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Studies on 2-Substituted Thiazolines. I.[1] Reaction with Cyanoacetic Acid

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2-Substituted thiazolines (IIa—d) were prepared from 2-thiothiazolidone. IIa—d were converted to 2-(ethoxycarbonylcyanomethylene)thiazolidine (III) and its N-acetate and N-methyl derivative. Thiolester analogs of III were obtained by the reaction of IIa—d and cyanoacetic acid in acetic anhydride.

The reaction of active methylene compounds with iminoethers, prepared from amides, is widely used in the syntheses of corrin derivatives by Eschenmoser[3] and of indole alkaloids by Ban.[4] On the other hand, few reports[5] on the reaction of active methylene compounds with iminothioethers have been published.

In this report, the condensation reactions of iminothioethers with aliphatic active methylene compounds are described.

The iminothioethers used in the present study were 2-ethylthiothiazoline (IIa), which was easily available from 2-thiothiazolidone (I) by treating with ethyl iodide, diethyl sulfate or the Meerwein reagent, and its homologs, such as benzylthio-(IIb), *p*-nitro benzylthio-(IIc) and allylthio thiazoline (IId).

Recently Kishida, *et al.*[6] reported the reaction of IIa with ethyl cyanoacetate and assigned the structure of the reaction product as the NH-ester *cis* isomer (IIIa) basing on the strongly hydrogenbonded NH absorption band in the infrared (IR) and the nuclear magnetic resonance (NMR) spectra. On the other hand, Shvo, *et al.*[7] prepared the methyl ester (IV) by another route. They concluded that IV exists in an equilibrium of two isomers (IVa) and (IVb), and the equilibrium extremely favors NH-ester *cis* isomer (IVa) basing on the activation energy ($G^{\neq}$) and IR spectrum.

The reaction of IIa with ethyl cyanoacetate in acetic acid in the presence of sodium acetate gave III but this condition was too drastic for other unstable compounds. In contrast, III was easily obtained in a high yield by hydrolysis of its acetate (V) which was prepared in acetic anhydride in the presence of sodium acetate at room temperature or slightly elevated temperature. Compounds (IIb), (IIc) and (IId) likewise gave the same acetate (V) in acetic anhydride. In ethanol, quarternaly salt (VI)[8] also condensed with ethyl cyanoacetate to form (VII) which was also prepared directly from III. Although geometric isomers are considerable in each products, V and VII, there are no detailed data at present (Chart 1, Chart 2).

When III was treated with methyl isothiocyanate in hot pyridine, yellow needles, mp>270°, were obtained in a low yield. The elementary analysis and the mass spectrum showed that

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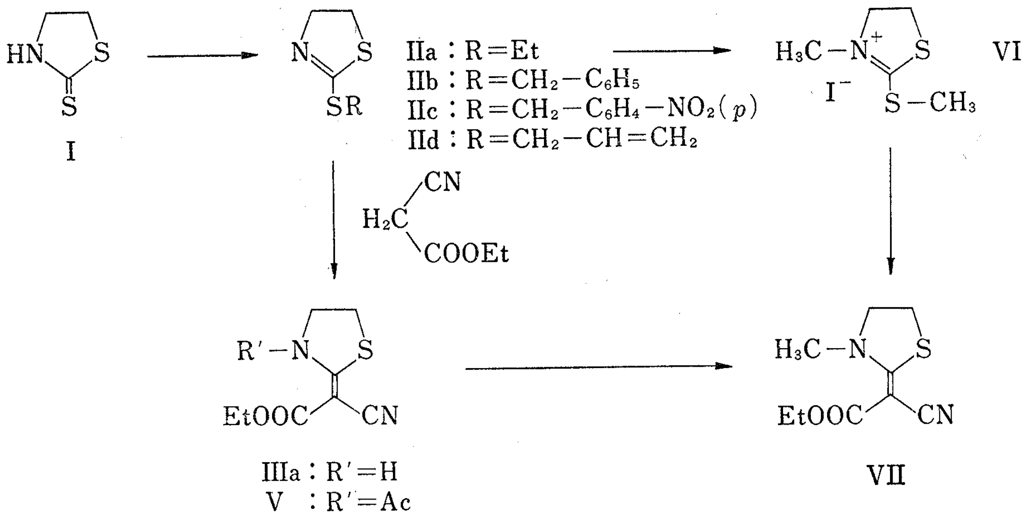


