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Studies on Isoxazoles. XI.[1] Pyrolyses of 4-Isoxazolin-3-thiones[2]

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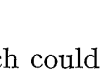
Novel pyrolysis reactions of 4-isoxazolin-3-thiones (X) are described, affording two regioisomeric 1,4-dithiins (III, IV) and thioacetamides (XI). Among the thioacetamides, N-methylbenzoylthioacetamide (XIe) was identical with an authentic sample prepared by the reduction of 2-methyl-5-phenyl-4-isoxazolin-3-thione (Xe) with thiophenol. The structures of the dithiins were deduced from the physicochemical data, especially the shielding and deshielding effects in the NMR spectra. A mechanism for the reactions is proposed by analogy with the thermal isomerization of 3-isoxazolones into 2-oxazolones. In order to account for the formation of the isomeric dithiins, a thiirene intermediate (II) was assumed to be involved in the reaction pathway.

Keywords——pyrolysis of 4-isoxazolin-3-thiones; thermal ring transformations; 1,4-dithiins; thioacetamides; thiirene intermediates; shielding and deshielding effects; sulfur radicals

In the previous paper,[4] it was reported that 3-alkylthio-2-benzylisoxazolium halides afforded 3-alkylthioisoxazoles on heating, with elimination of benzyl halides. Pyrolysis of the corresponding 2-ethyl derivatives, however, gave unexpected results, which are discussed in detail in the present paper.

Treatment of 3-ethoxycarbonylmethylthio-2-ethyl-5-methylisoxazolium bromide (I) (Chart 1) in boiling toluene gave fine yellow needles in poor yield. The structure was deduced from the physicochemical data. The results of elemental analysis and the molecular peak (M^+, *m/e* 286) indicated the formula $C_{12}H_{18}N_2O_2S_2$. The nuclear magnetic resonance (NMR) spectrum showed a triplet (3H, $J=7$ Hz) at δ 1.28, a singlet (0.5H) at δ 2.33, a singlet (2.5H) at δ 2.43, a quintet-like peak (2H) at δ 3.53 and a broad peak (1H) at δ 10.83, as shown in Fig. 1. On addition of deuterium oxide, the broad peak disappeared and the quintet turned into a quartet ($J=7$ Hz); this was ascribed to an ethylamino group ($NHCH_2CH_3$). The extraordinarily low chemical shift of NH suggested an intramolecular hydrogen bond[5] with a hetero atom, which was assumed to be a carbonyl oxygen. In fact, a carbonyl group conjugated with strong electron releasing functions[5] was indicated by ν_{CO}: 1580 cm^{-1} in the infrared (IR) spectrum. Fragment peaks in mass spectrum (MS) are shown in Fig. 2, where two peaks at *m/e* 243 (M^+-43) and *m/e* 43 indicate an acetyl group. Another peak (*m/e* 143) suggested a symmetrical structure for M^+ (*m/e* 286), in which two pairs of an acetyl (C_2H_3O) and an ethylamino group (C_2H_6N) might be included. Extrusion of one pair (C_4H_9NO) from the half molecule (C_6H_9NOS) leaves a C_2S group, which could be assigned to a thiirene ring (). Thus, a 2-acetyl-3-ethylaminothiirene (IIb) structure was assumed for the half molecule. The dimerization of IIb could give two regioisomers, 2,6-diacetyl-3,5-bis(ethylamino)-1,4-dithiin (IIIb) and 2,5-diacetyl-3,6-bis(ethylamino)-1,4-dithiin (IVb). Therefore, the two methyl peaks

