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Mercaptoacetate Derivatives. I. Reaction of Thiocyanatoacetic Esters with Aldehydes[1]

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An equimolar reaction of thiocyanatoacetic esters with aromatic aldehydes in the presence of sodium hydride, followed by treatment with hydrogen chloride, led to a mixture of 4-alkoxycarbonyl-5-aryl-2-imino-1,3-oxathiolane hydrochloride (**3**) and α-(*S*-carbamoylthio)-*β*-chlorodihydrocinnamic ester (**4**). When excess aldehyde was used in the reaction, a small amount of 2,10-bis(α-chlorobenzyl)-4,8-dioxo-6-phenyl-5,7-diaza-3,9-dithiaundecanedioate (**5**) was obtained, together with the products **3** and **4**. The NMR studies revealed that product **3** isolated exists all in one isomer which has the 4-ester and 5-aryl groups *cis* about a single bond in the ring. It was suggested that product **4** was formed by rearrangement of the *trans* isomer of **3**.

In a previous paper[2] it was shown that the reaction of thiocyanatoacetic esters (**1**) with aldehydes occurs in the presence of potassium carbonate or fluoride to give a mixture of 5-substituted-*N*-carbamoyl-2-imino-4-alkoxy carbonyl-1,3-oxathiolanes (**2**) and α,*β*-unsaturated esters. In the course of study, it was found that sodium hydride is also an effective condensing agent for this reaction. The reaction of **1** with an aromatic aldehyde in the presence of sodium hydride, when followed by treatment with dry hydrogen chloride, led to a mixture of 2-imino-4-alkoxycarbonyl-5-aryl-1,3-oxathiolane hydrochloride (**3**) and two unexpected compounds (**4** and **5**).

Results and Discussion

An equimolar reaction of **1** and an aromatic aldehyde in the presence of sodium hydride at room temperature, on prolonged standing, produced cinnamic ester exclusively. However, the reaction, when conducted at −5°C and followed by treatment with dry hydrogen chloride, afforded a mixture of two solid compounds **3** and **4** in good yield. These compounds could be separated easily by utilizing the difference of the solubility in acetone. The ratios of the two components, as evaluated from the integration of the area under the appropriate NMR signals, varied widely with aldehydes used. The yields and physical properties of **3** and **4** are summarized in Tables 1 and 2, respectively. When excess aldehyde was used in the reaction, a small amount of high-melting compound (**5**), along with **3** and **4**, was

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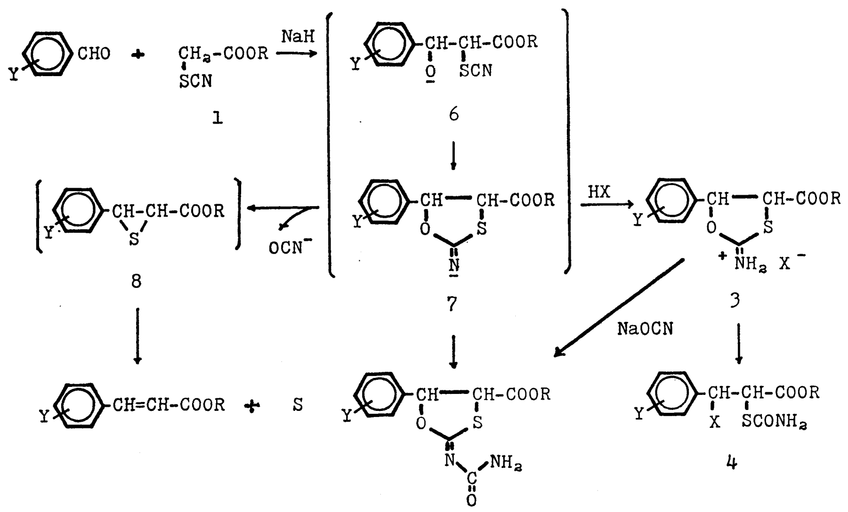
[1] Presented in part at the Autumn Meeting of the Chemical Society of Japan, Sapporo, August 29th (1970).

[2] S. Kambe, T. Hayashi, H. Yasuda, and H. Midorikawa, This Bulletin, **44**, 1357 (1971).



Scheme 1. 2

TABLE 1. 2-IMINO-4-ALKOXYCARBONYL-5-ARYL-1,3-OXATHIOLANE HYDROCHLORIDE (**3**)

No.	R	X	Y	Yield (%)	Mp (°C)	Formula	Anal. Found (Calcd) C (%)	H (%)	N (%)	S (%)	Cl (%)	Br (%)
3b	Et	Cl	H	7	158—159	$C_{12}H_{14}NO_3SCl$	50.24 (50.08)	4.98 (4.90)	4.91 (4.87)	11.48 (11.15)	12.29 (12.32)	
3c	Et	Br	H	23	145—146	$C_{12}H_{14}NO_3SBr$	43.20 (43.38)	4.27 (4.25)	4.15 (4.22)	9.72 (9.65)	23.95 (24.06)	
3d	*t*-Bu	Cl	H	17	154—155	$C_{14}H_{18}NO_3SCl$	53.39 (53.24)	5.85 (5.74)	4.54 (4.27)	10.21 (10.15)	11.32 (11.23)	
3f	Et	Cl	*p*-Cl	trace (38)[a]	166—166.5	$C_{12}H_{13}NO_3SCl_2$	44.48 (44.73)	4.11 (4.07)	4.27 (4.35)	9.57 (9.96)	21.82 (22.00)	
3h	Et	Cl	*p*-Br	24 (10)[a]	163—164	$C_{12}H_{13}NO_3SBrCl$	39.14 (39.31)	3.55 (3.57)	3.78 (3.82)	8.46 (8.75)	9.60 (9.67)	21.64 (21.80)

a) Potassium carbonate was used as a catalyst (see the experimental section).