Chart 1

the molecular formula of this substance was $C_{10}H_{10}ON_4S_3$ (M^+ 298) resulting from the addition of 2 mole of methyl isothiocyanate to III. The IR spectrum indicated the presence of carbonyl function but the absorptions due to NH, -CN and ester observed in that of III disappeared. From these observations, the structure (VIIIa) was given to this substance, the addition product of 2 mole of methyl isothiocyanate and 1 mole of IIIb which existed as a minor isomer. A possible reaction scheme is shown in Chart 3. Furthermore, phenyl isothiocyanate gave (VIIIb) in the same way.

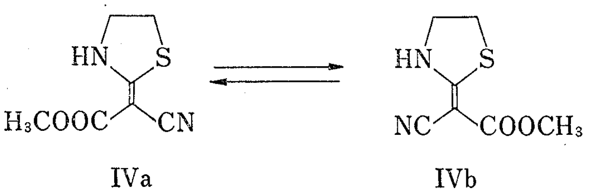


Chart 2

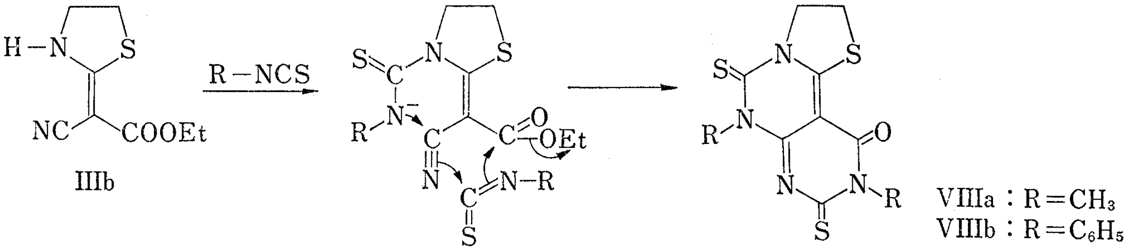
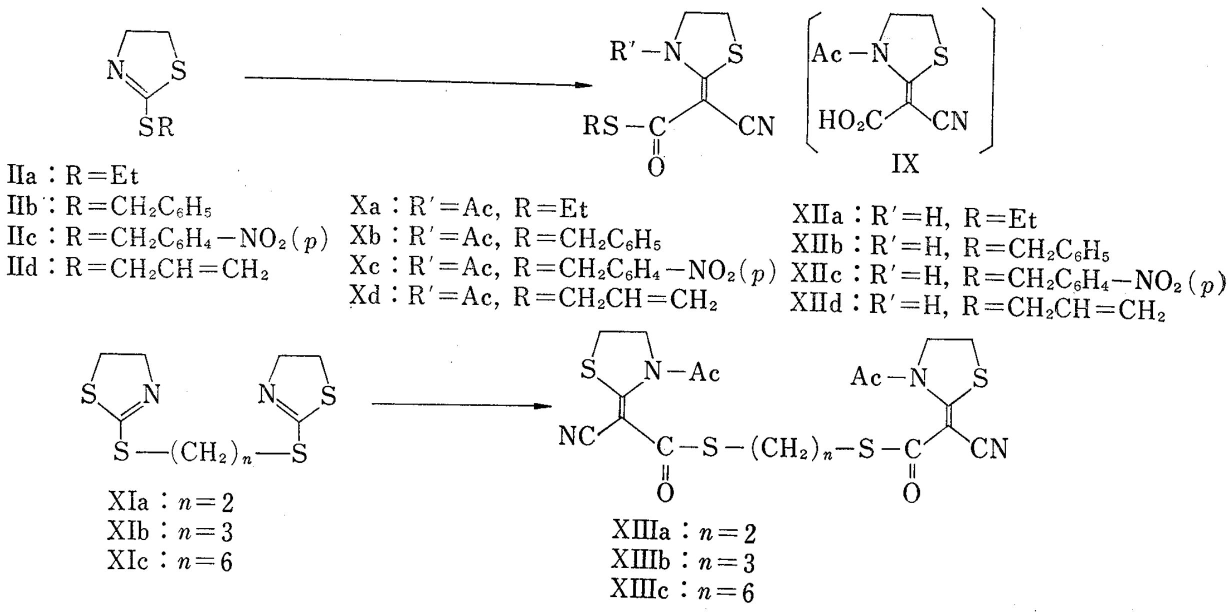


