 3.86; 5.96; 13.63 (56.10; 3.77; 5.95; 13.61)	D	7.11
H	H	Allyl Br	n	77.8	(n_D^{23} 1.5252)	C_6H_7NOS	51.04; 5.00; 9.92; 22.71 (50.96; 5.04;10.11; 22.95)	C	6.26
H	H	$BrCH_2CO_2H$	o	77.0	72— 73[f]	$C_5H_5NO_3S$	37.73; 3.17; 8.80; 20.15 (37.43; 3.08; 8.96; 20.32)	C	7.15
H	Me	Allyl Br	p	95.7	(n_D^{21} 1.5184)	C_7H_9NOS	54.17; 5.84; 9.02; 20.66 (54.28; 6.25; 9.10; 20.90)	S	5.77
H	Me	$PhCH_2Br$	q	99.7	(n_D^{22} 1.5774)	$C_{11}H_{11}NOS$	64.36; 5.40; 6.82; 15.62 (64.11; 5.62; 6.71; 15.47)	S	5.74
H	Me	$BrCH_2CO_2H$	r	83.9	93— 94[f]	$C_6H_7NO_3S$	41.61; 4.07; 8.09; 18.51 (41.63; 4.00; 8.04; 18.36)	C	7.15
H	Pr	$BrCH_2CO_2H$	s	77.4	60— 61[f]	$C_8H_{11}NO_3S$	47.75; 5.51; 6.96; 15.93 (48.02; 5.37; 6.80; 15.76)	C	5.95
Me	Me	$BrCH_2CO_2H$	t	67.0	97— 99[f]	$C_7H_9NO_3S$	44.91; 4.85; 7.48; 17.13 (45.02; 4.62; 7.41; 17.05)	C	1.88[c]
		$BrCH_2CO_2H$	u	60.6	153—156[e]	$C_9H_7NO_3S$	51.67; 3.37; 6.69; 15.33 (51.44; 3.18; 6.58; 15.03)	—	—

a) S (CCl_4); C ($CDCl_3$); D (DMSO-d_3).
b) KI added.
c) CH_3.
d) From chloroform.
e) From ethanol.
f) From isopropyl ether.

(IX), though this could be overcome to some degree by the addition of potassium iodide. In the case of a bulky halide such as ethyl α-bromoisovaleriate, no sulfide was obtained.

Bromination of IXi with bromine gave 4-bromoisoxazole (IXw) in 86.2% yield, while chlorination with chlorine afforded the 4-chloro isomer (IXx) in 21.1% yield. Alkaline hydrolysis of IXi gave the corresponding thioacetic acid (IXy), whereas that of the thiopropionate (IXl) afforded benzoylacetonitrile as a main product together with thiopropionic acid (IXz) in 10% yield. The ester exchange of IXl with formic acid gave IXz in 90.9% yield.

Among the compounds synthesized, we found that 3-isoxazolyl phenyl ethers and sulfides showed herbicidal activities, (5-phenyl-3-isoxazolylthio)acetic acid derivatives showed anti-inflammatory activities, and 7-(3-isoxazolylthio)acetamido cephalosporanic acid derivatives showed potent antibacterial activities.[7]

Experimental

Melting points are not corrected. Infrared (IR) spectra were recorded on a Hitachi G_3 spectrometer. NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

Reaction of 3-Chloro-2-methyl-5-phenylisoxazolium Chloride (Ia) with Phenol——A mixture of Ia (2.30 g) and phenol (0.94 g) in tetrachloroethane (6 ml) was heated at 140° for 4 hr with stirring. After cooling, ether (20 ml) was added to the solution. The organic layer was separated and washed with 1% aq. NaOH solution (20 ml×3) and H_2O (20 ml×2). The solvent was concentrated and the residue was purified by silica gel column chromatography. Elution with *n*-hexane gave 3-chloro-5-phenylisoxazole (1.4 g, 77.8%), mp 34.5—35°. The product was identical with that obtained by heating Ia in the absence of solvent.[1]