1) Part X: S. Sugai and K. Tomita, *Chem. Pharm. Bull.*, **27**, 2787 (1979).
2) A part of this work was presented at the 11th Congress of Heterocyclic Chemistry, Kanazawa, October 1978.
3) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140, Japan.*
4) K. Tomita, S. Sugai, and M. Saito (née Masuda), *Chem. Pharm. Bull.*, **27**, 2415 (1979).
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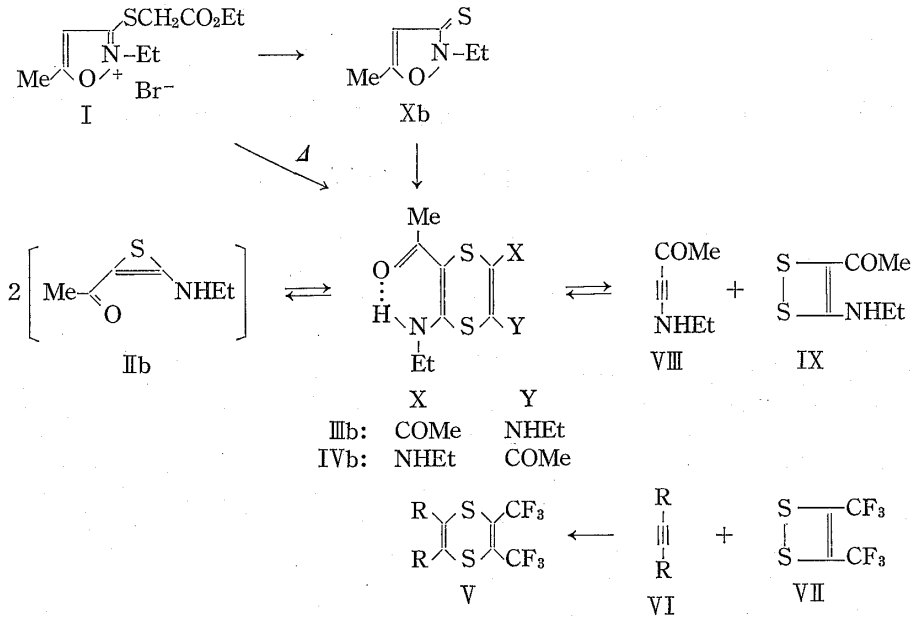

Chart 1

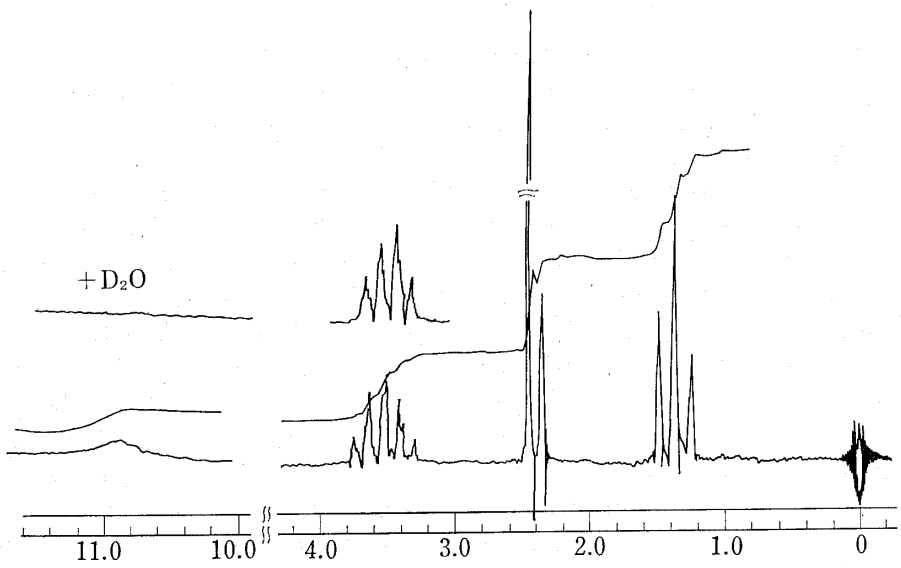

Fig. 1. NMR Spectrum ($CDCl_3$) of the Mixture of IIIb and IVb (5 : 1)

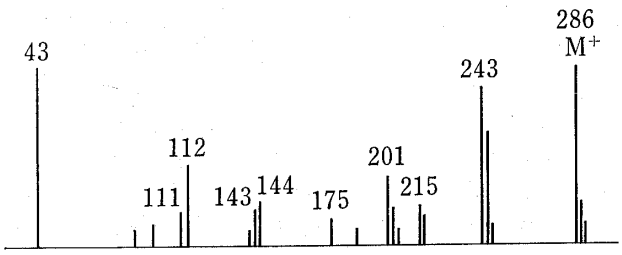

Fig. 2. MS of the Mixture of IIIb and IVb (5 : 1)

at δ 2.43 and δ 2.33 in the NMR spectrum (Fig. 1) were ascribed to the two kinds of acetyl groups in IIIb and IVb. On the other hand, 2,3-bis(trifluoromethyl)-1,4-dithiin (V) has been synthesized by the thermal reaction of an acetylene (VI) with 3,4-bis(trifluoromethyl)-1,2-dithietene (VII).[6] This reaction assisted the interpretation of two fragment peaks, which were tentatively assigned to an acetylene (VIII, *m/e* 111) and a dithietene (IX, *m/e* 175). This supports the proposed structures (IIIb, IVb) shown in Chart 1.