Chart 3

III was so stable as to resist to reduction and to hydrolysis. For the purpose of preparing the free acid (IX), IIa was treated with cyanoacetic acid in acetic anhydride. The product was not the expected compound (IX) but the thiol ester (Xa). The IR spectrum of Xa showed the bands at 2210 cm^{-1} (-CN), 1705 cm^{-1} (Ac-N) and 1634 cm^{-1} (-CO-S-). Furthermore the NMR spectrum showed the characteristic peaks at 1.33 ppm (3H, triplet) and 3.05 (2H, quartet) ($-S-CH_2-CH_3$), 2.43 (3H, singlet) (Ac-N) and 3.11 (2H, triplet) and 4.27 (2H, triplet) ($-S-CH_2-CH_2-N<$). These spectral data agreed with that of the proposed compound Xa. The IR spectra of Xa and the corresponding V are shown in Fig. 1.

Compounds IIb, IIc and IId also reacted with cyanoacetic acid in the same manner to give corresponding thiol esters, (Xb), (Xc) and (Xd). Bis thiol ester derivatives such as (XIIIa), (XIIIb) and (XIIIc) were obtained from the corresponding dithioethers (XIa), (XIb) and (XIc) in the same way. Geometric problem remains unclarified for these thiol esters at present. Preparation of these thiol esters proceeded with a high yield under the mild



IIa : R=Et
IIb : $R=CH_2C_6H_5$
IIc : $R=CH_2C_6H_4-NO_2(p)$
IId : $R=CH_2CH=CH_2$

Xa : R'=Ac, R=Et
Xb : $R'=Ac$, $R=CH_2C_6H_5$
Xc : $R'=Ac$, $R=CH_2C_6H_4-NO_2(p)$
Xd : $R'=Ac$, $R=CH_2CH=CH_2$

IX

XIIa : R'=H, R=Et
XIIb : $R'=H$, $R=CH_2C_6H_5$
XIIc : $R'=H$, $R=CH_2C_6H_4-NO_2(p)$
XIId : $R'=H$, $R=CH_2CH=CH_2$

XIa : $n=2$
XIb : $n=3$
XIc : $n=6$

XIIIa : $n=2$
XIIIb : $n=3$
XIIIc : $n=6$

Chart 4

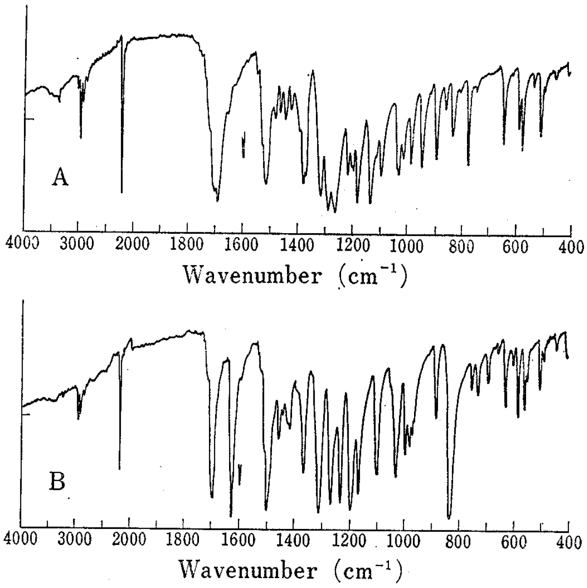


Fig. 1. A; IR Spectrum of Compound (V)
B; IR Spectrum of Compound (Xa)