2-Methyl-3-phenoxy-5-phenylisoxazolium Chloride (IIa)——A mixture of phenol (0.94 g) and triethylamine (1.11 g) in dry benzene (5 ml) was added to a suspension of Ia (2.3 g) in dry benzene (60 ml). The mixture was stirred for 2 hr, concentrated to one-fifth of the original volume, and filtered. The filtrate was evaporated to dryness under reduced pressure. The crude product was purified by precipitation from CH_2Cl_2 with ether to give IIa (1.95 g, 67.8%), mp 135—138°. NMR ($CDCl_3$) δ: 4.39 (3H, s, C$\underline{H}_3$), 7.0—8.0 (10H, m, 2×C$_6\underline{H}_5$), 8.46 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1620 (C=N), 1241, 1230 (C–O–C).

3-Phenoxy-5-phenylisoxazole (IVa)——A suspension of IIa (1.44 g) in xylene (10 ml) was heated under reflux for 30 min, and the reaction mixture was washed with H_2O (10 ml). After distilling the solvent off, the crude product was chromatographed over silica gel. Elution with benzene–*n*-hexane (1: 1) gave IVa (0.82 g, 69.5%), mp 55.5—56°. NMR ($CDCl_3$) δ: 6.17 (1H, s, 4-H), 7.0—7.73 (10H, m, 2×C$_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1620 (C=N), 1215, 1155 (C–O–C).

The other 3-phenoxyisoxazoles (IV) were prepared in the same way from the corresponding 3-chloro-2-methylisoxazolium chlorides and phenols in the presence of triethylamine without isolation of the 3-phenoxy-isoxazolium intermediates (II). The yields, physical constants and elemental analyses are listed in Table I.

Dinitrochlorobenzenes (VI)——General Procedure: A dinitrophenol (0.01 mol) and triethylamine (0.011 mol) in xylene (5 ml) were added to a suspension of Ia (0.01 mol) in xylene (15 ml). The mixture was stirred for 5 hr and then washed with 1% aq. NaOH solution. After removal of the solvent, the residue was purified by column chromatography over silica gel to afford 2-methyl-5-phenyl-4-isoxazolin-3-one and VI as follows (yield): 6-*sec*-butyl-2,4-dinitrochlorobenzene (VIa) (42.9%), mp 53—55° (lit.[8] mp 54—54.5°); 2,4-dinitrochlorobenzene (VIb) (64%), mp 50—52° (lit.[9] mp 52—54°); 2,6-dinitrochlorobenzene (VIc) (83.3%), mp 88—91° (lit.[10] mp 85—87°).

2-Methyl-5-phenyl-3-phenylthioisoxazolium Chloride (IIIa)——Ia (3.0 g) was added to a solution of sodium thiophenolate prepared from thiophenol (1.4 g) and sodium methoxide (0.7 g) in methanol (15 ml) and the mixture was stirred for 2 hr. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and filtered. The filtrate was condensed to one-third of the original volume. Ether (10 ml) was added to the resulting solution to give IIIa (3.84 g, 97.2%). mp 141—143°. *Anal.* Calcd. for $C_{16}H_{14}ClNOS$: C, 63.26; H, 4.64; Cl, 11.67; N, 4.61; S, 10.55. Found: C, 63.83; H, 4.69; Cl, 11.09; N, 4.57; S, 10.32. NMR (DMSO-d_6) δ: 4.42 (3H, s, C$\underline{H}_3$), 7.74 (1H, s, 4-H), 7.6—8.2 (10H, m, 2×C$_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1600 (C=N).