6) C.G. Krespan, B.C. Mukusick, and T.L. Cairns, *J. Am. Chem. Soc.*, **83**, 3438 (1961).

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It has been reported[4] that 2-benzyl-3-ethoxycarbonylmethylthio-5-phenylisoxazolium bromide was converted to 2-benzyl-5-phenyl-4-isoxazolin-3-thione in boiling acetonitrile, with elimination of ethyl bromoacetate. In the transformation of I into 1,4-dithiins (IIIb, IVb), therefore, 2-ethyl-5-methyl-4-isoxazolin-3-thione (Xb) derived from I could be involved as an intermediate (Chart 1). Because of the absence of aromaticity, the N–O bond of isoxazolines readily undergoes homolysis.[7] It thus seems reasonable to consider that homolytic cleavage of the N–O bond in Xb initiates the reaction, resulting in the formation of 1,4-dithiins (IIIb, IVb). Therefore, a series of 4-isoxazolin-3-thiones (X)[8] was pyrolyzed in boiling toluene. From each reaction (Xa—c, Table I), a mixture of the corresponding 1,4-dithiins (IIIa—c, IVa—c) was obtained (Chart 2). Two singlets assigned to the acetyl groups were observed (Table I) in the NMR spectrum of each reaction mixture. Among these peaks, only a singlet at δ 2.17 in the mixture of IIIc and IVc appeared at relatively high field compared with the other singlets; this can be attributed to a shielding effect of a benzene ring. In order to confirm this, the conformations of the two isomers (IIIc, IVc) were examined as shown in Chart 2. The methyl group in IVc could be distant from the benzene ring on the same side of the dithiin ring because of the hydrogen bond. However, it would be located over the benzene ring on the opposite side in a boat conformation of the dithiin ring.[9] Therefore, the methyl signals at δ 2.17 and δ 2.47 could be ascribed to the acetyl group in IVc and in IIIc, respectively. The two 1,4-dithiins (IIIc, IVc) were separated by several recrystallizations (Table I). There was no difference in the other spectral data (IR, ultraviolet (UV), MS) of IIIc and IVc. Comparing the chemical shifts of the methyl groups (R^1) in IIIc and IVc with those in the products from Xa and Xb, the isolated major

