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Syntheses and Antimicrobial Activities of N-Heterocyclic-β-mercaptocinnamamides and Related Compounds[1]

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In order to obtain useful antimicrobial compounds, a number of N-heterocyclic-β-mercaptocinnamamides (IIIa—i) and related compounds were prepared. N-Heterocyclic phenylpropiolamides (I) were obtained by the reaction of heterocyclic amines with phenylpropioloyl chloride. The addition of thiourea to I gave the isothiuronium salts (II), which were converted into the mercapto compounds (III) with aqueous sodium hydroxide.

In the reaction of 2-aminothiazole or 2-amino-4-methylthiazole with phenylpropioloyl chloride in the presence of triethylamine, thiazolo[3,2-*a*]pyrimidines (V, VII and VIII) were given together with the expected amides (If and Ig).

The hydrolysis of S-[2-(3-methyl-1-phenyl-5-pyrazolyl)carbamoyl-1-phenylvinyl]-isothiourea *p*-toluenesulfonate (IIe) with aqueous sodium hydroxide at 90° gave 6,7-dihydro-1,4-diphenyl-3-methyl-6-oxopyrazolo[3,4-*b*]pyridine (IX) and a small amount of the mercapto compound (IIIe).

Acyl migration from S to N was found in the acylthio derivatives of N-(2-thiazolyl)-(IIIf) and N-(4-methyl-2-thiazolyl)-β-mercaptocinnamamide (IIIg).

Most of the compounds synthesized were considerably active *in vitro* against various gram-positive bacteria and fungi. However, only three of them were effective against *Trichophyton* in the *in vivo* tests.

It has been considered that the metal chelating ability is essential for the antibacterial effects of a number of chemotherapeutic agents such as 8-hydroxyquinoline, tetracyclines and isoniazid. The report on N-alkyl- and N-aryl-β-mercaptocinnamamide derivatives as chelating agents by Tanaka[3] led us to a study of N-heterocyclic-β-mercaptocinnamamide derivatives (IIIa—i) in order to obtain useful antimicrobial compounds. This paper deals with the syntheses as well as the antimicrobial activities of IIIa—i and related compounds.

As shown in Chart 1, IIIa—i were prepared according to Tanaka's method.[3] N-Heterocyclic phenylpropiolamides (Ia—q) were given by the reaction of heterocyclic amines with phenylpropioloyl chloride. In the reaction of two molar equivalents of 2-aminothiazole with phenylpropioloyl chloride in dry chloroform at 0° N-(2-thiazolyl)phenylpropiolamide (If) was obtained in 80% yield. However, the use of triethylamine to remove hydrogen chloride resulted in the formation of 46% yield of If and 24% yield of 5-oxo-7-phenyl-5H-thiazolo[3,2-*a*]pyrimidine (V). The change of the reaction temperature from 0° to room temperature raised the yield of V from 24% to 58%.

The structure of V was supported by the following data: elemental analysis ($C_{12}H_8ON_2S$), infrared (IR) spectrum ($\nu_{C\equiv C}$ absent, $\nu_{C=O}$ 1660 cm^{-1}) and nuclear magnetic resonance (NMR) spectrum (a singlet at 6.73 ppm for one olefinic proton, no deuterium exchangeable proton). The possibility of the structure of this compound being 7-oxo-5-phenyl-7H-thiazolo[3,2-*a*]pyrimidine (VI),[4] the isomer of V, was excluded by its ultraviolet (UV) spectro-

1) This work was presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April 1969.
2) Location: *Enoki-cho 33-94, Suita, Osaka.*
3) A. Yokoyama, K. Ashida, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **12**, 690 (1964).
4) Recently VI and VIII were prepared by the reaction of the corresponding 2-aminothiazoles with ethyl phenylpropiolate (D.W. Dunwell and D. Evans, *J. Chem. Soc.* (*C*), **1971**, 2094). Their IR and UV spectra agree with those listed in Table I.

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metric evidence as described below. VI was obtained along with V on heating If with concentrated sulfuric acid[5] at 55° for 5 hr and their spectroscopic data are summarized in Table I.