TABLE 2. α-(*S*-CARBAMOYLTHIO)-β-ARYL-β-CHLORODIHYDROCINNAMIC ESTERS (**4**)

No.	R	X	Y	Yield (%)	Mp (°C)	Formula	Anal. Found (Calcd) C (%)	H (%)	N (%)	S (%)	Cl (%)	Br (%)
4a	Me	Cl	H	32	129—130	$C_{11}H_{12}NO_3SCl$	48.22 (48.26)	4.44 (4.42)	5.33 (5.12)	11.57 (11.71)	13.01 (12.95)	
4b	Et	Cl	H	85	158—158.5	$C_{12}H_{14}NO_3SCl$	49.98 (50.08)	4.85 (4.90)	4.88 (4.87)	11.35 (11.15)	12.18 (12.32)	
4c	Et	Br	H	53	148—149	$C_{12}H_{14}NO_3SBr$	43.63 (43.38)	4.25 (4.25)	4.17 (4.22)	9.75 (9.65)		23.99 (24.06)
4d	*t*-Bu	Cl	H	45	125—126	$C_{14}H_{18}NO_3SCl$	53.32 (53.24)	5.75 (5.74)	4.49 (4.44)	10.22 (10.15)	10.83 (11.23)	
4e	Me	Cl	*p*-Cl	85	159—161	$C_{11}H_{11}NO_3SCl$	43.12 (42.87)	3.66 (3.60)	4.47 (4.55)	10.48 (10.40)	23.20 (23.01)	
4f	Et	Cl	*p*-Cl	95	152—153	$C_{12}H_{13}NO_3SCl_2$	44.67 (44.73)	4.03 (4.07)	4.25 (4.35)	9.72 (9.96)	21.85 (21.99)	
4g	Et	Cl	*o*-Cl	65	132—133	$C_{12}H_{13}NO_3SCl_2$	44.72 (44.73)	4.01 (4.07)	4.51 (4.35)	9.85 (9.96)	22.10 (22.01)	
4h	Et	Cl	*p*-Br	73	148—150	$C_{12}H_{13}NO_3SBrCl$	39.31 (39.31)	3.55 (3.57)	3.80 (3.82)	8.70 (8.75)	9.75 (9.67)	21.98 (21.80)
4i	Et	Cl	*p*-CN	50	137—138	$C_{13}H_{13}N_2O_3SCl$	50.12 (49.92)	4.21 (4.64)	9.09 (8.96)	9.30 (10.25)	11.30 (11.34)	
4j	Et	Cl	*p*-NO_2	50	149—149.5	$C_{14}H_{17}N_2O_5SCl$	46.55 (46.60)	4.64 (4.75)	7.80 (7.77)	9.00 (8.89)	9.67 (9.83)	
4k	Et	Cl	*p*-CH_3	38	142—143	$C_{13}H_{16}NO_3SCl$	51.62 (51.73)	5.31 (5.34)	4.89 (4.64)	10.51 (10.63)	11.82 (11.75)	
4l	Et	Cl	*p*-CH_3O	12	70— 73	$C_{13}H_{16}NO_4SCl$	49.35 (49.13)	5.34 (5.07)	4.62 (4.41)			

TABLE 3. PRODUCTS 5

No.	R	X	Y	Mp (°C)	Formula	Anal. Found (Calcd) C (%)	H (%)	N (%)	S (%)	Cl (%)
5b	Et	Cl	H	190—191	$C_{31}H_{32}N_2O_6S_2Cl_2$	56.06 (56.10)	4.86 (4.86)	4.33 (4.22)	9.87 (9.66)	10.36 (10.69)
5d	*t*-Bu	Cl	H	161	$C_{35}H_{40}N_2O_6S_2Cl_2$	58.49 (58.40)	5.48 (5.60)	3.92 (3.89)	8.78 (8.91)	9.78 (9.85)
5c	Et	Cl	*p*-Cl	194—195	$C_{31}H_{29}N_2O_6S_2Cl_5$	48.31 (48.56)	3.87 (3.81)	3.54 (3.65)	8.74 (8.36)	22.27 (23.11)
5h	Et	Cl	*p*-Br	196—196.5	$C_{31}H_{29}N_2O_6S_2Br_3Cl_2$	41.49 (41.35)	3.26 (3.25)	3.22 (3.11)	6.85 (7.12)	

obtained. The yield and physical properties of **5** are summarized in Table 3. As can be seen from the Table, the yields of **3** and **4** are extremely low, when benzaldehydes having an electron-donating substituent are used. Aliphatic aldehydes and ketones did not give any solid compound. In contrast, the reactions with benzaldehydes having an electron-attractive group produced **3** and **4** in fair to excellent yield. It was found that the esters **4** with an electron-donating group on the benzene nucleus decompose gradually in solid state and more rapidly in the solutions.

The structural assignments were made on the basis of elemental analysis, spectral studies, and chemical reactivity. As shown in the Tables, **3** and **4** have the

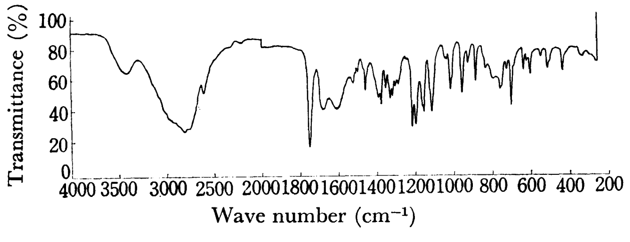


Fig. 1. IR spectrum of 2-imino-4-ethoxycarbonyl-5-phenyl-1,3-oxathiolane hydrochloride (**3b**) (KBr pellet).

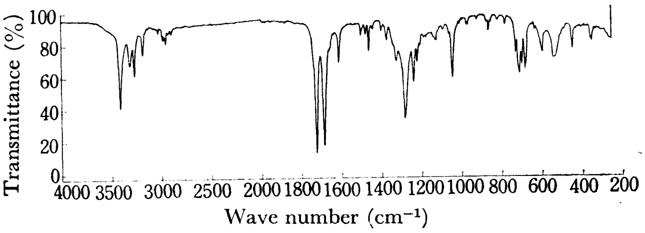


Fig. 2. IR spectrum of ethyl α-(S-carbamoylthio)-β-chlorodihydrocinnamate (**4b**) (KBr pellet).

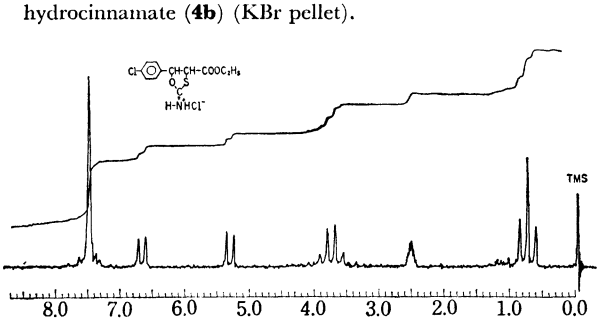


Fig. 3. NMR spectrum of 2-imino-4-ethoxycarbonyl-5-(*p*-chlorophenyl)-1,3-oxathiolane hydrochloride (**3f**) in DMSO-d_6 (60 MHz).