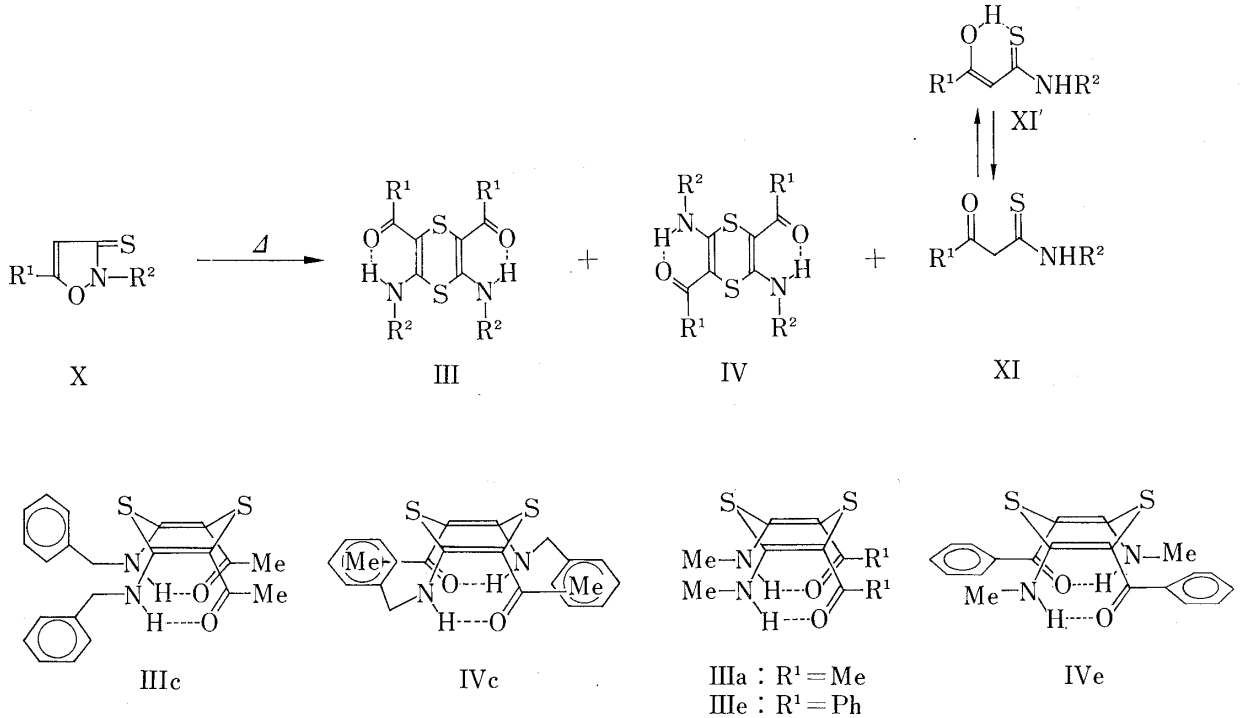

Chart 2

7) N.K. Kochetkov and S.D. Sokolov, "Recent Developments in Isoxazole Chemistry," ed. A.R. Katritzky, A.J. Boulton, and J.M. Lagowki, "Advances in Heterocyclic Chemistry," Vol II, Academic Press, New York and London **1963**, pp. 365—422.
8) K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.*, **27**, 2398 (1979).
9) P.A. Howell, R.M. Curtis, and W.N. Lipcomb, *Acta Cryst.*, **7**, 498 (1954).

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isomers could be assigned as IIIa and IIIb, and the minor isomers as IVa and IVb, respectively.

The reaction[8] of 3-chloro-5-methyl-2-phenylisoxazolium chloride with sodium hydrosulfide gave a single 1,4-dithiin (IIId) instead of 5-methyl-2-phenyl-4-isoxazolin-3-thione (Xd), which might be too labile to permit its isolation. The structure of IIId was deduced from the chemical shifts of its acetyl groups, which were compatible with those in the corresponding 1,4-dithiins (IIIa—c) (Table I).

Table I. Pyrolyses[a] of 4-Isoxazolin-3-thiones (X)

	X		III							
				NMR ($CDCl_3$) δ			IR (Nujol) ν cm^{-1}			
	R^1	R^2	Yield %	R^1	R^2	NH	NH	CO	UV (EtOH) λ_{max} nm	
a	Me	Me	20.8	Me 2.42 (s)	Me 3.17 (d)[f]	10.77 (br)	3130	1580	321,	240
b	Me	Et	27.6	Me 2.43 (s)	CH_2 3.53 (q)[e] Me 1.28 (t)[h]	10.83 (br)	3120	1580	323,	248
c	Me	CH_2Ph	20.0	Me 2.47 (s)	CH_2 4.37 (d)[g] Ph 6.85—7.25 (m)	11.07 (br)	3160	1585	321,	244
d[b]	Me	Ph	5.0	Me 2.53 (s)	Ph 6.80—7.20 (m)	12.28 (br)	3130	1590	326	
e	Ph	Me	9.0	Ph 7.17—7.50 (m)	Me 3.11 (d)[f]	11.27 (br)	3150	1585	339,	233

	IV[d]					XI
		NMR ($CDCl_3$) δ				
	Yield %	R^1	R^2		NH	Yield %
a	(0.8)[c]	Me 2.33 (s)	Me 3.21 (d)[f]		10.77 (br)	2.0
b	(5.5)[c]	Me 2.33 (s)	CH_2 3.53 (q)[e]	Me 1.28 (t)[h]	10.83 (br)	2.2
c	5.3	Me 2.17 (s)	CH_2 4.80 (d)[g]	Ph 7.20—7.40 (m)	11.38 (br)	0.9
d[b]	0					25.8
e	4.6	Ph 7.10—7.46 (m)	Me 3.26 (d)[f]		11.42 (br)	2.8