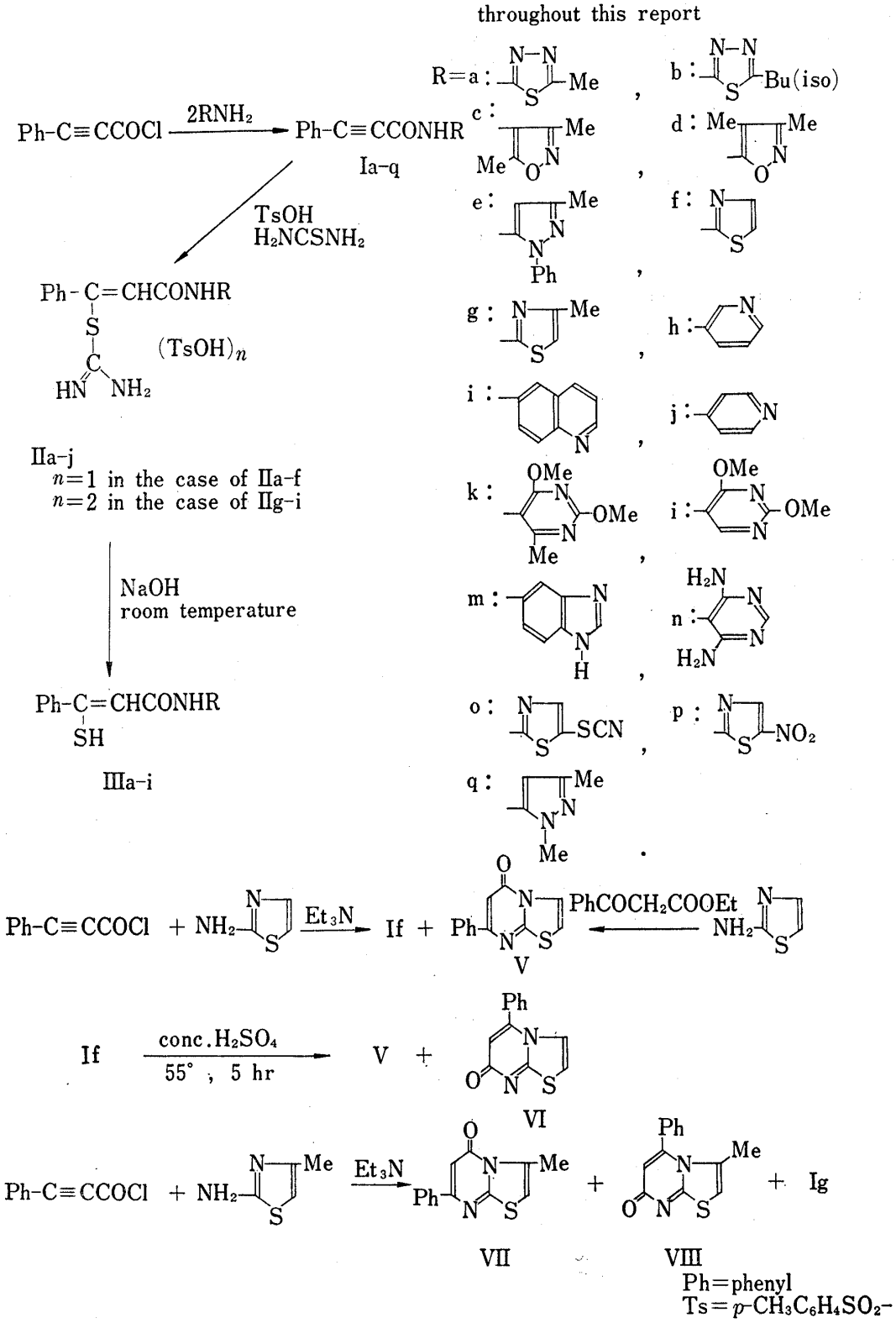

Chart 1

5) M. Ohta and K. Tanaka, *Yakugaku Zasshi*, **74**, 966 (1954).

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Table I. Spectroscopic Data of Thiazolo[3,2-*a*]pyrimidines

	Compound			
	V	VI	VII	VIII
IR ν_{max}^{KBr} cm^{-1}	1660	1630, 1605	1665	1630, 1603
UV λ_{max}^{EtOH} mμ (logε)	260 (4.48)	237 (4.32)	266 (4.45)	236 (4.26)
	282 (4.30)	277 (4.20)	284 (4.19)	283 (4.07)
	339 (3.97)		350 (3.90)	
NMR δ (in $CDCl_3$)	6.73	6.32	6.60	6.22
	(1H, s)	(1H, s)	(1H, s)	(1H, s)
	6.99	6.93	2.81	1.67
	(1H, d, J=5 cps)	(1H, d, J=5 cps)	(3H, d, J=1 cps)	(3H, d, J=1 cps)
	7.99	7.24	6.40	6.42
	(1H, d, J=5 cps)	(1H, d, J=5 cps)	(1H, q, J=1 cps)	(1H, q, J=1 cps)

abbreviation
s: singlet, d: doublet, q: quartet

The report of Allen[6] describes that the UV spectra of 5-oxo-5H-thiazolo[3,2-*a*]pyrimidines exhibit a high-intensity absorption band (ε 9400—18600) at 313—352 mμ in contrast to those of 7-oxo-7H-thiazolo[3,2-*a*]pyrimidines which show no absorption in the region beyond 300 mμ. This report supported the structure of V. Finally, V was identified with the compound alternatively prepared from 2-aminothiazole and ethyl benzoylacetate according to the method for the preparation of 7-methyl-5-oxo-5H-thiazolo[3,2-*a*]pyrimidine given by Allen.[6]

Although the similar result was expected in the reaction of 2-amino-4-methylthiazole with phenylpropioloyl chloride in the presence of triethylamine, two isomers, 3-methyl-5-oxo-7-phenyl-5H-thiazolo[3,2-*a*]pyrimidine (VII) and 3-methyl-7-oxo-5-phenyl-7H-thiazolo-[3,2-*a*]pyrimidine (VIII),[4] were obtained together with N-(4-methyl-2-thiazolyl)phenylpropiolamide (Ig). The structures of VII and VIII were established in the same manner as described in the case of V and VI and these spectroscopic data are also summarized in Table I.

The isothiuronium salts (IIa—j) were given by the reaction of the corresponding N-heterocyclic phenylpropiolamides (Ia—j) and thiourea in the presence of *p*-toluenesulfonic acid. Attempts to prepare IIk—q were unsuccessful. The hydrolyses of IIa—i with aqueous sodium hydroxide at room temperature afforded the mercapto compounds (IIIa—i) in good yield. However, the yields were reduced in the cleavage reactions carried out on a steam bath. For example, the treatment of S-[2-(3-methyl-1-phenyl-5-pyrazolyl)-carbamoyl-1-phenylvinyl]isothiourea *p*-toluenesulfonate (IIe) with aqueous sodium hydroxide on a steam bath for 2 hr gave only 10% of the desired product, N-(3-methyl-1-phenyl-5-pyrazolyl)-β-mercaptocinnamamide (IIIe), and the main product (57%) was found to be 6,7-dihydro-1,4-diphenyl-3-methyl-6-oxopyrazolo[3,4-*b*]pyridine (IX) as shown in Chart 2. The structure of IX was supported by its elemental analysis ($C_{19}H_{15}ON_3$), spectroscopic data and the fact that IX was soluble in aqueous sodium hydroxide. The NMR spectrum of IX in deuteriochloroform exhibited a singlet at 2.10 ppm due to the methyl protons of pyrazole ring, a singlet at 6.37 ppm for one olefinic proton and a broad singlet at 10.5 ppm for one amide proton. The UV spectrum showed λ_{max}^{EtOH} 301 mμ (log ε 4.06) in addition to λ_{max}^{EtOH} 261 mμ (log ε 4.57) and was similar to those of 1-phenylpyrazolo[3,4-*b*]pyridines[7] which showed λ_{max} 252—257 mμ (log ε 4.32—4.52) and λ_{max} 292—310 mμ (log ε 3.94—4.30).

6) C.F.H. Allen, H.R. Beilfuss, D.M. Burness, G.A. Reynolds, J.F. Tinker, and J.A. VanAllan, *J. Org. Chem.*, **24**, 779 (1959).
7) Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **10**, 612 (1962); I.I. Grandberg and S.V. Tabak, *Khim. Geterotsikl. Soedin.*, **1965**, 112 [*C.A.*, **63**, 5625 g (1965)].