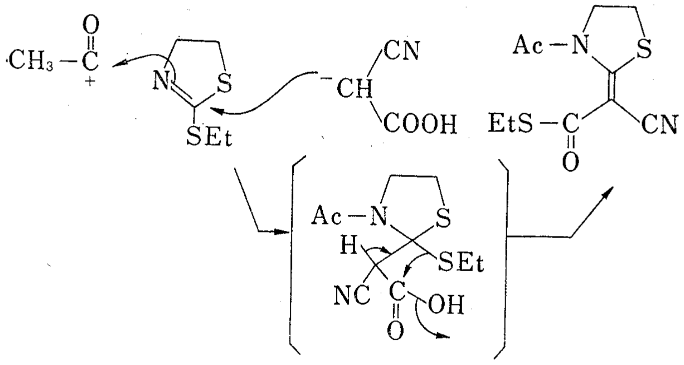


Chart 5

condition, at room temperature. Although the intramolecular rearrangement as shown in Chart 5 is proposed, further investigation to clarify the reaction mechanism is now in progress. An acyl group of a thiol ester was easily hydrolyzed in alkaline solution in a high yield to give a secondary amine, (XIIa—d), (XIVa—c).

Experimental

All melting points are uncorrected. The NMR spectra were measured in a $CDCl_3$ solution using a Varian T-60 spectrometer and the chemical shifts were expressed in ppm unit from the internal standard of tetramethylsilane. The IR spectra were measured in KBr disk by a Nippon Bunko IR-G instrument. The Mass spectra were measured on a Hitachi RMS-4 spectrometer.

2-Ethylthiothiazoline (IIa)——A solution of 20 g of 2-thiothiazolidone in 100 ml of CH_2Cl_2 was added dropwise to a stirred solution of 30 g of the Meerwein reagent ($Et_3O^+BF_4^-$) in 100 ml of CH_2Cl_2 and after addition stirring was continued at room temperature for about 2 hr. The reaction mixture was poured into 100 ml of 20% K_2CO_3 solution and stirred for 1 hr under ice-cooling. After removal of the precipitate, the organic layer was separated from aqueous layer, dried (Na_2SO_4) and concentrated *in vacuo* to give a pale brown oil. Distillation of the oil under reduced pressure gave IIa as a colorless oil (25 g) (bp 84—90°/9 mmHg). *Anal.* Calcd. for $C_5H_9NS_2$: C, 40.82; H, 6.12; N, 9.52. Found: C, 40.94; H, 6.31; N, 9.71.

2-(Ethoxycarbonylcyanomethylene)thiazolidine (III)——A solution of 1.5 g of 2-ethylthiothiazoline and 1.2 g of ethyl cyanoacetate in 5 ml of acetic acid containing 0.8 g of sodium acetate was refluxed for 9 hr. The mixture was then poured into ice water and the separated crystals were collected by filtration. After being washed with water several times, recrystallization from methanol gave colorless needles, mp 132—132.5°, identical with that reported by Kishida, *et al.* (IR, NMR, mp reported 125°).