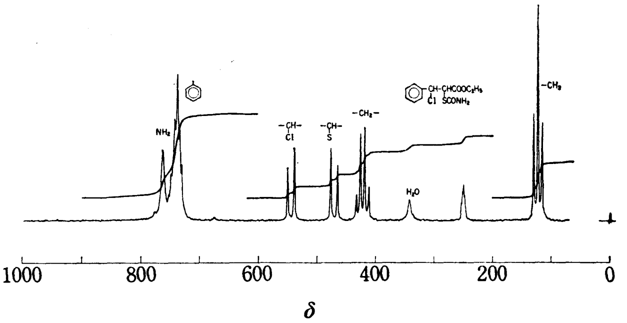


Fig. 4. NMR spectrum of ethyl α-(*S*-carbamoylthio)-β-chlorodihydrocinnamate (**4b**) in acetone-d_6 (100 MHz).

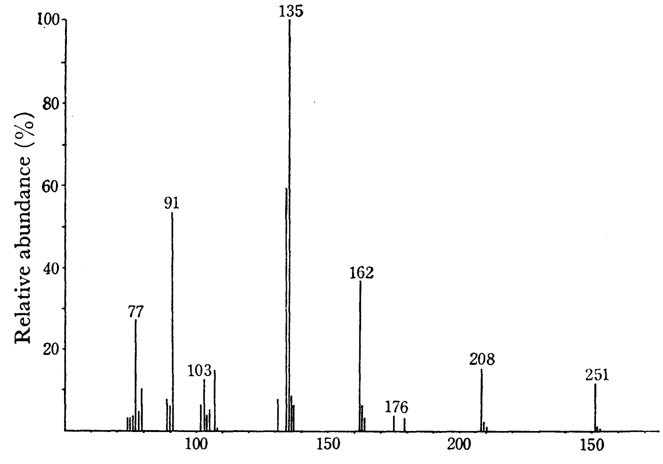


Fig. 5. Mass spectrum of 2-imino-4-ethoxycarbonyl-5-phenyl-1,3-oxathiolane hydrochloride (**3b**).

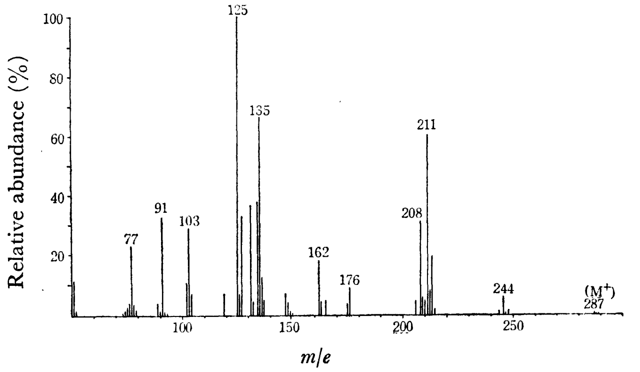
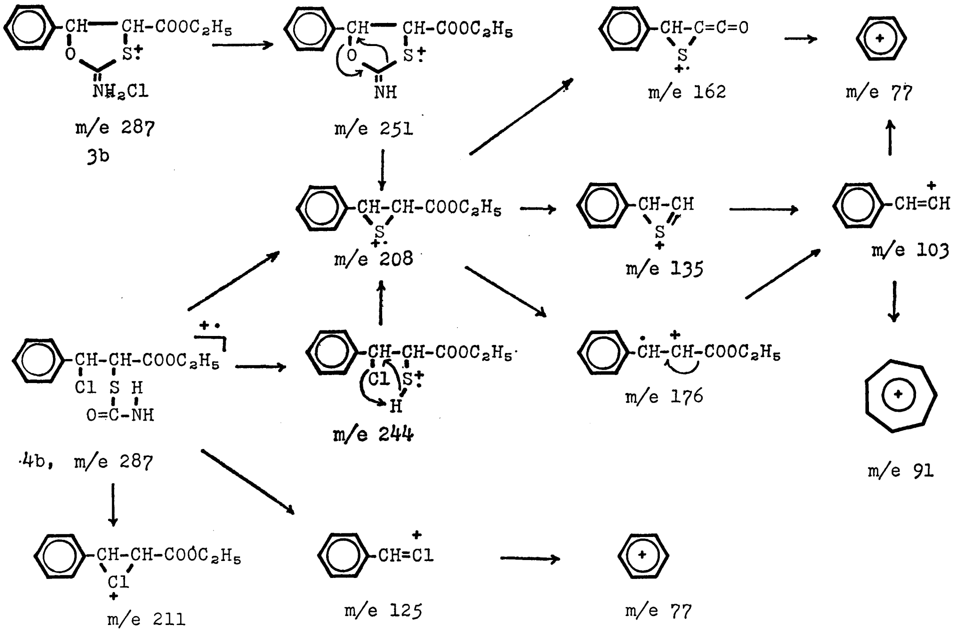


Fig. 6. Mass spectrum of ethyl α-(*S*-carbamoylthio)-β-chlorodihydrocinnamate (**4b**).



Scheme 2.

TABLE 4. IR DATA OF PRODUCTS **3** IN KBr (cm^{-1})

No.	NH_2 stretching	$\nu C{=}O$	$\nu C{=}N$	δNH_2
3b	3420 br 2800 br	1750 s	1680 s	1610 m
3c	3420 br 2860 br	1750 s	1670 s	
3d	3420 br 2840 br	1754 s	1680 s	1615 m
3f	3450 br 2860 br	1745 s	1680 s	1615 m
3h	2850 br	1745 s	1680 s	1610 m

br=broad, s=strong, m=medium.

same molecular formula, but their IR, NMR, and mass spectra showed marked differences (Figs. 1 to 6). In the IR spectrum of **3b** (KBr pellet), a complex series of absorptions between 3500 and 2500 cm^{-1} suggests the presence of the imine hydrochloride, while with **4b**, rather sharp bands in the ranges 3410—3182 cm^{-1} are due to the NH_2 stretching vibrations. These assignments may be supported by the following facts: **3**'s were readily soluble in water and when treated with silver nitrate reagent, showed a positive test for chloride ion. Convincing evidence for the structure of **3** may be supplied by the fact that **3b**, when treated with an equimolar amount of potassium cyanate, produced *N*-carbamoyl-2-imino-4-ethoxycarbonyl-5-phenyl-1,3-oxathiolane (**2b**), which was synthesized alternatively in previous papers.[2,3] Hence, the structure of **3** was determined to be 2-imino-4-alkoxycarbonyl-5-aryl-1,3-oxathiolane hydrochloride. The NMR and mass spectra support this assignment. In the mass spectrum of **3b** (Fig. 5), one observed a M–HCl ion as the highest mass peak, which is not seen in the spectrum of **4b**. Subsequent fragmentations may proceed in the way shown in Scheme 2. The base peak appears at *m/e* 135, which may correspond to C_6H_5–C_2H_2S.