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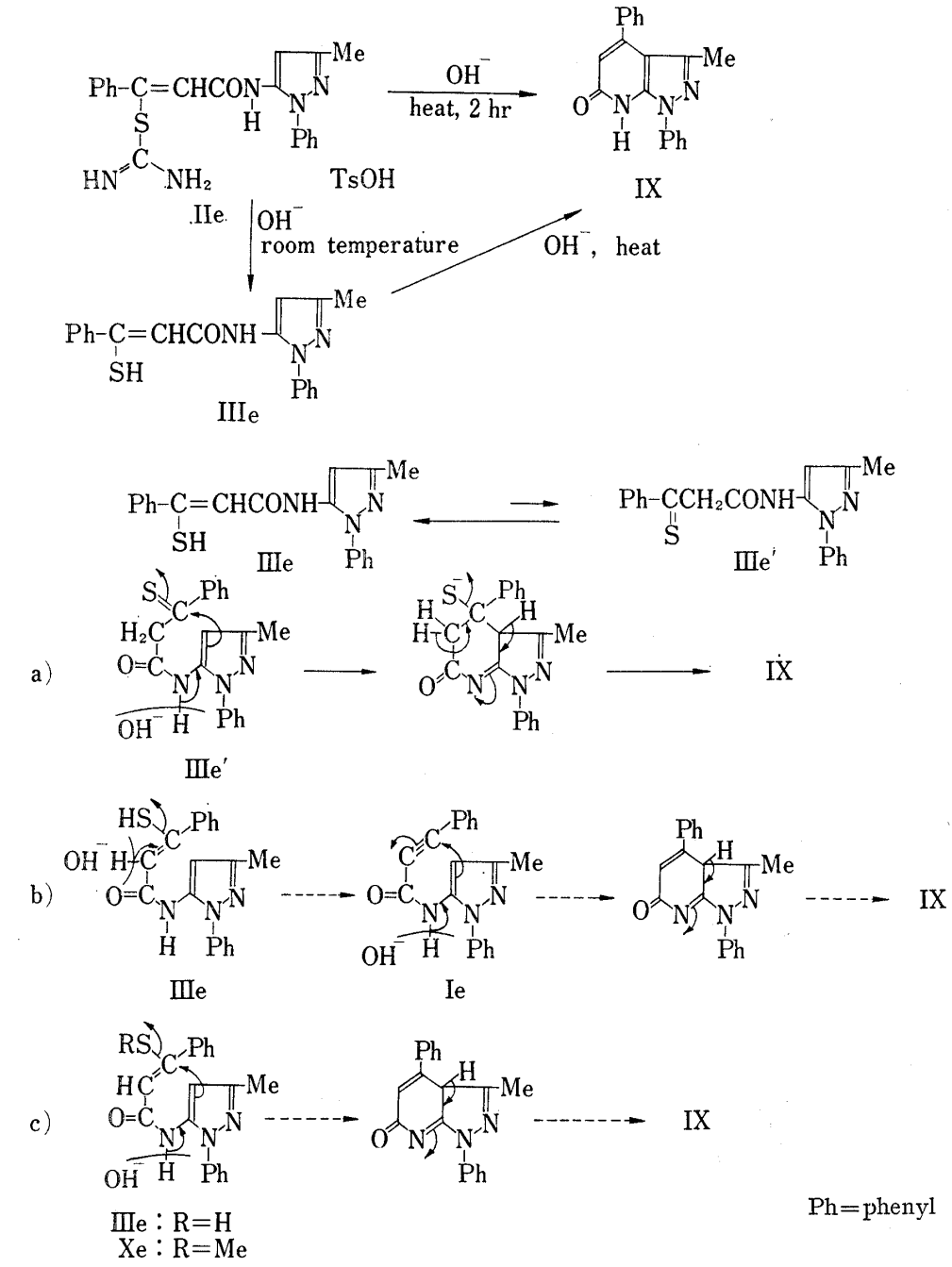

Chart 2

The treatment of IIIe with sodium hydroxide on a steam bath for 2 hr also resulted in the formation of IX with the elimination of hydrogen sulfide detected as lead (II) sulfide. This indicates that the conversion of IIe into IX proceeds *via* IIIe as the intermediate. The NMR spectra showed that the olefinic proton of IIIe (6.03 ppm) was exchangeable by deuterium in deuteriochloroform in contrast to the olefinic protons of other N-heterocyclic-β-mercaptocinnamamides (exchangeable in deuteriodimethylsulfoxide, but not in deuteriochloroform). On the basis of the existence of this mobile olefinic proton in IIIe, the ring closure of IIIe to IX might be explained as below. As the tautomeric equilibrium between IIIe and IIIe' would be possible, IIIe would be transformed into IX through the mechanistic course (*a*) involving the initial abstraction of the amide proton in the thioxo-tautomer (IIIe') by base as shown in Chart 2. The possibility of the pathway (*b*) in which IX is given by the ring closure of Ie was excluded by the fact that Ie was recovered unchanged when heated with aqueous sodium hydroxide on a steam bath for 2 hr. The pathway (*c*) in which the

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reaction species is the thioenol-tautomer (IIIe) was also excluded by the fact that N-(3-methyl-1-phenyl-5-pyrazolyl)-β-(methylthio)cinnamamide (Xe) having a fixed thioenol moiety could not be converted into IX under the similar condition as employed in the case of IIIe.