N-Acetyl-2-(ethoxycarbonylcyanomethylene)thiazolidine (V)——A solution of 1.47 g of 2-ethylthiothiazoline (IIa) and 1.13 g of ethyl cyanoacetate in 5 ml of acetic anhydride containing 0.8 g of sodium acetate was kept standing overnight with continuous stirring at room temperature. The mixture was then poured into ice water and the separated crystals were collected by filtration. Recrystallization from methanol gave colorless needles, mp 159—160°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_2S$: C, 50.00; H, 5.00; N, 11.67. Found: C, 50.19; H, 5.26; N, 11.92. IR_{max} cm^{-1}: 2200 (-CN), 1701, 1690 (Ac-N, -COOEt). NMR: 1.37 (3H, triplet, $J=7.0$ Hz, -N-CH$_2$-C$\underline{H}_3$), 2.43 (3H, singlet, Ac-N), 3.07 (2H, triplet, $J=7.0$ Hz, -N-CH$_2$-C$\underline{H}_2$-S-), 4.28 (2H, triplet, $J=7.0$ Hz, -N-C$\underline{H}_2$-CH$_2$-S-), 4.34 (2H, quartet, $J=7.0$ Hz, -C$\underline{H}_2$-CH$_3$).

Hydrolysis of V——A solution of 0.24 g of V in 5 ml of 10% NaOH was warmed on a water bath for 10 min. The clear solution was filtered and the filtrate was acidified with 10% HCl. The white material precipitated was collected by filtration. Recrystallization from methanol gave colorless needles, III.

N-Methyl-2-(ethoxycarbonylcyanomethylene)thiazolidine (VII)——1) A mixture of 0.7 g of the quarternary salt (VI), 1 ml of ethyl cyanoacetate and 0.5 ml of triethylamine in 10 ml of ethanol was refluxed for 3 hr. After cooling the precipitated material was collected and recrystallized from ethanol to give colorless needles, mp 112—113°. *Anal.* Calcd. for $C_9H_{12}O_2N_2S$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.42; H, 5.81, N, 13.30. IR_{max} cm^{-1}: 2200 (-CN), 1670 (-COOEt). NMR: 1.33 (3H, triplet, $J=7.0$ Hz, -CH$_2$-C$\underline{H}_3$), 3.13 (2H, triplet, $J=8.3$ Hz, -N-CH$_2$-C$\underline{H}_2$-S-), 3.55 (3H, singlet, Ac-N), 3.94 (2H, triplet, $J=8.3$ Hz, -N-C$\underline{H}_2$-CH$_2$-S-), 4.28 (2H, quartet, $J=7.0$ Hz, -C$\underline{H}_2$-CH$_3$).

2) A mixture of 0.4 g of III, 0.9 g of methyl iodide and 0.9 g of silver oxide in 10 ml of methanol was stirred for 20 hr at room temperature under protection from the light. The methyl derivative (VII) was isolated by preparative thin-layer chromatography (silica gel, solvent system: ethyl acetate: benzene=1: 1).

Preparation of VIIIa from III——A mixture of 0.9 g of methyl isothiocyanate and 1.0 g of III in 5 ml of pyridine was refluxed for 4 hr. The reaction mixture was then poured into ice water and the solution was stirred overnight. The precipitated material was collected and recrystallized from DMF (dimethyl formamide), mp>270°. *Anal.* Calcd. for $C_{10}H_{10}ON_4S_3$: C, 40.27; H, 3.38; N, 18.79. M 298. Found: C, 40.61; H, 3.39, N, 18.64. M^+ 298. IR_{max} cm^{-1}: 1665 (-C=C-C=O).

Preparation of VIIIb from III——A mixture of 2.0 g of III and 3.0 g of phenyl isothiocyanate in 10 ml of pyridine was refluxed for 3 hr. After cooling the precipitated material was collected and recrystallized from DMF-methanol, mp 225° (decomp.). *Anal.* Calcd. for $C_{20}H_{14}ON_4S_3 \cdot DMF$: C, 55.75; H, 4.27; N, 14.14. M 495. Found: C, 55.89; H, 4.42; N, 14.29. M^+ 495. IR_{max} cm^{-1}: 1675 (-C=C-C=O).