a) All reactions except for that of Xd[b] were carried out at 100—110° for 3 hr in toluene.
b) The reaction was carried out at 10° for 48 hr in $CHCl_3$.
c) The yields were calculated from the NMR spectral data.
d) IVc: IR ν_{max}^{Nujol} cm^{-1}: 3150, 1580. UV λ_{max}^{EtOH} nm: 324, 244. IVe : IR ν_{max}^{Nujol} cm^{-1}: 3130, 1585. UV λ_{max}^{EtOH} nm: 339, 240.
e) A quintet-like peak.
f) J=5 Hz.
g) J=6 Hz.
h) J=7 Hz.

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On the pyrolysis of 2-methyl-5-phenyl-4-isoxazolin-3-thione (Xe),[8] two 1,4-dithiins were obtained. The chemical shifts of the N-methyl groups in the major isomer were equivalent to those in IIIa (Table I). This suggested that the isomer was IIIe, as shown in Chart 2. In minor isomer, which was tentatively assigned as IVe, the N-methyl groups were assumed to be located near the benzene rings coplanar with the conjugated enone functions; the methyl signal was, therefore, shifted downfield by a deshielding effect.

Thioacetamides (XIa—e) were also obtained from the reactions of Xa—e (Chart 2, Table I). The thioacetamides in solution were in equilibrium with the corresponding enols (XI'), which were detected by means of the hydroxylic and vinylic proton peaks in the NMR spectra. Among them, a stable N-methylbenzoylthioacetamide (XIe) was shown to be identical with an authentic sample unambiguously prepared by mild reduction of Xe with thiophenol.

Table II. Physical Data for 1,4-Dithiins (III, IV) and Thioacetamides (XI)

	mp °C	Formula	Analyses (%) Calcd C; H; N; S	Found C; H; N; S
IIIa	195—196	$C_{10}H_{14}N_2O_2S_2$	46.49; 5.46; 10.84; 24.82	46.20; 5.45; 10.63; 24.58
IIIb	164—166	$C_{12}H_{18}N_2O_2S_2$	50.32; 6.33; 9.78; 22.39	50.52; 5.93; 9.74; 22.65
IIIc[a]	182—183	$C_{22}H_{22}N_2O_2S_2$	64.36; 5.40; 6.82; 15.62	64.06; 5.52; 7.00; 15.85
IIId	166—168	$C_{20}H_{18}N_2O_2S_2$	62.80; 4.74; 7.32; 16.77	62.67; 4.68; 7.26; 16.75
IIIe	196—198	$C_{20}H_{18}N_2O_2S_2$	62.80; 4.74; 7.32; 16.77	62.57; 4.74; 7.51; 16.98
IVc	182—183	$C_{22}H_{22}N_2O_2S_2$	MS *m/e*: 410 (M^+), 367 (M^+-COCH_3), 205 ($M^+/2$).	
IVe	190—192	$C_{20}H_{18}N_2O_2S_2$	62.80; 4.74; 7.32; 16.77	62.64; 4.67; 7.24; 16.51
XIa	Oil	C_5H_9NOS	45.78; 6.91; 10.68; 24.44	45.65; 6.88; 10.99; 24.25
XIb	Oil	$C_6H_{11}NOS$	MS *m/e*: 145(M^+), 102 (M^+-COCH_3).	
XIc	43— 44	$C_{11}H_{13}NOS$	63.74; 6.32; 6.76; 15.47	63.74; 6.16; 6.48; 15.78
XId	70— 73	$C_{10}H_{11}NOS$	62.15; 5.74; 7.25; 16.59	62.20; 5.69; 7.25; 16.65
XIe	120—122	$C_{10}H_{11}NOS$	62.15; 5.74; 7.25; 16.59	61.78; 5.49; 7.45; 16.19

a) MS *m/e*: 410 (M^+), 367 (M^+-COCH_3), 205 ($M^+/2$).

Thermal transformations of Isoxazoles into oxazoles are well known,[10] but no isomerizations into other heterocycles are known. Compounds similar to Xd, 2-phenyl-4-isoxazolin-3-ones (XII, R^2=phenyl), were reported to be thermally converted to 3-phenyl-4-oxazolin-2-ones (XV, R^2=phenyl)[11] (Chart 3). A kinetic study of this reaction suggested that resonance-stabilized diradicals (XIII) might be involved in the first step. They cyclized into α-lactams (XIV), then four-center rearrangements would lead to the final products (XV).