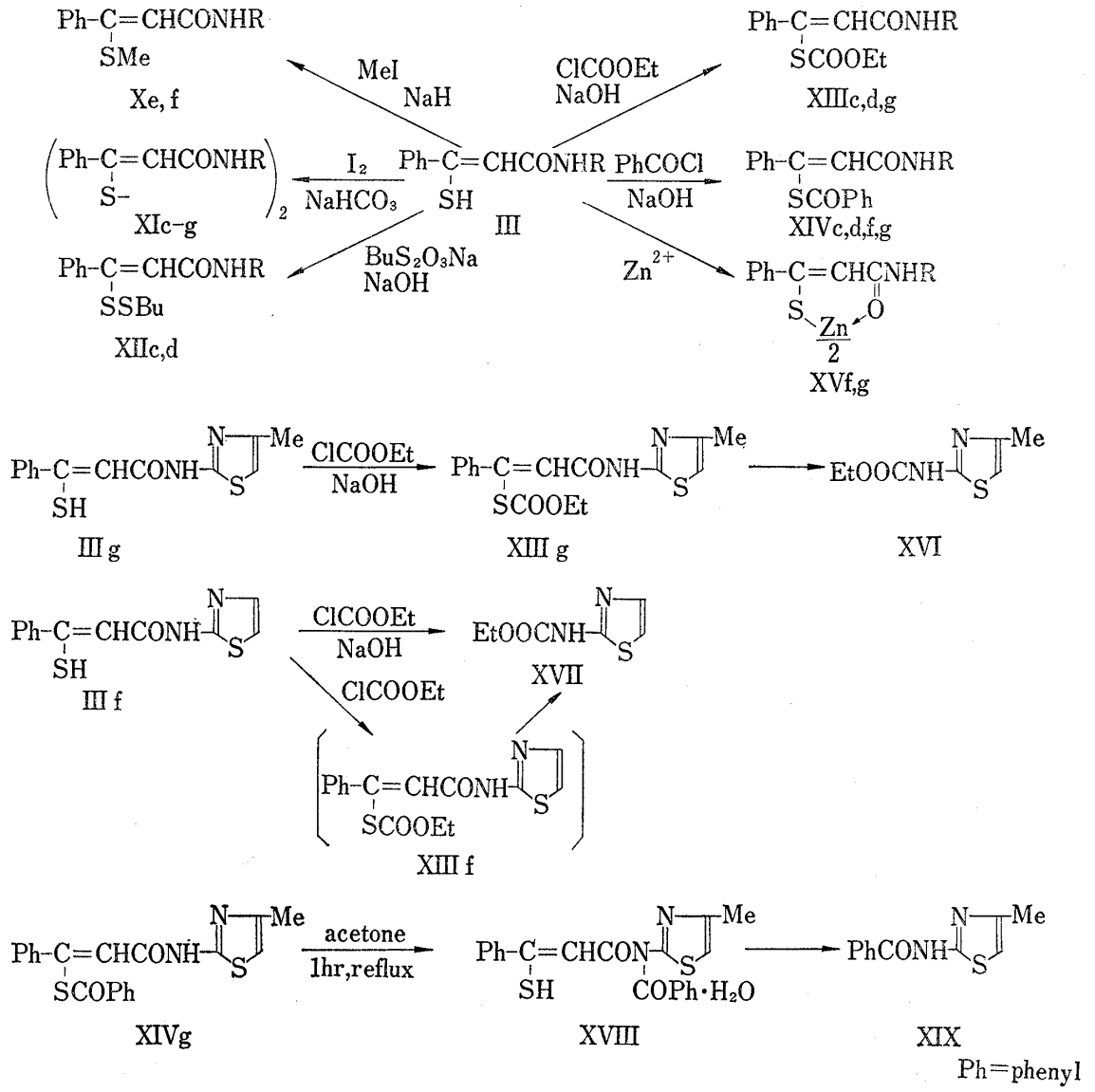

Chart 3

Such modifications of the thiol group as are well known in the field of Vitamin B_1 were tried on several mercapto compounds (III) (Chart 3). Xe and N-(2-thiazolyl)-β-(methylthio)cinnamamide (Xf) were derived from the corresponding mercapto compounds (IIIe and IIIf) and methyl iodide in the presence of sodium hydride. Oxidation of IIIc—g with iodine gave the disulfide derivatives (XIc—g). The reaction of IIIc and IIId with sodium *n*-butylthiosulfate (Bunte salt) in the presence of sodium hydroxide gave the corresponding *n*-butyldithio compounds (XIIc and XIId). The treatment of IIIc, IIId, and IIIg with an equimolar amount of ethyl chloroformate in the presence of sodium hydroxide at 0° for 2 hr resulted in the formation of the ethoxycarbonylthio compounds (XIIIc, XIIId, and XIIIg) whose IR spectra have two characteristic absorption bands at 1724—1735 cm^{-1} and 1685—1698 cm^{-1}. XIIIg was too unstable and recrystallization from benzene–*n*-hexane resulted in the formation of 2-ethoxycarbonylamino-4-methylthiazole (XVI). It would be

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considered that XVI was obtained by the decomposition of N-ethoxycarbonyl-N-(4-methyl-2-thiazolyl)-β-mercaptocinnamamide which was formed by migration of the ethoxycarbonyl group from S to N in XIIIg. In the case of IIIf, the same reaction condition employed above gave 2-ethoxycarbonylaminothiazole (XVII) in 15% yield and the treatment with a large excess of ethyl chloroformate in the absence of sodium hydroxide at room temperature for 9 hr afforded a crystalline product. The IR spectrum of this compound showed the expected absorption bands at 1730 cm^{-1} and 1685 cm^{-1} but the result of its elemental analysis was not consistent with the calculated value for XIIIf. It was converted to XVII by sodium hydrogen carbonate, probably due to the same migration as in the case of XIIIg.

Benzoylthio derivatives (XIVc, XIVd, XIVf, and XIVg) were obtained by the reaction of the mercapto compounds (IIIc, IIId, IIIf, and IIIg) with benzoyl chloride in the presence of sodium hydroxide. The treatment of N-(4-methyl-2-thiazolyl)-β-(benzoylthio)cinnamamide (XIVg) with refluxing acetone for one hour gave **a** compound, $C_{20}H_{18}O_3N_2S_2$. This, if formulated as $C_{20}H_{16}O_2N_2S_2 \cdot H_2O$, would exactly correspond to the monohydrate of the rearranged product, N-benzoyl-N-(4-methyl-2-thiazolyl)-β-mercaptocinnamamide (XVIII). The structure of XVIII was supported by its NMR spectrum and the observation that the treatment of XVIII with refluxing methanol for 3 hr resulted in the cleavage to 2-benzamido-4-methylthiazole (XIX). The NMR spectrum of XVIII in deuteriochloroform showed a doublet at 2.35 ppm (J=1 cps) due to the methyl group of thiazole ring, a quartet at 6.55 ppm (J=1 cps) for the proton of thiazole ring, a singlet at 6.30 ppm for the olefinic proton, a broad singlet at 12.5 ppm for two protons and a multiplet at 7.33—8.37 ppm due to the aromatic protons. Although it is difficult to give an exact assignment of the signal at 12.5 ppm, it was tentatively assigned to the protons of the water molecule strongly hydrogen-bonded. In the case of N-(3,4-dimethyl-5-isoxazolyl)-β-(benzoylthio)cinnamamide (XIVd), XIVd was recovered on heating in acetone or methanol. The facile acyl migration in XIIIf, XIIIg and XIVg would be attributed to the acidity[8] of the amide protons in these acylaminothiazoles. The similar acyl migration in β-acetoxy-cinnamanilide was reported by Woodward.[9]

The chelate compounds (XVf and XVg) were also prepared by the treatment of alcoholic solutions of IIIf and IIIg with aqueous zinc acetate.

In order to examine the influence of the amide proton in IIIf on its antibacterial activity, N-methyl-N-(2-thiazolyl)-β-mercaptocinnamamide (XXII) was prepared. As 2-acylaminothiazoles have weakly acidic properties and form potassium salts,[8] N-methyl-N-(2-thiazolyl)-phenylpropiolamide (XX) was obtained by the reaction of the potassium salt of If with a large excess of methyl iodide. The isothiuronium salt (XXI) and the mercapto compound (XXII) were prepared in the same manner as described above.

In vitro antimicrobial activities of the compounds synthesized were tested by the serial tube dilution methods[10a] and the results are shown in Table II. *In vivo* effects of most of the compounds were also tested in mice infected with *Staphylococcus aureus*[10b] and *Mycobacterium tuberculosis* Kurono,[10c] and in guinea pigs infected with *Trichophyton asteroides*[10d]

Most of the isothiuronium salts, the mercapto derivatives and the modified mercapto compounds were considerably active *in vitro* against various gram-positive bacteria includ-

8) R.C. Elderfield (ed.), "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N.Y., 1957, p. 595; K. Tsuda, H. Sakamoto, H. Matsuda, and T. Sugano, *Yakugaku Zasshi*, **60**, 462 (1940).