TABLE 6. IR DATA OF PRODUCTS **3** IN KBr (cm^{-1})

No.	νNH_2	Ester $\nu C{=}O$	Amide $\nu C{=}O$	δNH_2
4a	3440 s, 3340 s, 3300 s, 3190 s	1730 vs	1685 vs	1610 m
4b	3410 s, 3312 s, 3272 s, 3185 s	1726 vs	1687 vs	1611 m
4c	3410 s, 3315 s, 3270 s, 3185 s	1730 vs	1690 vs	1613 m
4d	3410 s, 3310 s, 3270 s, 3180 s	1722 vs	1695 vs	1610 m
4e	3400 s, 3292 s, 3230 s, 3160 s	1724 vs	1694 vs	1605 m
4f	3408 s, 3290 s, 3230 s, 3170 s	1720 vs	1690 vs	1605 m
4g	3365 s, 3305 s, 3235 s, 3180 s	1730 vs	1680 vs	1625 m
4h	3415 s, 3320 s, 3282 s, 3190 s	1720 vs	1692 vs	1610 m
4i	3410 s, 3350 s, 3292 s, 3170 s	1723 vs	1687 vs	1608 m
4j	3410 s, 3315 s, 2372 s, 3187 s	1730 vs	1692 vs	1610 m
4k	3400 s, 3305 s, 3265 s, 3183 s	1730 vs	1690 vs	1611 m

TABLE 5. NMR DATA OF PRODUCTS **3** IN DMSO-d_6 (δ-values from TMS)

No.	H_α	H_β	$J_{\alpha\beta}$ (Hz+0.1)	COOR CH_3	COOR CH_2	NH	Aromatic protons
3b	5.30 d	6.65 d	6.1	0.70 t	3.73 q	11.75 br	7.45 s
3c	5.34 d	6.72 d	6.1	0.70 t	3.72 q	11.75 br	7.45 s
3d	5.24 d	6.65 d	6.0	1.02 s		11.75 br	7.42 s
3f	5.31 d	6.67 d	6.1	0.75 t	3.77 q	11.75 br	near 7.57 m
3h	5.30 d	6.62 d	6.1	0.75 t	3.78 q	11.75 br	*ca.* 7.35 *ca.* 7.67

s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad

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3) T. Hayashi, M. Akano, T. Yokono, J. Uzawa, S. Kambe, and H. Midorikawa, This Bulletin, **45**, 578 (1972).

Table 7. NMR data of products **4** in acetone-d_6 (δ-values from TMS)

No.	H_α	H_β	$J_{\alpha\beta}$ (Hz±0.1)	COOR CH_3	COOR CH_2	NH_2	Aryl protons
4a	4.84 d	5.36 d	11.3	3.78 s		6.98 br	7.45 m
4b	4.83 d	5.33 d	11.3	1.27 t	4.25 q	6.98 br	7.45 m
4c[a)]	4.89 d	5.54 d	12.0	1.26 t	4.27 q	7.66 br	near 7.50 m
4d	4.74 d	5.30 d	11.3	1.50 s		7.92 br	7.47 m
4e	4.81 d	5.35 d	11.3	3.78 s		7.00 br	7.40 m, 7.46 m
4f	4.76 d	5.34 d	11.3	1.27 t	4.24 q	6.99 br	7.40 m, 7.46 m
4g	4.88 d	5.80 d	11.3	1.28 t	4.27 q	7.04 br	7.30—7.80 m
4h	4.76 d	5.34 d	11.3	1.27 t	4.24 q	6.97 br	near 7.46 m
4i	4.80 d	5.47 d	11.3	1.28 t	4.28 q	7.00 br	7.77 m
4j	4.82 d	5.54 d	11.3	1.28 t	4.28 q	7.03 br	7.80 m, 8.25 m
4k	4.80 d	5.30 d	11.3	1.27 t	4.24 q	6.96 br	7.32 s
4l[a)]	4.67 d	5.49 d	11.3	1.23 t	4.21 q	7.66 br	near 7.28 m

a) in DMSO-d_6

Table 8. IR data of products **5** in KBr (cm^{-1})

No.	NH	Ester $\nu C=O$	Amide $\nu C=O$	δNH	No.	NH	Ester $\nu C=O$	Amide $\nu C=O$	δNH
5b	3300 m	1744 vs	1676 vs	1605 w	**5e**	3315 m	1750 vs	1675 s	1603 w
5d	3306 m	1738 vs	1680 s	1590 w	**5h**	3405 m	1742 vs	1661 s	1601 w

Table 9. NMR data of products **4** and **5** in DMSO-d_6 (δ-values from TMS)

No.	H_α	H_β	$J_{\alpha\beta}$(Hz)	H_γ	$J_{\gamma NH}$(Hz)	COOR CH_3	COOR CH_2	Aryl protons		NH	$J_{\gamma NH}$(Hz)
5b	4.75 d	5.47 d	11.3	6.35 t	7.6	1.19 t	4.19 q	6.94 m	7.60 m	9.00 d	7.6
5b′	4.78 d	5.44 d	11.3	6.35 t	7.6	1.26 t	4.25 q	6.94 m	7.60 m	9.12 d	7.6
4b	4.71 d	5.44 d	11.3			1.22 t	4.22 q		7.45 m	7.62 br	
5d	4.63 d	5.39 d	11.3	6.33 t	7.6	1.43 s		6.94 m	7.33 m	8.94 d	7.6
5d′	4.64 d	5.37 d	11.3	6.33 t	7.6	1.49 s		6.94 m	7.33 m	9.07 d	7.6
4d	4.71 d	5.32 d	11.3			1.50 s			7.47 m	7.92 br	
5e	4.68 d	5.52 d	11.3	6.23 t	7.6	1.24 t	4.24 q	6.72 m	7.40 m	9.15 d	7.6
4e	4.66 d	5.55 d	11.3			1.24 t	4.23 q		7.43 m	7.70 br	
5h	4.64 d	5.42 d	11.3	6.23 t	7.6	1.16 t	4.16 q	6.70 m	7.46 m	9.08 d	7.6
5h′	4.67 d	5.48 d	11.3	6.23 t	7.6	1.29 t	4.25 q	6.70 m	7.46 m	9.29 d	7.6
4h	4.59 d	5.45 d	11.3			1.23 t	4.22 q		7.46 m	7.70 br	