By comparison with the pathway of XII to XV, a mechanism for the reactions of X to III, IV and XI can be proposed as shown in Chart 3. The N–O bond of X undergoes homolysis to afford a C,N-diradical (XVI) similar to XIII. This rapidly isomerizes to a C,S-diradical (XVII), and then to another diradical (XVIII) *via* a thiirene (II). From the radicals (XVII, XVIII) in equilibrium, two competitive reactions affording III and IV are presumed to proceed. Under the reaction conditions used, the intermediate radicals (XVI, XVII) would be terminated to give XI. Thiirenes similar to II have been considered as intermediates in photolysis and thermolysis reactions of 1,2,3-thiadiazoles[12] and 1,2,3-benzothiadiazoles.[13]

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11) A.R. Gagneux and R. Göschke, *Tetrahedron Lett.*, **1966**, 5451.
12) *a*) K.P. Zeller, H. Meier, and E. Müller, *Ann. Chem.*, **766**, 32 (1972); *b*) S. Braslawsky and J. Heicklen, *Chem. Rev.*, **77**, 473 (1977).
13) *a*) K.P. Zeller, H. Meier, and E. Müller, *Tetrahedron Lett.*, **1971**, 537; *b*) T. Wooldridge and T.D. Roberts, *Tetrahedron Lett.*, **1977**, 2643.

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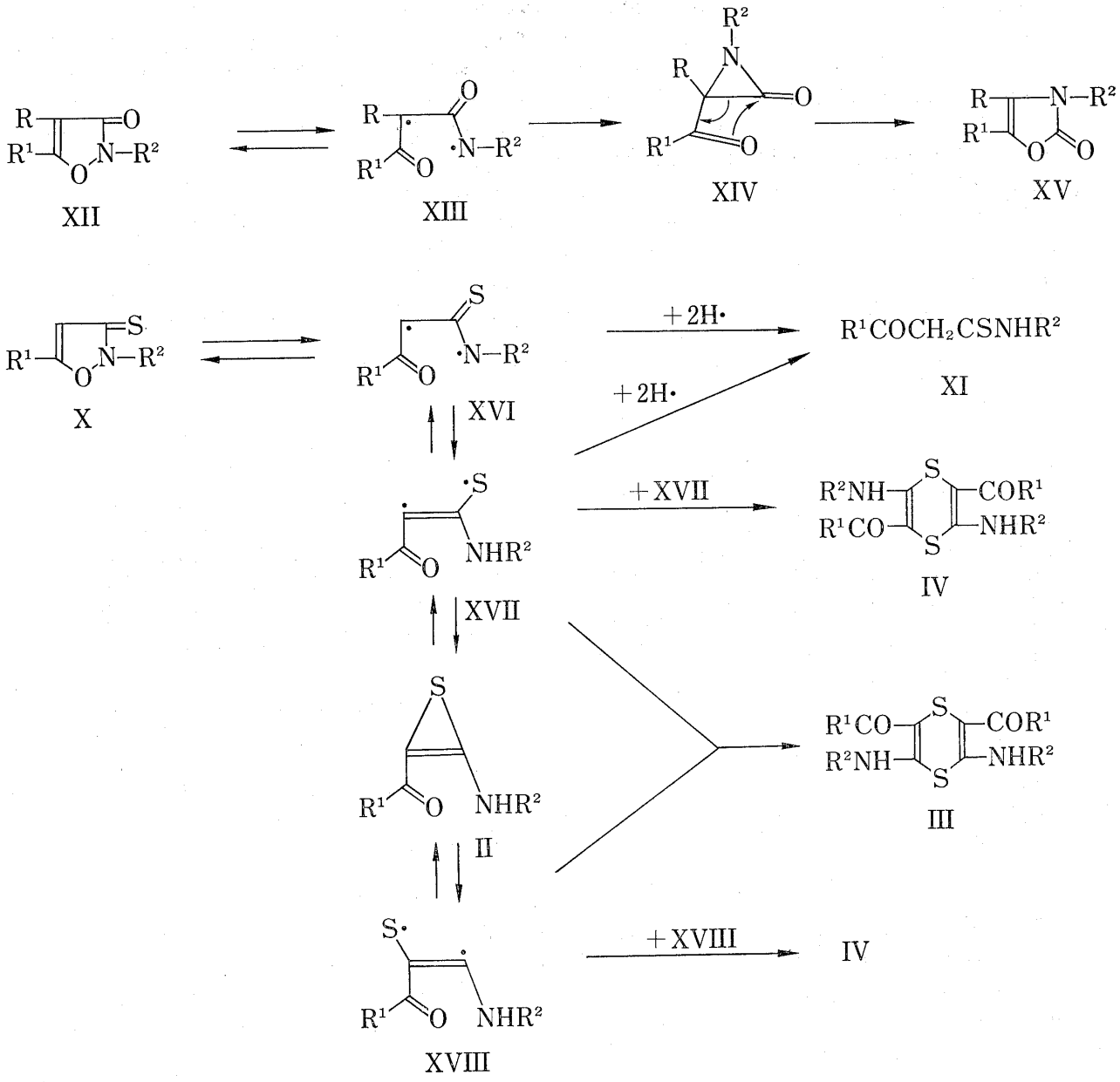