9) R.B. Woodward, D.J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

10) Details of the methods were described in the following literatures; *a*) K. Fujimoto, *Chemotherapy*, **15**, 228 (1967) (antibacterial activity); *idem*, *ibid.*, **15**, 246 (1967) (antitubercular activity); K. Fujimoto, M. Shimizu, and Y. Takase, *ibid.*, **15**, 527 (1967) (antimycotic activity); K. Fujimoto, M. Shimizu, Y. Takase, I. Nakanishi, and S. Nakamura, *ibid.*, **15**, 535 (1967) (antitrichomonal activity); *b*) M. Shimizu, S. Nakamura, and Y. Takase, *Antimicrob. Ag. Chemother.*, **1970**, 117 (1971); *c*) H. Nishimura, K. Nakajima, and Y. Tanaka, *Shionogi Kenkyusho Nempo*, **14**, 216 (1964); *d*) T. Iwamoto, Y. Miura, and H. Fujimura, *Nippon Yakurigaku Zasshi*, **58**, 235 (1962).

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ing *Mycobacterium tuberculosis* and fungi, especially *Dermatophytes* (*Trichophyton, Microsporum* and *Epidermophyton*). They were usually more active than N-alkyl- and N-aryl-β-mercaptocinnamamide derivatives as shown in Table II and Table III. However, they were all inactive against gram-negative bacteria and *Trichomonas vaginalis*.

Since it could not be considered that the modified mercapto compounds were converted to the parent mercapto compounds in the course of the *in vitro* tests, they would be lacking in chelating ability. Nevertheless most of them were considerably active against gram-positive bacteria and fungi, their activities being inferior to those of the mercapto compounds. Moreover, N-methyl-N-(2-thiazolyl)-β-mercaptocinnamamide (XXII) was found to possess chelating ability without detectable antibacterial activity. The results indicate that the chelating ability of IIIa—i may not be responsible for the antibacterial activity and the amide proton may be indispensable for it.

In the *in vivo* tests the effective compounds were only three, namely IIIf, XIf, and XIId, which showed considerable activity against *Trichophyton* with moderate skin irritation.

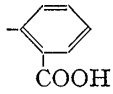
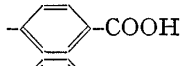
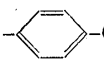
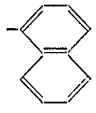
Table II. *In Vitro* Antimicrobial Activity

Compd.	A	B (MIC: μg/ml)	C	Compd.	A	B (MIC: μg/ml)	C
IIa	1	3	1	Xf	10	10	>30
IIb	3	1	3	XIc	10	3	10
IIc	30	3	10	XId	3	3	3
IId	3	3	3	XIe	1	3	10
IIe	3	3	10	XIf	1	1	< 1
IIf	3	0.1	1	XIg	1	1	30
IIg	3	1	10	XIIc	>100	3	>30
IIh	10	<1	3	XIId	1	1	1
IIi	3	1	10	XIIIc	>100	3	>30
IIIa	0.3	1	0.3	XIIId	3	3	30
IIIb	0.3	3	1	XIVc	100	3	10
IIIc	30	>30	30	XIVd	>100	10	>30
IIId	0.3	3	1	XIVf	10	10	>30
IIIe	1	3	10	XIVg	10	10	>30
IIIf	0.3	1	0.1	XVf	10	1	>30
IIIg	1	1	3	XVg	0.3	0.3	3
IIIh	3	1	3	XXI	>100	>30	>30
IIIi	10	10	10	XXII	30	>30	30

abbreviation
MIC: minimum inhibitory concentration, A: *Staphylococcus aureus* Terajima, B: *Mycobacterium tuberculosis*, C: *Trichophyton asteroides*

Table III. *In Vitro* Antimicrobial Activity of N-Alkyl- and N-Aryl-β-mercaptocinnamamide

Ph-C(SH)=CHCONHR

R	A	B (MIC: μg/ml)	C	R	A	B (MIC: μg/ml)	C
-Et	100	100	30		30	100	100
	30	3	10		3	100	100
	>100	10	10		100	10	30

The abbreviations used are the same as those in Table II.

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Experimental

All melting points were determined on a Yanagimoto Micromelting-point Apparatus and are uncorrected. IR spectra were recorded in KBr disk by use of a Hitachi EPI-S spectrophotometer. UV spectra were recorded with a Hitachi EPS-2U spectrophotometer. NMR spectra were run with a Varian A-60 spectrometer, TMS serving as internal standard.

General Procedure for the Preparation of N-Heterocyclic Phenylpropiolamide (I, Table IV)——To a stirred suspension of heterocyclic amine (0.04 mole) in dry $CHCl_3$ at $-10°$ was added dropwise a solution of phenylpropioloyl chloride (0.02 mole) in dry $CHCl_3$. After the addition, stirring was continued for 3—5 hr below 10° (at room temperature for Ii, m, n and p). The reaction mixture was worked up as usual. Recrystallization from an appropriate solvent yielded an analytical sample.

Table IV. N-Heterocyclic Phenylpropiolamide
Ph-C≡CCONHR

Compd.	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
Ia	210—211[a]	90.0	scales	$C_{12}H_9ON_3S$	59.26	3.73	17.28	13.16	58.61	3.92	17.03	13.05
Ib	183—189[b]	91.3	needles	$C_{15}H_{15}ON_3S$	63.15	5.30	14.73	11.21	62.86	5.41	14.46	11.20
Ic	143—145[c]	38.3	needles	$C_{14}H_{12}O_2N_2$	69.99	5.03	11.66	—	69.71	5.22	11.89	—
Id	153—157[c]	27.0	needles	$C_{14}H_{12}O_2N_2$	69.99	5.03	11.66	—	70.12	5.14	11.47	—
Ie	184—188[c] (decomp.)	58.3	needles	$C_{19}H_{15}ON_3$	75.73	5.02	13.95	—	75.58	4.98	14.19	—
If	176—180[d]	80.0	needles	$C_{12}H_8ON_2S$	63.16	3.53	12.28	14.02	62.98	3.65	11.98	14.01
Ig	141—142[e]	31.6	needles	$C_{13}H_{10}ON_2S$	64.46	4.16	11.57	13.21	64.72	3.89	11.51	13.36
Ih	155—157[c] (decomp.)	45.7	needles	$C_{14}H_{10}ON_2$	75.65	4.54	12.61	—	75.86	4.61	12.53	—
Ii	193—194[d]	60.0	needles	$C_{18}H_{12}ON_2$	79.39	4.44	10.29	—	79.51	4.41	10.32	—
Ij	174—175[d] (decomp.)	7.2	prisms	$C_{14}H_{10}ON_2$	75.65	4.54	12.61	—	75.38	4.81	12.44	—
Ik	120—122[c]	50.0	prisms	$C_{16}H_{15}O_3N_3$	64.63	5.09	14.14	—	64.44	5.24	13.99	—
Il	183—186[d]	60.0	plates	$C_{15}H_{13}O_3N_3$	63.59	4.63	14.83	—	63.30	4.67	14.58	—
Im	>250[d]	38.3	needles	$C_{16}H_{11}ON_3$	73.55	4.24	16.08	—	73.53	4.18	16.04	—
In	236—238[c]	2.3	plates	$C_{13}H_{11}ON_5$	61.65	4.38	27.66	—	61.61	4.47	27.92	—
Io	213—215[d] (decomp.)	53.6	needles	$C_{13}H_7ON_3S_2$	54.74	2.47	14.73	22.44	54.56	2.48	14.56	22.27
Ip	237—240[b] (decomp.)	23.6	scales	$C_{12}H_7O_3N_3S$	52.75	2.58	15.38	11.71	52.90	2.58	15.18	11.68
Iq[f]	233[b] (decomp.)	52.6	needles	$C_{21}H_{21}O_4N_3S$	61.31	5.15	10.21	7.78	61.40	5.13	10.06	7.82