General Procedure for The Syntheses of N-Acetyl Thiol Esters (X*a*—*b*, XIII*a*—*c*)——A mixture of 2-substituted thiazoline IIa—d (1 mmole) and cyanoacetic acid (1 mmole) or *ω,ω'*-bis(2-thiazolinyl-2-thio)-alkane XIa—c (1 mmole) and cyanoacetic acid (2 mmole) in 10 ml of acetic anhydride was stirred at room temperature overnight in the presence of catalytic amount of sodium acetate. Then the reaction mixture was poured into ice water. Several recrystallization from a suitable solvent gave the pure sample. Data of Xa—d and XIIIa—c are summarized in the Table I.

TABLE I

Compd.	mp (°C)	Recryst. solv.	IR ν_{max}^{KBr} cm^{-1}		Formula	Analysis					
						Calcd.			Found		
			Ac-N	-S-C=O		C	H	N	C	H	N
Xa	142—143	AcOEt–hexane	1705	1634	$C_{10}H_{12}O_2N_2S_2$	46.85	4.72	10.93	47.01	4.94	10.97
Xb	150—151	benzene	1712	1627	$C_{15}H_{14}O_2N_2S_2$	56.60	4.40	8.81	56.15	4.51	9.10
Xc	160—161	acetone–EtOH	1711	1633	$C_{15}H_{13}O_4N_3S_2$	49.59	3.58	11.57	49.70	3.76	11.47
Xd	88—89	MeOH	1708	1634	$C_{11}H_{12}O_2N_2S_2$	49.25	4.51	10.45	49.23	4.79	10.64
XIIIa	250—252	DMF–MeOH	1695	1636	$C_{18}H_{18}O_4N_4S_4$	44.81	3.73	11.62	44.89	4.02	11.65
XIIIb	207—208	DMF–MeOH	1699	1632	$C_{19}H_{20}O_4N_4S_4$	45.97	4.03	11.29	45.85	4.19	11.46
XIIIc	147—148	DMF–MeOH	1715	1630	$C_{22}H_{26}O_4N_4S_4$	49.07	4.83	10.41	48.60	5.06	10.38

General Procedure for The Hydrolysis of N-Acetyl Thiol Esters——A solution of 1 mmole of N-acetyl thiol esters (Xa—d, XIIIa—c) in 10 ml of 10% NaOH was warmed in a water bath for 20 min. The solution was then filtered and the filtrate was neutralized with 10% HCl. The crystals precipitated were collected by filtration and recrystallized from a suitable solvent. Data of XIIa—d and XIVa—c are summarized in the Table II.

TABLE II

Compd.	mp (°C)	Recryst. solv.	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}		Formula	Analysis Calcd.			Analysis Found		
			NH	-S-C=O		C	H	N	C	H	N
XIIa	126—127	AcOEt–hexane	3260	1603	$C_8H_{10}ON_2S_2$	44.83	4.70	13.07	44.95	4.90	12.87
XIIb	120—121	MeOH	3250	1615	$C_{13}H_{12}ON_2S_2$	56.52	4.38	10.14	56.58	4.54	10.32
XIIc	179—180	AcOEt	3260	1620	$C_{13}H_{11}O_3N_3S_2$	48.60	3.45	13.08	48.60	3.45	12.91
XIId	66—67	EtOH	3255	1612	$C_9H_{10}ON_2S_2$	47.79	4.46	12.39	47.74	4.55	12.48
XIVa	286—287	DMF–MeOH	3245	1605	$C_{14}H_{14}O_2N_4S_4$	42.21	3.52	14.07	41.90	3.67	13.89
XIVb	216—217	DMF–MeOH	3250	1609	$C_{15}H_{16}O_2N_4S_4$	43.69	3.88	13.59	43.53	3.98	13.42
XIVc	208—209	DMF–MeOH	3255	1612	$C_{18}H_{22}O_2N_4S_4$	47.58	4.85	12.33	47.85	5.11	12.57

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