2-Benzyl-5-phenyl-3-phenylthioisoxazolium Chloride (IIIb)——Thiophenol (0.56 g) was added to a solution of sodium methoxide (0.27 g) in methanol (20 ml), followed by the addition of 2-benzyl-3-chloro-5-phenylisoxazolium chloride[1] (1.7 g). The mixture was stirred for 2 hr and worked up as described for the

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synthesis of IIIa. The crude product was purified by precipitation from CH_2Cl_2 with ether to give IIIb (0.55 g, 26.1%), mp 87—89°. *Anal.* Calcd. for $C_{22}H_{18}ClNOS+HCl$: C, 63.46; H, 4.60; Cl, 17.03; N, 3.36; S, 7.70. Found: C, 63.12; H, 4.94; Cl, 13.33; N, 3.31; S, 7.69. NMR ($CDCl_3$) δ: 6.20 (2H, s, $C\underline{H}_2$), 6.63 (1H, s, 4-H), 6.8—8.2 (15H, m, $3\times C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1605 (C=N).

5-Phenyl-3-phenylthioisoxazole (Va)——a) From IIIa: A suspension of IIIa (3 g) in toluene (30 ml) was heated at 130° for 30 min, and the solvent was distilled off. Chromatography of the residue on silica gel, eluting with *n*-hexane–acetone (30: 1) gave Va (1.91 g, 75.5%), mp 66—67°. NMR ($CDCl_3$) δ: 6.29 (1H, s, 4-H), 7.3—7.9 (10H, m, $2\times C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1610 (C=N).

b) From IIIb: A solution of IIIb (0.6 g) in CH_3CN (10 ml) was heated at 70—80° for 3 hr. After removal of the solvent, the residue was chromatographed over silica gel. Elution with *n*-hexane–acetone (30: 1) afforded Va (0.29 g, 81.2%).

The other 3-phenylthioisoxazoles (V) were prepared as above from 3-chloro-2-methylisoxazolium chlorides (I) and thiophenols in the presence of sodium methoxide, without purification of the 3-phenylthioisoxazolium salts (III). The yields, physical constants and elemental analyses are listed in Table II.

3-Methoxycarbonylmethylthio-2-methyl-5-phenylisoxazolium Chloride (VIIIa)——A solution of sodium methoxide (1.1 g) in methanol (50 ml) was treated with methyl thioglycolate (2.12 g), followed by Ia (4.6 g), and the mixture was stirred for 2 hr. The solvent was evaporated off *in vacuo* to leave solids, which were dissolved in CH_2Cl_2. Insoluble materials were filtered off, and the filtrate was concentrated. The crude product was purified by precipitation from CH_2Cl_2 with ether to give VIIIa (5.0 g, 79.6%), mp 146—147°. *Anal.* Calcd. for $C_{13}H_{14}ClNO_3S$: C, 52.09; H, 4.71; Cl, 11.83; N, 4.67; S, 10.07. Found: C, 52.00; H, 4.57; Cl, 11.96; N, 4.82; S, 10.99. NMR ($CDCl_3$) δ: 3.74 (3H, s, $OC\underline{H}_3$), 4.46 (3H, s, $NC\underline{H}_3$), 4.95 (2H, s, $C\underline{H}_2$), 7.4—8.2 (5H, m, $C_6\underline{H}_5$), 9.38 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO), 1180 (C–O–C).