Recryst. solvt.
a) MeOH, *b*) EtOH, *c*) aq. acetone, *d*) acetone, *e*) benzene-hexane
f) *p*-Toluenesulfonate of N-(1,3-dimethyl-5-pyrazolyl)phenylpropiolamide

Reaction of 2-Aminothiazole with Phenylpropioloyl Chloride in the Presence of Triethylamine——To a stirred mixture of 2-aminothiazole (1.37 g) and triethylamine (1.39 g) in dry $CHCl_3$ at 0° was added dropwise a solution of phenylpropioloyl chloride (2.24 g) in dry $CHCl_3$. The mixture was stirred for 1.5 hr at the same temperature. The precipitate was filtered and washed with 5% HCl, 5% $NaHCO_3$ and H_2O to yield 0.62 g of If. The filtrate was washed similarly. Evaporation of the dried solution afforded 1.56 g of a crystalline product, from which 0.74 g (23.7%) of V was separated by washing with warm dilute aqueous NaOH. An analytical sample of V was recrystallized from acetone as pale yellow needles, mp 175—176°. *Anal.* Calcd. for $C_{12}H_8ON_2S$ (V): C, 63.16; H, 3.53; N, 12.28; S, 14.02. Found: C, 63.13; H, 3.55; N, 12.04; S, 14.04.

The alkaline washing was made acidic with 20% AcOH to afford an additional crop of If (0.82 g; total yield: 46.2%).

Reaction of If with conc. H_2SO_4——A solution of If (0.50 g) in conc. H_2SO_4 (5 ml) was warmed at 55° for 5 hr. After cooling, the reaction mixture was poured into ice-water and the precipitate collected was recrystallized from acetone-*n*-hexane to give 0.01 g (2%) of V melting at 175—176°. The filtrate was made alkaline with conc. NH_4OH and extracted with $CHCl_3$. Evaporation of the dried extract afforded a crys-

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talline solid which was recrystallized from acetone–*n*-hexane to give 0.10 g (20%) of VI as colorless needles, mp 218—219°. *Anal.* Calcd. for $C_{12}H_8ON_2S$ (VI): C, 63.16; H, 3.53; N, 12.28; S, 14.02. Found: C, 62.72; H, 3.63; N, 11.89; S, 14.25.

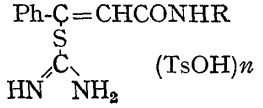
Alternative Synthesis of 5-Oxo-7-phenyl-5H-thiazolo[3,2-*a*]pyrimidine (V)——A solution of 2-aminothiazole (1.00 g) and ethyl benzolylacetate (2.11 g) in AcOH (9 ml) was allowed to reflux for 6 hr and concentrated *in vacuo* to give an oil. This oily residue was taken up in $CHCl_3$ and washed with 5% NaOH, 5% HCl and H_2O. Evaporation of the dried extract gave 0.95 g of an oily product which was chromatographed on silica gel using $CHCl_3$ as eluent. The eluate gave 0.11 g (4.8%) of V, which was shown to be identical with V described above by the mixed melting point and comparison of the IR spectra.

Reaction of 2-Amino-4-methylthiazole with Phenylpropioloyl Chloride in the Presence of Triethylamine——To a solution of 2-amino-4-methylthiazole (1.56 g) and triethylamine (1.39 g) in dry $CHCl_3$ at 0° was added dropwise a solution of phenylpropioloyl chloride (2.24 g) in dry $CHCl_3$. After the addition, the reaction mixture was stirred for 0.5 hr at the same temperature and washed with H_2O, 5% $NaHCO_3$ and H_2O. Evaporation of the dried solution gave an oil which was treated with acetone–ether to give 0.16 g (4.8%) of a crystalline solid. Recrystallization from $CHCl_3$ afforded VIII as colorless needles, mp 260—262°. *Anal.* Calcd. for $C_{13}H_{10}ON_2S$ (VIII): C, 64.46; H, 4.16; N, 11.57; S, 13.21. Found: C, 64.34; H, 4.15; N, 10.91; S, 13.38.

The mother liquors from VIII were concentrated to dryness and the crystalline residue was extracted with warm dilute aqueous NaOH. Ig (1.03 g) was obtained by acidification of the alkaline solution with 20% AcOH. Insoluble material in dilute aqueous NaOH was washed with a small amount of acetone and chromatographed on silica gel, using $CHCl_3$ as eluent, to afford 0.05 g (1.5%) of VII. Recrystallization from acetone–*n*-hexane gave yellow needles, mp 201—202°. *Anal.* Calcd. for $C_{13}H_{10}ON_2S$ (VII): C, 64.46; H, 4.16; N, 11.57; S, 13.21. Found: C, 64.48; H, 4.04; N, 11.33; S, 13.31.

General Procedure for the Preparation of S-[2-(Heterocyclic)carbamoyl-1-phenylvinyl]isothiourea *p*-Toluenesulfonate (II, Table V)——A mixture of I (0.01 mole), thiourea (0.01 mole) and *p*-toluenesulfonic acid (0.01 mole) (0.02 mole in the case of Ig—i) in absolute EtOH was refluxed on a steam bath for several hours (Table V) and evaporated to half of its original volume. After cooling, dry ether was added to the cloud point and the solution was kept in the refrigerator until crystallization was complete. Recrystallization of the crystalline solid from an appropriate solvent afforded II.