In the spectrum of **4b**, a rearrangement peak (M−HOCN) is observed at m/e 244, which may arise by the four-center mechanism from the molecular ion. Similar rearrangement peak has been observed in the case of *S*-methyl phenylthiocarbonate[4)] and *S*-(2-chloropropyl)-thiocarbamate.[5)] The base peak at m/e 125 and an abundant peak at m/e 211 evidently contain a chloride atom, because the peaks are accompanied by a +2 isotope peak amounting to about a third of the intensity. Other abundant peaks appear at the same positions as observed in the case of **3b**. A plausible explanation for these fragmentation processes is depicted in Scheme 2. It is postulated that **4b** has the structure of ethyl α-*S*-carbamoylthio-β-chloro-dihydrocinnamate. The IR and NMR spectra of **4b** (Figs. 2 and 4) are in agreement with this assignment. The spectral data of **4** are summarized in Tables 6 and 7. The chemical shifts of the α-protons are in the ranges 4.67 to 4.89 ppm and those

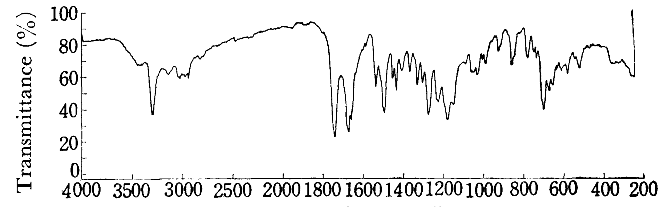

Fig. 7. IR spectrum of **5b** (KBr pellet).

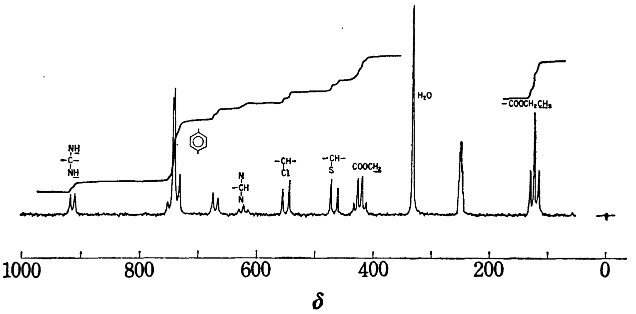

Fig. 8. NMR spectrum of **5f** in DMSO-d_6 (100 MHz).

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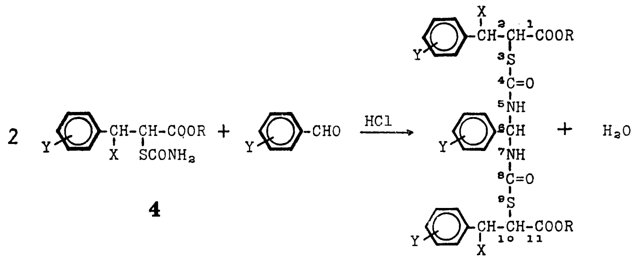
4) J. B. Thomson, P. Brown, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 4049 (1966).

5) See the experimental section.

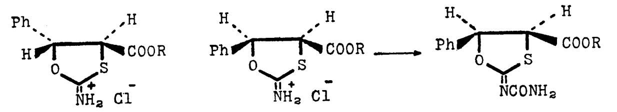
of the β-protons are in the ranges 5.30 to 5.54 ppm, except for **4g**.

The analytical and spectral data of the high-melting solid products (**5**) are summarized in Tables 3, 8, and 9. The NMR spectrum revealed that the condensation occurred between the NH_2 groups of **4** and the C=O group of an aldehyde. In the spectrum of **5e** (Fig. 8), a triplet at 6.23 ppm and a doublet at 9.15 ppm (J= 7.6 Hz), whose coupling was confirmed by double resonance experiment, are attributable to the proton at the 6-position and the two NH protons, respectively, this being indicative of the NH–CH–NH system. This assignment may be supported by the fact that **5** was alternatively synthesized by treating a mixture of **4** and an aldehyde (mole ratio=2: 1) with dry hydrogen chloride. In Table 9, the chemical shifts of the corresponding **4**'s are given along with those of **5**'s for comparison. The signals of the H_α, H_β, and alkoxycarbonyl protons for **5** appeared at almost the same positions as those for **4**. The IR spectrum showed a single absorption band in the NH stretching frequency region (Fig. 7 and Table 8). On the basis of the above data, the structure of **5** was determined to be 2,10-bis(α-chlorobenzyl)-4,8-dioxo-6-phenyl-5,7-diaza-3,9-dithiaundecanedioate.

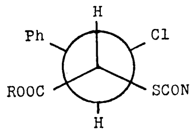


5

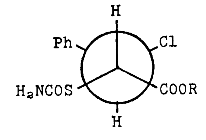
Geometric Configurations. 2-Imino-4-alkoxycarbonyl-5-aryl-1,3-oxathiolane hydrochlorides (**3**) can exist in two isomeric forms, relative to arrangements of the aryl and alkoxycarbonyl groups about a single bond in the ring. The isolated **5**, which proved to contain only one isomer, when treated with an equimolar amount of sodium cyanate, led to the *cis* isomer of the corresponding *N*-carbamoyl drivative (**2**), whose geometric configuration was established in a previous paper.3) It may be safely assumed that the geometric configuration is retained during the conversion of **3** to **2**. Therefore, **3** has the *cis* configuration. Further supports for this may be supplied by the fact that the alkoxycarbonyl protons of **3** are located at higher field by *ca.* 0.50 ppm rather than those of the corresponding ester **4**, and that the $J_{\alpha\beta}$ values for **3** are in the ranges 6.1±0.1 Hz. It was established in a previous paper3) that the *cis* forms for **2** have the alkoxycarbonyl signals at higher field by *ca.* 0.50 ppm than the *trans* forms, whose alkoxycarbonyl protons appear at almost the same positions as the ordinary esters, and that the $J_{\alpha\beta}$ values for the *cis* forms are in the range of 6.0 to 6.4 Hz. Presumably, the conformations of **3** do not differ too greatly from those of **2**.