3-Alkylthioisoxazolium Salts (VIIIb—g)——General Procedure: A mixture of 4-isoxazolin-3-thione (VII) (0.01 mol) and alkyl halide (0.015 mol) in acetone (5 ml) was stirred for 4 hr. The precipitated crystals were collected by filtration and washed with acetone (10 ml) to give VIII as follows (yield): 3-ethoxycarbonylmethylthio-2-methyl-5-phenylisoxazolium bromide (VIIIb): (87.2%), mp 139—140°. *Anal.* Calcd. for $C_{14}H_{16}BrNO_3S$: C, 46.94; H, 4.50; Br, 22.30; N, 3.91; S, 8.95. Found: C, 46.91; H, 4.29; Br, 22.30; N, 3.96; S, 8.91. NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.23 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.43 (3H, s, $NC\underline{H}_3$), 4.83 (2H, s, $SC\underline{H}_2$), 7.4—8.25 (5H, m, $C_6\underline{H}_5$), 9.02 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1740 (CO), 1610 (C=N), 1185 (C–O–C); 3-ethoxycarbonylmethylthio-2-ethyl-5-phenylisoxazolium bromide (VIIIc): (83.5%), mp 115—117°. *Anal.* Calcd. for $C_{15}H_{18}BrNO_3S$: C, 48.40; H, 4.87; Br, 21.46; N, 3.76; S, 8.61. Found: C, 47.87; H, 4.82; Br. 21.61; N, 3.76; S, 8.69. NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.5 Hz, $OCH_2C\underline{H}_3$), 1.69 (3H, t, J=7.5 Hz, $NCH_2C\underline{H}_3$), 4.23 (2H, q, J=7.5 Hz, $OC\underline{H}_2$), 4.81 (2H, q, J=7.5 Hz, $NC\underline{H}_2$), 4.90 (2H, s, $SC\underline{H}_2$), 7.3—8.3 (5H, m, $C_6\underline{H}_5$), 10.77 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1725 (CO), 1605 (C=N), 1190 (C–O–C); 2-allyl-3-ethoxycarbonylmethylthio-5-phenylisoxazolium bromide (VIIId): (86.7%), mp 117—118°. *Anal.* Calcd. for $C_{16}H_{18}BrNO_3S$: C, 50.01; H, 4.72; Br, 20.79; N, 3.64; S, 8.34. Found: C, 49.69; H, 4.60; Br, 20.55; N, 3.61; S, 8.47. NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.5 Hz, $C\underline{H}_3$), 4.22 (2H, q, J=7.5 Hz, $OC\underline{H}_2$), 4.92 (2H, s, $SC\underline{H}_2$), 5.3—6.4 (3H, m, $\underline{H}\rangle=\langle\underline{H}$), 5.67 (2H, doublet like, J=5 Hz, $NC\underline{H}_2$), 7.4—8.4 (5H, m, $C_6\underline{H}_5$), 9.17 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO), 1605 (C=N), 1190 (C–O–C); 2-benzyl-3-ethoxycarbonylmethylthio-5-phenylisoxazolium bromide (VIIIe): (85.5%), mp 110—111°. *Anal.* Calcd. for $C_{20}H_{20}BrNO_3S$: C, 55.31; H, 4.64; Br, 18.40; N, 3.22; S, 7.38. Found: C, 54.96; H, 4.59; Br, 18.18; N, 3.20; S, 7.66. NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz, $C\underline{H}_3$), 4.23 (2H, q, J=7 Hz, $OC\underline{H}_2$), 4.70 (2H, s, $SC\underline{H}_2$), 6.02 (2H, s, $NC\underline{H}_2$), 7.4—8.2 (10H, m, $2\times C_6\underline{H}_5$), 8.45 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO), 1610 (C=N), 1180 (C–O–C); 2-benzyl-3-benzylthio-5-phenylisoxazolium bromide (VIIIf): (89.3%), mp 145—146°. *Anal.* Calcd. for $C_{23}H_{20}BrNOS$: C, 63.02; H, 4.60; Br, 18.23; N, 3.20; S, 7.31. Found: C, 62.50; H, 4.49; Br, 17.80; N, 3.09; S, 7.86. NMR ($CDCl_3$) δ: 5.10 (2H, s, $SC\underline{H}_2$), 5.85 (2H, s, $NC\underline{H}_2$), 7.15—8.02 (10H, m, $2\times C_6\underline{H}_5$), 9.19 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1605 (C=N); 3-ethoxycarbonylmethylthio-2-ethyl-5-methylisoxazolium bromide (VIIIg): (84.5%), mp 133—135°. *Anal.* Calcd. for $C_{10}H_{16}BrNO_3S$: C, 38.72; H, 5.20; Br, 25.76; N, 4.52; S, 10.34. Found: C, 38.22; H, 5.16; Br, 26.45; N, 4.41; S, 10.31. NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.64 (3H, t, J=7 Hz, $NCH_2C\underline{H}_3$), 2.73 (3H, s, 5-$C\underline{H}_3$), 4.25 (2H, q, J=7 Hz, $OC\underline{H}_2$), 4.68 (2H, q, J=7 Hz, $NC\underline{H}_2$), 4.71 (2H, s, $SC\underline{H}_2$), 7.98 (1H, s, 4-H). IR ν_{max}^{Nujol} cm^{-1}: 1735 (CO), 1290 (CO), 1170 (C–O–C).