TABLE V. S-[2-(Heterocyclic)carbamoyl-1-phenylvinyl]isothiourea *p*-Toluenesulfonate



Compd.	*n*	Reaction Time (hr)	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
IIa	1	1.3	206—207[a]	58.1	plates	$C_{20}H_{21}O_4N_5S_3$	48.88	4.31	14.25	19.54	49.20	4.48	13.92	19.29
IIb	1	3	208—209[a] (decomp.)	67.4	plates	$C_{23}H_{27}O_4N_5S_3$	51.78	5.10	13.13	17.99	51.47	4.96	12.34	18.57
IIc	1	2	206—207[b]	83.9	needles	$C_{22}H_{24}O_5N_4S_2$	54.09	4.95	11.47	13.10	53.79	5.11	11.64	12.83
IId	1	1	172—175[b]	62.0	needles	$C_{22}H_{24}O_5N_4S_2$	54.09	4.95	11.47	13.10	53.99	5.03	11.08	13.58
IIe	1	2	205—206[b]	66.4	needles	$C_{27}H_{27}O_4N_5S_2$	59.01	4.95	12.75	11.65	58.87	4.82	12.79	11.77
IIf	1	3	187—189[b]	52.6	needles	$C_{20}H_{20}O_4N_4S_3$	50.42	4.23	11.76	20.15	50.39	4.11	11.51	19.83
IIg	2	1	147—149[b],[c]	58.3	needles	$C_{28}H_{30}O_7N_4S_4$	50.74	4.56	8.45	19.35	50.49	4.85	8.14	18.72
IIh	2	5	214—215[a]	51.6	needles	$C_{29}H_{30}O_7N_4S_3$	54.19	4.70	8.72	14.97	54.14	4.69	8.52	14.71
IIi	2	3.5	197—200[b]	70.4	prisms	$C_{33}H_{32}O_7N_4S_3$	57.21	4.66	8.09	13.88	57.03	4.79	7.80	13.49
IIj	2	2	275—277[a] (decomp.)	38.1	needles	$C_{29}H_{30}O_7N_4S_3$	54.19	4.70	8.72	14.97	55.46	4.71	8.70	14.94

Recryst. solvt.
a) EtOH, *b*) EtOH–ether *c*) IIg melted at 147—149°, resolidified and finally melted at 178—179°

General Procedure for the Preparation of N-Heterocyclic-β-mercaptocinnamamide (III, Table VI)——To a stirred suspension of II (0.0021 mole) in H_2O (7 ml) at room temperature under N_2 atmosphere was added dropwise 10% NaOH until the solution became clear. After stirring for 1 hr, the solution was neutralized carefully with 20% AcOH to give a crystalline solid, which was recrystallized from aqueous EtOH or EtOH to give III.

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Table VI. N-Heterocyclic-β-mercaptocinnamamide
Ph-Ç=CHCONHR
SH

Compd.	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
IIIa	213—218[a]	90.0	needles	$C_{12}H_{11}ON_3S_2$	51.99	4.00	15.16	23.09	52.29	4.04	14.76	23.24
IIIb	201—203[a]	91.3	needles	$C_{15}H_{17}ON_3S_2$	56.42	5.37	13.16	20.04	56.74	5.42	13.08	19.93
IIIc	136—140[b]	69.2	needles	$C_{14}H_{14}O_2N_2S$	61.31	5.15	10.21	11.67	61.51	5.22	9.85	11.66
IIId	156—158[b]	87.8	plates	$C_{14}H_{14}O_2N_2S$	61.31	5.15	10.21	11.67	61.26	5.15	10.25	11.51
IIIe	158—161[b]	86.0	needles	$C_{19}H_{17}ON_3S$	68.05	5.11	12.53	9.54	67.85	5.18	12.25	9.61
IIIf	167—169[b]	90.0	needles	$C_{12}H_{10}ON_2S_2$	54.96	3.84	10.68	24.41	54.94	3.91	10.27	24.07
IIIg	168—170[b]	80.5	needles	$C_{13}H_{12}ON_2S_2$	56.52	4.38	10.14	23.17	56.63	4.20	9.98	23.33
IIIh	154—156[b]	60.0	needles	$C_{14}H_{12}ON_2S$	65.62	4.72	10.93	12.49	65.41	4.72	10.75	12.33
IIIi	163—165[b]	56.8	needles	$C_{18}H_{14}ON_2S$	70.58	4.61	9.15	10.45	70.70	4.59	9.10	10.36

Recryst. solvt.
a) EtOH, *b*) aq. EtOH

6,7-Dihydro-1,4-diphenyl-3-methyl-6-oxopyrazolo[3,4-*b*]pyridine (IX)——i) To a stirred suspension of IIe (0.50 g) in H_2O (8 ml) was added portionwise 10% NaOH (2.2 ml) at room temperature under N_2 atmosphere and then the mixture was heated on a steam bath for 2 hr. After cooling, the reaction mixture was acidified with 20% AcOH and the precipitate collected was recrystallized from aqueous acetone to yield 0.16 g (57%) of IX, colorless scales, which melted at 187—189°, resolidified and finally melted at 193—195°. *Anal.* Calcd. for $C_{19}H_{15}ON_3$ (IX): C, 75.73; H, 5.02; N, 13.95. Found: C, 75.52; H, 4.97; N, 13.98. IIIe (0.01 g) was obtained from the mother liquors. Addition of aqueous $Pb(OAc)_2$ solution to the acidic solution gave the precipitated lead (II) sulfide.

ii) To a stirred suspension of IIIe (0.20 g) in H_2O (9 ml) was added dropwise 10% NaOH (1.2 ml) at room temperature under N_2 atmosphere and then the mixture was heated on a steam bath for 2 hr. After cooling, acidification of the reaction mixture with 20% AcOH afforded a precipitate, which was collected and recrystallized from aqueous acetone to give 0.09 g (50%) of IX as colorless scales, melting at 187—189°, resolidifying and finally melting at 193—195°. This was identical with the sample obtained in (i) by the mixed melting point and comparison of the IR spectra.

Reaction of N-(3-Methyl-1-phenyl-5-pyrazolyl)phenylpropiolamide (Ie) with Aqueous NaOH——A stirred mixture of Ie (0.02 g) and 10% NaOH (0.14 ml) in H_2O (5 ml) was heated on a steam bath for 2 hr. After cooling, the solution was acidified with 20% AcOH to recover Ie.

N-(3-Methyl-1-phenyl-5-pyrazolyl)-β-(methylthio)cinnamamide (Xe)——To a cooled solution of IIIe (0.25 g) in dry benzene (30 ml) was added NaH (0.04 g) in mineral oil (content 50%) with stirring under N_2 atmosphere. After stirring at room temperature for 1 hr, methyl iodide (0.07 ml) was added to the mixture, which was heated at 65—70°. After 1 hr, an additional 0.07 ml of methyl iodide was added and stirring was continued for 2 hr. The precipitated NaI was filtered off and the filtrate was washed with 5% NaOH and H_2O. Evaporation of the dried benzene solution gave an oil, which was chromatographed on silica gel using $CHCl_3$ as eluent. The eluate was recrystallized from $CHCl_3$–*n*-hexane to afford 0.07 g (19%) of Xe. An analytical sample was recrystallized from acetone–*n*-hexane as colorless prisms, mp 155—157°. *Anal.* Calcd. for $C_{20}H_{19}ON_3S$: C, 68.75; H, 5.48; N, 12.03; S, 9.16. Found: C, 68.84; H, 5.49; N, 11.77; S, 8.92.