Chart 3

It is interesting that there is such a major difference between the products of the thermal reactions of 4-isoxazolin-3-thiones (X) and 4-isoxazolin-3-ones (XII). This can be interpreted in terms of differences in the stabilities of sulfur and oxygen radicals.

Experimental

All 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 Hitachi-Perkin Elmer R-24 (60 MHz) 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), br (broad). Preparative thin-layer chromatography (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.).

Pyrolysis of 3-Ethoxycarbonylmethylthio-2-ethyl-5-methylisoxazolium Bromide (I)[4]——A suspension of I (2.2 g) in toluene (20 ml) was heated at 110° for 1 hr. The solvent was evaporated off, and the residue was

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purified by column chromatography (*n*-hexane–acetone=30: 1) to give a mixture of 2,6-diacetyl-3,5-bis-(ethylamino)-1,4-dithiin (IIIb) and 2,5-diacetyl-3,6-bis(ethylamino)-1,4-dithiin (IVb) (5: 1 by NMR) (0.15 g, 7.4%), mp 155—157°. *Anal.* Calcd. for $C_{12}H_{18}N_2O_2S_2$: C, 50.32; H, 6.33; N, 9.78; S, 22.39. Found: C, 50.20; H, 6.27; N, 9.91; S, 22.74. IR ν_{max}^{Nujol} cm^{-1}: 3120 (NH), 1580 (CO). The NMR peaks are shown in Fig. 1, and the mass fragment peaks in Fig. 2.