Pyrolysis of VIIIa——A suspension of VIIIa (4.0 g) in toluene (30 ml) was heated at 130—145° for 2 hr and the resulting mixture was washed with H_2O (10 ml). After removal of the solvent, the residue was chromatographed on silica gel using *n*-hexane–acetone (20: 1) to give methyl (5-phenyl-3-isoxazolylthio)-acetate (IXa) (0.13 g, 4.0%), mp 79—79.5°. *Anal.* Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.86; H, 4.32; N, 5.36; S, 13.04. NMR ($CDCl_3$) δ: 3.78 (3H, s, $C\underline{H}_3$), 3.96 (2H, s, $C\underline{H}_2$), 6.46 (1H, s, 4-H), 7.35—7.9 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1735 (CO), 1660 (C=N), 1170 (C–O–C).

Pyrolysis of VIIIe——A solution of VIIIe (1.5 g) in CH_3CN (30 ml) was heated at 70° for 4.5 hr. After removal of the solvent, chromatography of the residue on silica gel gave the following four compounds (eluting solvents, yield): benzyl bromide (*n*-hexane, 0.12 g); ethyl bromoacetate [*n*-hexane–acetone (80: 1), 0.02 g]; 3-benzylthio-5-phenylisoxazole (IXf) [*n*-hexane–acetone (50: 1), 0.14 g, 14.9%], mp 115—117°; ethyl (5-phenyl-3-isoxazolylthio)acetate (IXi) [*n*-hexane–acetone (30: 1), 0.63 g, 68.8%], mp 77—78°. IXf: NMR

($CDCl_3$) δ: 4.37 (2H, s, $C\underline{H}_2$), 6.34 (1H, s, 4-H), 7.2—7.8 (10H, m, $2\times C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1615 (C=N). IXi: NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.5 Hz, $C\underline{H}_3$), 3.83 (2H, s, $SC\underline{H}_2$), 4.17 (2H, q, J=7.5 Hz, $OC\underline{H}_2$), 6.36 (1H, s, 4-H), 7.3—7.8 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1715 (CO), 1605 (C=N), 1175 (C–O–C).

Reaction of VIIIe or VIIIf with Alkyl Halide (R^5X)——A solution of VIIIe or VIIIf (0.01 mol) and a selected amount of R^5X in CH_3CN (40 ml) was heated at 70—80° for 4.5 hr and then worked up as above. The results are given in Table IV: 3-(*p*)-methylbenzyl-5-phenylisoxazole (IXv): mp 90—93°. *Anal.* Calcd. for $C_{17}H_{15}NOS$: C, 72.58; H, 5.38; N, 4.98; S, 11.40. Found: C, 72.42; H, 5.33; N, 4.79; S, 10.88. NMR ($CDCl_3$) δ: 2.28 (3H, s, $C\underline{H}_3$), 4.31 (2H, s, $C\underline{H}_2$), 6.28 (1H, s, 4-H), 7.0—7.9 (9H, m, $C_6\underline{H}_5$, $C_6\underline{H}_4$). IR ν_{max}^{Nujol} cm^{-1}: 1610 (C=N).

3-Alkylthioisoxazoles (IX)——General Procedure from VII: A mixture of VII (0.01 mol), alkyl halide (R^4X) (0.04—0.1 mol) and/or KI (0.04—0.1 mol) in CH_3CN (10 ml) was heated at 70° for 4—8 hr. After filtration, the solvent and the excess R^4X were evaporated off under reduced pressure. The crude product was purified by chromatography or recrystallization to give IX. The yields, physical constants and elemental analyses are listed in Table V.