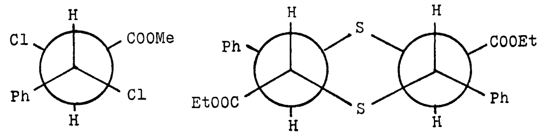
trans-**3** *cis*-**3** *cis*-**2**



threo-s



erythro-s



9

The product **4** can exist in two diastereoisomeric forms as shown below. However, the NMR spectra revealed that all the products **4** obtained in the present work consisted of single diastereomer. The vicinal $J_{\alpha\beta}$ values for **4** are consistently 11.3±0.1 Hz except for **4c**. It was reported that the $J_{\alpha\beta}$ values for *erythro*- and *threo*-α,β-dichlorodihydrocinnamic esters are 11.0 and 8.6 Hz, respectively6) and that the $J_{\alpha\beta}$ value for methyl *erythro-p*-methoxy-α,β-dibromodihydrocinnamate is 12.0 Hz.7) The *erythro* forms of α,β-dihalodihydrocinnamic esters are considered to be heavily populated in a conformation having the two protons in *trans* position as shown.8) Since the electronegativities of the carbamoylthio group and the chlorine atom are estimated to be almost the same,9) the displacement of the α-chlorine atom by the carbamoylthio group should not lead to any significant effect on the magnitude of the $J_{\alpha\beta}$ value. Therefore, the Karplus rule10) suggests that products **4** may be present predominantly in a conformation with the two protons in *trans* positions as shown above, whether *threo*-s or *erythro*-s.11) If the steric requirement of the alkoxycarbonyl group would be larger than that of the carbamoylthio group, **4** might have the *erythro*-s configuration, and if the reverse would be true, the *threo*-s.12) If the carbamoylthio group would be bulkier than the alkoxycarbonyl group, the displacement of the ethoxycarbonyl by the bulkier group should lead to the decrease in the $J_{\alpha\beta}$ value. However, the introduction of the *tert*-butyl group into the ester moiety made no change on the $J_{\alpha\beta}$

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6) M. C. Cabaleiro and M. D. Johnson, *J. Chem. Soc., B*, **1967**, 565.

7) G. P. Newsoro and S. Sternhell, *Aust. J. Chem.*, **21**, 7471 (1968).

8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y. (1969), p. 291.

9) Estimated from the equation of Dailey and Shoolery; B. P. Dailey and J. N. Shoolery, *J. Amer. Chem. Soc.*, **77**, 3977 (1956); J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1099 (1961).

10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

11) The suffix s indicates that the definition of *erythro* and *threo* is based on the size of groups; H. E. Zimmerman and W. Chang, *J. Amer. Chem. Soc.*, **81**, 3634 (1959).

12) M. Hanack, "Conformational Theory," Academic Press, New York, N. Y. (1965), p. 331.

value. Barbieux and Martin[13] reported that in the case of ethyl α,β-dialkyl-*p*-methoxydihydrocinnamates, the $J_{\alpha\beta}$ values are not a reliable indication of configurations, but that the chemical shifts of the ester protons are located at higher field for the *threo* forms by *ca.* 0.27 to 0.33 ppm than for the *erythro* forms, presumably due to the long-range shielding of the benzene ring. Examination of available data on α,β-dihalodihydrocinnamic esters also demonstrates that the ester protons resonate at higher field for the *threo* isomers by *ca.* 0.3 ppm than for the *erythro* isomers. On the other hand, it is interesting to observe that the chemical shifts of the ester protons for 2,5-diphenyl-3,6-diethoxycarbonyl-1,4-dithiane (**9**) appear at higher field by *ca.* 0.30 ppm than those of the ordinary ester. Since the $J_{\alpha\beta}$ value (10.5 Hz) indicates that the protons are in the axial conformation, the phenyl and ester groups should be present in the *equatorial* conformation. Therefore, as shown above, the spatial relationships of the phenyl and ester groups are the same for the dithiane **9** and the *threo*-s form of **4**. Consequently, if **4** has the *threo*-s configuration, the ester protons should resonate at higher field by *ca.* 0.3 ppm rather than the ordinary ester protons. However, the observed chemical shifts for the ester protons of **4** are at almost the same position as the ordinary ester, this being suggestive of the *erythro*-s configuration. All attempts to detect the *threo*-s form were unsuccessful and the solvent effects on the $J_{\alpha\beta}$ value for **4** were not observed.

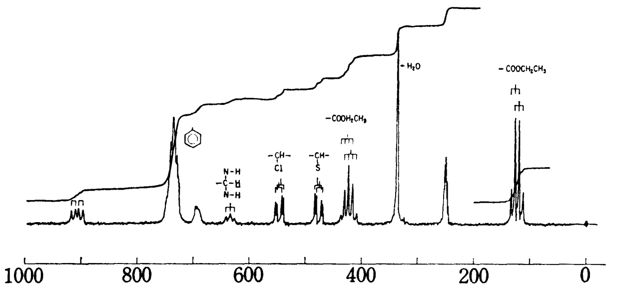
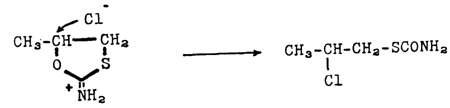


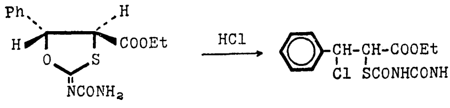
Fig. 9. NMR spectrum of **5b** in DMSO-d_6 (100 MHz).

One further problem to explain concerns the NMR spectra of product **5** (Table 9 and Fig. 9). As can be seen from Fig. 9, all the signals are duplicated with almost equal intensities. This is not due to the magnetic non-equivalence of the two cinnamate moieties in a molecule of **5**, because in the case of **5d**, two sets of signals with unequal intensities (**5d**: **5d′**=2.1: 1) were observed. Therefore, this duplication should be attributed to the presence of two chemical species. A plausible explanation is that the two enantiomers of **4** condenced with an aldehyde to give new diastereomers, which showed slightly different chemical shifts.

Reaction Mechanism. A possible mechanistic pathways for the reaction of the ester **1** with aldehydes are proposed in Scheme 1. There is little doubt that the reactions proceed through the intermediacy of α-thiocyanato-β-hydroxydihydrocinnamic ester (**6**) and 2-imino-4-alkoxycarbonyl-5-aryl-1,3-oxathiolane (**7**). The pathway leading to α,β-epithio-ester (**8**) is analogous to the route established by van Tamelen[14] for the conversion of oxiranes to thiiranes. Accordingly, this reaction has been at first considered to be a convenient one-step synthetic route to unknown α,β-epithio-esters.[15] However, the α,β-epithio-esters are unstable and readily lose sulfur, forming cinnamic esters.[16] In fact, when the reactions were conducted at room temperature and followed by prolonged standing, cinnamic esters were exclusively obtained.