Pyrolysis of 4-Isoxazolin-3-thiones (Xa—c,e)[8]——General Procedure: A solution of Xa—c or e in toluene was heated at 100—110° for 3 hr. The solvent was evaporated off, and the residue was separated by column chromatography followed by preparative TLC to give the corresponding thioacetamides (XIa—c,e) and a mixture of 1,4-dithiins (IIIa—c,e, IVa—c,e). The contents of the 1,4-dithiins (IVa,b) were calculated from the NMR spectra of the mixtures. Pure 1,4-dithiins (IIIa—c,e, IVc,e) were obtained by several recrystallizations from acetone. The spectral data are listed in Table I, and the physical constants and the elemental analyses in Table II. N-Methylacetothioacetamide (XIa); NMR ($CDCl_3$) δ: 1.98 (0.45H, s, $C\underline{H}_3$ of XI'a), 2.31 (2.55H, s, $C\underline{H}_3$ of XIa), 3.23 (3H, d, J=7.5 Hz, $NHC\underline{H}_3$ of XIa and XI'a), 4.03 (1.7H, s, $C\underline{H}_2$ of XIa), 5.39 (0.15H, s, =C<u>H</u>– of XI'a), 9.27 (1H, br, N<u>H</u> of XIa and XI'a), 13.97 (0.15H, s, O<u>H</u> of XI'a). IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH), 1715 (CO). MS *m/e*: 131 (M^+), 88 (M^+-COCH_3). N-Ethylacetothioacetamide (XIb); NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$ of XIb and XI'b), 2.28 (0.3H, s, $COC\underline{H}_3$ of XI'b), 2.31 (2.7H, s, $COC\underline{H}_3$ of XIb), 3.72 (2H, a quintet-like peak, $C\underline{H}_2CH_3$ of XIb and XI'b), 3.98 (1.8H, s, $COC\underline{H}_2$ of XIb), 5.32 (0.1H, s, =C<u>H</u>– of XI'b), 9.12 (1H, br, N<u>H</u> of XIb and XI'b), 13.97 (0.1H, s, O<u>H</u> of XI'b). IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (NH), 1715 (CO). N-Benzylacetothioacetamide (XIc): NMR ($CDCl_3$) δ: 1.93 (0.6H, s, $C\underline{H}_3$ of XI'c), 2.21 (2.4H, s, $C\underline{H}_3$ of XIc), 3.92 (1.6H, s, $COC\underline{H}_2$ of XIc), 4.82 (2H, d, J=5 Hz, $NHC\underline{H}_2$ of XIc and XI'c), 5.30 (0.2H, s, =C<u>H</u>– of XI'c), 9.20 (1H, br, N<u>H</u> of XIc and XI'c), 13.97 (0.2H, s, O<u>H</u> of XI'c). IR ν_{max}^{Neat} cm^{-1}: 3280 (NH), 1710 (CO). MS *m/e*: 207 (M^+), 164 (M^+-COCH_3). N-Methylbenzoylthioacetamide (XIe); NMR ($CDCl_3$) δ: 3.10 (0.45H, d, J=5 Hz, $C\underline{H}_3$ of XI'e), 3.19 (2.55H, d, J=5 Hz, $C\underline{H}_3$ of XIe), 4.47 (1.7H, s, $C\underline{H}_2$ of XIe), 6.00 (0.15H, s, =C<u>H</u>– of XI'e), 7.2—8.2 (5H, m, $C_6\underline{H}_5$ of XIe and XI'e), 9.30 (1H, br, N<u>H</u> of XIe and XI'e), 14.41 (0.15H, s, O<u>H</u> of XI'e). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1675 (CO). MS *m/e*: 193 (M^+), 105 ($C_6H_5CO^+$), 88 ($M^+-COC_6H_5$).

Reaction of 3-Chloro-5-methyl-2-phenylisoxazolium Chloride[8] **with NaSH**——An aq. solution (30 ml) of 3-chloro-5-methyl-2-phenylisoxazolium chloride (5.34 g) was treated with NaSH (2.73 g) under ice-cooling. The mixture was stirred at room temperature for 1 hr then extracted with $CHCl_3$ (20 ml×3). The extract was allowed to stand at 10° for 48 hr. After removal of the solvent, the residue was separated by column chromatography (*n*-hexane–acetone=30: 1) to give 2,6-diacetyl-3,5-dianilino-1,4-dithiin (IIId) (0.22 g, 5.0%) and N-phenylacetothioacetamide (XId) (1.16 g, 25.8%). The physical data are listed in Table I and Table II. XId: NMR ($CDCl_3$) δ: 1.97 (1.2H, s, $C\underline{H}_3$ of XI'd), 2.30 (1.8H, s, $C\underline{H}_3$ of XId), 4.07 (1.2H, s, $C\underline{H}_2$ of XId), 5.50 (0.4H, s, =C<u>H</u>– of XI'd), 7.1—7.9 (5H, m, $C_6\underline{H}_5$ of XId and XI'd), 8.30 (0.4H, br, N<u>H</u> of XI'd), 10.75 (0.6H, br, N<u>H</u> of XId), 14.33 (0.4H, s, O<u>H</u> of XI'd). IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1625 (CO). MS *m/e*: 193 (M^+), 150 (M^+-COCH_3).

N-Methylbenzoylthioacetamide (XIe)——A mixture of 2-methyl-5-phenyl-4-isoxazolin-3-thione (Xe) (1.0 g), thiophenol (1.15 g) and triethylamine (3 drops) in toluene (12 ml) was stirred at room temperature for 48 hr. After removal of the solvent, the crude product was purified by column chromatography (*n*-hexane–acetone=10: 1) to give XIe (0.82 g, 81.2%), mp 123—124°. The compound was identical (by NMR and IR spectra) with that obtained by the pyrolysis of Xe.

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