Ethyl (4-Bromo-5-phenyl-3-isoxazolylthio)acetate (IXw)——A mixture of IXi (0.43 g) and bromine (0.26 g) in $CHCl_3$ (7 ml) was stirred for 2 hr and then washed with H_2O (10 ml). The solvent was evaporated off to leave a residue, which was chromatographed on silica gel. Elution with *n*-hexane–acetone (5: 1) gave IXw (0.5 g, 86.2%), mp 67—68°. *Anal.* Calcd. for $C_{13}H_{12}BrNO_3S$: C, 45.63; H, 3.53; Br, 23.35; N, 4.09; S, 9.37. Found: C, 45.79; H, 3.63; Br, 23.73; N, 4.07; S, 9.74. NMR (CCl_4) δ: 1.31 (3H, t, J=7 Hz, $C\underline{H}_3$), 3.92 (2H, s, $SC\underline{H}_2$), 4.24 (2H, q, J=7 Hz, $OC\underline{H}_2$), 7.4—8.2 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO), 1610 (C=N), 1165 (C–O–C).

Ethyl (4-Chloro-5-phenyl-3-isoxazolylthio)acetate (IXx)——A solution of IXi (0.5 g) in $CHCl_3$ (6 ml) was treated with chlorine (0.16 g), and the reaction mixture was stirred for 4 hr. After removal of the solvent, the residue was separated by preparative TLC, developing with *n*-hexane–acetone (3: 1), to yield IXx (0.12 g, 21.1%), mp 65—66°. MS *m/e*: 297 (M^+), 252 ($M^+-OCH_2CH_3$). NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $C\underline{H}_3$), 4.01 (2H, s, $SC\underline{H}_2$), 4.28 (2H, q, J=7 Hz, $OC\underline{H}_2$), 7.4—8.1 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 1745 (CO), 1620 (C=N), 1165 (C–O–C).

(5-Phenyl-3-isoxazolylthio)acetic Acid (IXy)——A mixture of IXi (1.2 g) and NaOH (1.2 g) in ethanol (30 ml) and H_2O (24 ml) was allowed to stand for 14 hr. After acidification with conc. HCl, the precipitate was collected by filtration, then washed with H_2O (20 ml) and ether (30 ml) to yield IXy (1.03 g, 95.4%), mp 145—146°, which was identical with the material obtained from VIIe and bromoacetic acid. NMR (DMSO-d_6) δ: 4.0 (2H, s, $C\underline{H}_2$), 4.95 (1H, broad, $O\underline{H}$), 7.11 (1H, s, 4-H), 7.5—8.0 (5H, m, $C_6\underline{H}_5$). IR ν_{max}^{Nujol} cm^{-1}: 3100—2450 (OH), 1700 (CO), 1610 (C=N).

β-(5-Phenyl-3-isoxazolylthio)propionic Acid (IXz)——a) A solution of ethyl β-(5-phenyl-3-isoxazolylthio)propionate (IXl) (170 mg) in ethanol (4 ml) was treated with NaOH (1.2 g) in H_2O (5 ml). The mixture was stirred for 4 hr. The precipitate was collected by filtration, and suspended in H_2O. After acidification with conc. HCl, extraction with $CHCl_3$ gave IXz (15 mg, 10.0%), mp 118—119°. The filtrate was acidified with conc. HCl and extracted with CH_2Cl_2. The solvents were evaporated off and the crude product was recrystallized from ligroin to yield benzoylacetonitrile (80 mg, 89.8%), mp 80—81° (lit.[11] 80—81°). IXz: *Anal.* Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.56; H, 4.39; N, 5.62; S, 12.91. IR ν_{max}^{Nujol} cm^{-1}: 3200—2500 (OH), 1700 (CO), 1620 (C=N).

b) A mixture of IXl (0.25 g) and formic acid (20 ml) was heated under reflux for 6 hr and the excess formic acid was distilled off *in vacuo*. The crude product was dissolved in aq. sat. $NaHCO_3$ solution, washed with ether (20 ml), and acidified with conc. HCl. The precipitated crystals were collected and washed with H_2O (10 ml) to afford IXz (0.2 g, 90.9%).

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