The most probable route leading to ester **4** from hydrochloride **3** would be considered to be the molecular rearrangement of the hydrochloride **3**. It is known that 2-imino-1,3-oxathiolane hydrochloride readily isomerize on heating or prolonged standing into *S*-alkyl thiocarbamate.[17,18] However, it is suprising that hydrochloride **3** resisted all our attempts to effect ring-opening, only starting material being recovered. Under the more drastic conditions, cinnamic esters and unidentified decompsotion compounds were obtained. A possible explanation may be offered as follows. There is a marked difference in the reaction rates between the *cis* and *trans* isomers of **3**, presumably due to the steric reason. Similar stereoselectivity has been observed before in the case of three-membered ring.[19] All attempts to detect the *trans* isomer of **3** have failed, but when the reaction mixture was neutralized carefully with hydrogen chloride gas at low temperature, *trans*-*N*-carbamoyl derivative **2** was obtained in 10% yield. Since it was confirmed that *cis*-**2** could not be isomerized into *trans*-**2**,[3] this means that *trans*-**7** should exist in the reaction mixture. Presumably, *trans*-**3** may be attacked very rapidly at the 5-position by halide ion to give the ester **4**, whereas *cis*-**3** may resist to be attacked by the halide ion and therefore, can be isolated as the hydrochloride **3**. This speculation may be supported by the fact that *trans*-**2**, when treated with hydrochloric acid, is readily converted into α-(ureidocarbonylthio)-β-chlorodihydrocinnamic ester (**10**), whereas *cis*-**2** does not undergo the ring-opening under the similar conditions.





trans-**2b** **10b**

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[13] M. Barbieux and R. H. Martin, *Tetrahedron Lett.*, **1965**, 2919.

[14] E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 3444 (1951).

[15] M. Sander, *Chem. Rev.*, **66**, 297 (1966); C. C. Tung and A. J. Speziale, *J. Org. Chem.*, **29**, 1577 (1964).

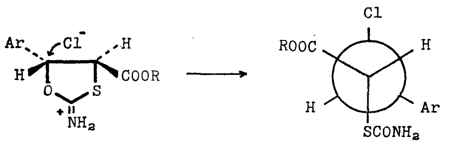
[16] T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, **1962**, 501, 656.

[17] P. G. Sergeev and B. S. Kolychev, *J. Gen. Chem.* (USSR), **7**, 1390 (1937): *Chem. Abstr.*, **32**, 2534 (1938); P. G. Sergeev, B. S. Kolychev, and V. S. Kolychev, *J. Gen. Chem.* (USSR), **7**, 2863 (1937): *Chem. Abstr.*, **32**, 2940 (1938).

[18] T. Wagner-Jauregg and M. Haering, *Helv. Chim. Acta*, **61**, 377 (1958).

[19] T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **36**, 1068 (1971).

Furthermore, if *trans*-**3** would undergo an S_N2-type ring opening reaction, as in the case of the reaction of aziridines with hydrochloric acid,[20] only the *erythro*-s isomer should be produced as shown below. If the reaction would proceed by an S_N1-type mechanism, a mixture of two diastereomers should be obtained. The results suggest that the rearrangement of *trans*-**3** to **4** might be an S_N2-type reaction. Further studies on the mechanism for this are now in progress.



trans-**3** *erythro*-s-**4**

Experimental

All the melting points are uncorrected. NMR spectra were obtained with Varian HA-100D and JEOL C-60 spectrometers in DMSO-d_6, acetone-d_6, and $CDCl_3$ solutions using tetramethylsilane as internal standard. IR spectra were determined in KBr pellet using a Perkin-Elmer 521 spectrophotometer. Mass spectra were taken with a JMS-01SG instrument operating at 75 eV.

Preparation of Thiocyanatoacetic Esters (1). The esters were prepared by a modification of Heintz's method.[21] A mixture of chloroacetic ester (1 mol) and ammonium thiocyanate (1.5 mol) in 200 m*l* of ethanol was stirred at 50°C for 3 hr. After cooling the mixture, the precipitated ammonium chloride was removed by filtration, and the filtrate was concentrated under reduced pressure. The deposited ammonium chloride was again removed by filtration and washed with ether. The filtrate and the washings were combined and washed with a small amount of water. The ethereal solution was subjected to distillation, bp 108—109°C/12 mmHg for methyl ester, 108—111°C/8 mmHg for ethyl ester, and 110—112°C/8 mmHg for *tert*-butyl ester. *tert*-Butyl ester is a new compound. IR (neat): 2160 (νSC≡N), and 1736 cm^{-1} (νC=O).

Found: C, 48.61; H, 6.41; N, 7.72; S, 18.04%. Calcd for $C_7H_{11}NO_2S$: C, 48.56; H, 6.41; N, 8.09; S, 18.52%.

Reaction of Thiocyanatoacetic Esters (1) with an Aldehyde in the Presence of Sodium Hydride. *General Procedure*: In a three-necked round-bottomed flask fitted with an apparatus specially designed for addition of sodium hydride, a thermometer, and a reflux condenser protected with a calcium chloride tube, was placed thiocyanatoacetic ester (0.03 mol), an aldehyde (0.03 mol) and 40 m*l* of dried glyme. After the air in the flask was replaced with dry nitrogen, the flask was cooled to −5°C in a freezing mixture. Sodium hydride (0.03 mol) was slowly added to the solution so that the temperature did not rise over −2°C. After the addition of sodium hydride was over, the solution was stirred at −5°C for additional 30 min. Dry hydrogen chloride gas was passed through the solution below 0°C for 10 min, and the resulting sodium chloride was removed by filtration. The solvent was removed under reduced pressure and the residue was washed with ether repeatedly, until colored materials were removed. A fraction of the solid products was subjected to the NMR analysis for the measurement of the ratio of **3** to **4**. The solid products were dissolved in 15 m*l* of acetone and the insoluble material was collected on a filter. The filtrate was concentrated on a steam bath to yield a purple-tinged white needles (**4**). The acetone-insoluble material obtained above was dissolved in ethanol and an insoluble solid was removed by filtration. The filtrate was concentrated under reduced pressure to give almost pure hydrochloride **3**.[22]

Reaction of Thiocyanatoacetic Esters (1) with Excess Aldehyde in the Presence of Sodium Hydride. A solution of thiocyanatoacetic ester (0.03 mol) and an aldehyde (0.05 mol) in 40 m*l* of dry glyme was treated with 0.03 mol of sodium hydride, as described above. The reaction mixture was saturated with dry hydrogen chloride, the resulting sodium chloride was removed by filtration, and the filtrate was concentrated under reduced pressure. The residues were washed with ether and then dissolved in 20 m*l* of acetone. The insoluble materials were washed with 20 m*l* of ethanol and recrystallized from glyme–ethanol (1:1) to give compound **5**. The washings were concentrated to yield hydrochloride **3**. The acetone solution obtained above, when the solvent was removed, gave ester **4**, which was recrystallized from ethanol.

Reaction of Thiocyanatoacetic Esters (1) with an Aldehyde in the Presence of Potassium Carbonate. A mixture of thiocyanatoacetic ester (0.03 mol) and an aldehyde (0.03 mol) in 20 m*l* of moist ether was stirred in the presence of potassium carbonate (5.0 g) at room temperature for 4 hr. After the catalyst was removed by filtration and washed with 20 m*l* of acetone, the filtrate and the washings were combined and then saturated with dry hydrogen chloride. The solvents were removed by blowing air on the solution and the resulting solid products were washed with ether. Hydrochloride **3** and ester **4** were separated and purified as described above. It was found that this method gave a higher yield of **3** than the method using sodium hydride.

Conversion of Hydrochloride 3 to Ester 4. To a solution of hydrochloride **3** (1.5 g) in 3 m*l* of water was added a solution of sodium cyanate (0.4 g) in 2.0 m*l* of water and the solution was allowed to stand at room temperature for 10 min. The resulting precipitate was recystallized from ethanol, mp 159—160°C. The mixture of this crystals with an authentic sample of *trans*-**2b** did not show a depression in melting point.

Preparation of Compound 5 from Ester 4 and an Aldehyde. General Procedure: A mixture of ester **4** (0.01 mol) and an aldehyde (0.005 mol) in 10 m*l* of glyme was saturated with dry hydrogen chloride and then allowed to stand overnight in a refrigerator. The resulting crystals were collected on a filter, washed with ether, and then recrystallized from glyme–ethanol mixture (1 : 1). In some cases, crystals did not appear in the solutions, but concentration and cooling of the solution yielded the product **5**.

Conversion of 2-Imino-5-methyl-1,3-oxathiolane Hydrochloride into S-*(2-chloropropyl)thiocarbamate.* 2-Imino-5-methyl-1,3-oxathiolane hydrochloride was prepared according to the method of Price and Kirk.[23] The white needles were very hygroscopic, mp 115—118°C (lit,[23] 112—115°C). IR (KBr) 3100—2800 cm^{-1} (νNH_3), 1660 (νC=N); NMR (DMSO-d_6) δ 1.56 (CH_3, d, J_{ab}=6.6 Hz), 3.95 (CH_a, J_{ab}=11.4, J_{ax}=5.9 or 8.6), 3.97 (CH_b, m, J_{ab}=11.4, J_{bx}=8.6 or 5.9), 5.48 (CH_x, m), and 11.85 (NH_3, broad); Mass spectra, molecular

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20) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y. (1969), p. 208, and references listed therein.

21) A. Heinz, *Ann. Chem.*, **136**, 223 (1865).

22) Although the hydrochlorides **3** might be formed in all the experiments, only five of them (**3b**, **3c**, **3d**, **3f**, and **3h**) have been isolated pure. The yields of other hydrochlorides **3** have also not been measured.

23) C. C. Price and P. F. Kirk, *J. Amer. Chem. Soc.*, **75**, 2396 (1953).

ion *m/e* 153, base peak *m/e* 117, and a peak at *m/e* 74.

2-Imino-5-methyl-1,3-oxathiolane hydrochloride (2.0 g) was heated to 120°C for 30 min. The solid was recrystallized from ether–carbon tetrachloride mixture (1: 1), mp 92°C. IR (KBr) 3380, 3320, 3210, 3180 cm^{-1} (ν NH_2), and 1655 (ν C=O). NMR ($CDCl_3$) δ 1.57 (CH_3, d, *J*=6.6 Hz), 3.26 (CH_2, d, *J*=6.0), 5.17 (CH, m), and 5.87 (NH_2, broad); molecular ion, *m/e* 153, 117 (M—HCl), 110 (M—HOCN), and base peak *m/e* 74.

Found: C, 31.08; H, 5.12; N, 9.33; S, 20.64; Cl, 23.06%. Calcd for C_4H_8NOSCl: C, 31.27; H, 5.25; N, 9.12; S, 20.87; Cl, 23.08%.

Attempted Rearrangement of cis-*3b to 4b*. *a)*: A solution of 0.5 g of *cis*-**3b** in 5 m*l* of glyme was bubbled with dry hydrogen chloride gas for five min, and then allowed to stand at room temperature for two days. Concentration of the solution gave the starting material only.

b): In a round-bottomed flask was placed 0.3 g of *cis*-**3b** and then heated to the melting point for five min. The solid mass was washed with ether and then recrystallized from ethanol. The melting point measurement and IR spectrum of the crystals were in agreement with those of *cis*-**3b**. The residue obtained from the washings proved to be ethyl cinnamate by glc.

c): A solution of 0.3 g of *cis*-**3b** in 5 m*l* of 99% ethanol was saturated with hydrogen chloride gas and then refluxed for 30 min. Concentration of the solution gave a high-melting product, which did not melt at 250°C. The structure of this product remains unsolved.

Conversion of trans-**2b** *to* **10b**. Dry hydrogen chloride was passed through 5.0 m*l* of glacial acetic acid for five min, and then 0.5 g of *trans*-*N*-carbamoyl-2-imino-4-ethoxycarbonyl-5-phenyl-1,3-oxathiolane (*trans*-**2b**) was dissolved. The solution was kept at 100°C for three min and then acetic acid was removed under reduced pressure. The residue was recrystallized from ethanol to give 0.3 g of **10b** melting at 167—168.5°C. IR spectrum (KBr pellet) 3397, 3320, 3215 cm^{-1} (ν NH_2 and ν NH), 1748 (ester C=O), 1730 (carbamoyl C=O), 1674 (allophanate C=O), and 1620 cm^{-1} (δ NH_2). NMR spectrum (acetone-d_6) 1.27 ppm (ester CH_3, t), 4.25 (ester CH_2, q), 4.85 (H_α, d, *J*=11.0 Hz), 5.39 (H_β, d, *J*=11.0), 6.80 (NH_2, br), 7.40 (C_6H_5, m), and 9.70 (NH, br).

Found: C, 46.90; H, 4.58; N, 8.49; S, 9.61; Cl, 10.13%. Calcd for $C_{13}H_{15}N_2O_4SCl$: C, 47.20; H, 4.57; N, 8.47; S, 9.69; Cl, 10.72%.

Attempted Conversion of cis-*2b to 10b*. Dry hydrogen chloride was passed through 5.0 m*l* of glacial acetic acid for five min, and then 0.5 g of *cis*-*N*-carbamoyl-2-imino-4-ethoxycarbonyl-5-phenyl-1,3-oxathiolane (*cis*-**2b**) was dissolved. The solution was kept at 100°C for five min, and then acetic acid was removed under reduced pressure. The residue was recrystallized from ethanol to give the starting material.

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