Reaction of N-(3-Methyl-1-phenyl-5-pyrazolyl)-β-(methylthio)cinnamamide (Xe) with Aqueous NaOH——To a stirred suspension of Xe (0.035 g) in H_2O (5 ml) was added 10% NaOH (0.5 ml) and minimum amount of EtOH which was needed for dissolving Xe. The solution was refluxed for 3 hr and acidified with 20% AcOH after cooling. The precipitate was collected and recrystallized from aqueous acetone to yield the starting material (Xe).

N-(2-Thiazolyl)-β-(methylthio)cinnamamide (Xf)——IIIf (0.20 g) in dry benzene (40 ml) was methylated with methyl iodide in the same manner as described for Xe. Evaporation of the dried benzene solution gave a crystalline solid, which was recrystallized from benzne–*n*-hexane to yield 0.07 g (33%) of Xf, colorless needles, mp 204—207°. *Anal.* Calcd. for $C_{13}H_{12}ON_2S_2$: C, 56.52; H, 4.38; N, 10.14; S, 23.17. Found: C, 56.79; H, 4.31; N, 9.87; S, 23.32.

General Procedure for the Preparation of 2-(Heterocyclic)carbamoyl-1-phenylvinyl Disulfide (XI, Table VII)——To a stirred solution of III (2.9 mmole) and 10% $NaHCO_3$ (2.4 ml) in EtOH (20 ml) was added dropwise an ethanolic solution of iodine (0.40 g). After the addition, stirring was continued for 30 min.

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After excess iodine was decomposed by the careful addition of dilute aqueous $Na_2S_2O_3$, the reaction mixture was neutralized with 5% $NaHCO_3$, diluted with H_2O (100 ml) and extracted with $CHCl_3$. Evaporation of the dried extract afforded a crystalline solid, which was recrystallized from an appropriate solvent to yield XI.

Table VII. 2-(Heterocyclic)carbamoyl-1-phenylvinyl Disulfide $\left(\text{Ph-}\underset{\text{S-}}{\text{C}}\text{=CHCONHR}\right)_2$

Compd.	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
XIc	121—123[a]	70.4	needles	$C_{28}H_{26}O_4N_4S_2$	61.53	4.80	10.25	11.71	61.81	4.44	10.09	11.96
XId	200—201[b] (decomp.)	85.6	needles	$C_{28}H_{26}O_4N_4S_2$	61.53	4.80	10.25	11.71	61.43	4.85	10.05	11.72
XIe	138—140[c]	50.0	needles	$C_{38}H_{32}O_2N_6S_2$	68.25	4.82	12.57	9.57	68.48	4.57	12.69	9.82
XIf	138—141[c]	79.2	needles	$C_{24}H_{18}O_2N_4S_4$	55.17	3.47	10.73	24.50	55.38	3.18	10.44	24.65
XIg	179—180[d]	73.5	needles	$C_{26}H_{22}O_2N_4S_4$	56.73	4.03	10.18	23.26	56.78	3.71	9.89	23.03

recryst. solvt.
a) ether–hexane, *b*) EtOH, *c*) aq. acetone, *d*) benzene–hexane

N-(3,5-Dimethyl-4-isoxazolyl)-β-(butyldithio)cinnamamide (XIIc)——The Bunte salt was prepared in the usual way.[11] To a solution of $Na_2S_2O_3 \cdot 5H_2O$ (1.50 g) in H_2O (4.5 ml) was added *n*-butyl bromide (0.83 g) in EtOH (4.5 ml). The mixture was refluxed on a steam bath for 1 hr and distilled to remove EtOH. To the resulting Bunte salt solution was added dropwise an aqueous solution of the sodium salt of N-(3,5-dimethyl-4-isoxazolyl)-β-mercaptocinnamamide (IIIc) (1.08 g). The mixture was stirred at room temperature for 10 hr. The precipitate was collected and recrystallized from benzene–*n*-hexane to afford 0.32 g (24.2%) of XIIc, colorless needles, mp 157—158°. *Anal.* Calcd. for $C_{18}H_{22}O_2N_2S_2$: C, 59.66; H, 6.12; N, 7.73; S, 17.66. Found: C, 60.17; H, 6.15; N, 7.28; S, 17.61.

N-(3,4-Dimethyl-5-isoxazolyl)-β-(butyldithio)cinnamamide (XIId)——N-(3,4-Dimethyl-5-isoxazolyl)-β-mercaptocinnamide (IIId) (1.08 g) was converted to XIId in the same manner as described for XIIc. Recrystallization from aqueous acetone afforded 0.61 g (46.2%) of XIId, colorless needles, mp 148—150°. *Anal.* Calcd. for $C_{18}H_{22}O_2N_2S_2$: C, 59.66; H, 6.12; N, 7.73; S, 17.66. Found: C, 59.46; H, 6.13; N, 7.54; S, 17.51.

N-(3,5-Dimethyl-4-isoxazolyl)-β-(ethoxycarbonylthio)cinnamamide (XIIIc)——To a stirred aqueous solution (7 ml) of IIIc (0.20 g) and 10% NaOH (0.29 ml) at 0° was added dropwise ethyl chloroformate (0.14 ml). The mixture was stirred at the same temperature for 2 hr and extracted with benzene. Evaporation of the dried extract under reduced pressure gave a crystalline solid, which was recrystallized from benzene–*n*-hexane to afford 0.14 g (55.5%) of XIIIc, colorless needles, mp 144—145° (decomp.). *Anal.* Calcd. for $C_{17}H_{18}O_4N_2S$: C, 58.95; H, 5.24; N, 8.09; S, 9.24. Found: C, 59.25; H, 5.23; N, 8.16; S, 9.43. IR ν_{max} cm^{-1}: 1724, 1698 (C=O).

N-(3,4-Dimethyl-5-isoxazoyl)-β-(ethoxycarbonylthio)cinnamamide (XIIId)——The reaction of IIId (0.7 g) with ethyl chloroformate (0.49 ml) was carried out in the same manner as described for XIIIc. After stirring at 0° for 2 hr, the precipitate was collected, washed with H_2O and recrystallized from aqueous acetone to give 0.60 g (80%) of XIIId as colorless prisms, mp 133—135°. *Anal.* Calcd. for $C_{17}H_{18}O_4N_2S$: C, 58.95; H, 5.24; N, 8.09; S, 9.24. Found: C, 59.17; H, 5.23; N, 7.96; S, 9.33. IR ν_{max} cm^{-1}: 1735, 1685 (C=O).

N-(2-Thiazolyl)-β-(ethoxycarbonylthio)cinnamamide (XIIIf)——i) The reaction of IIIf (0.20 g) with ethyl chloroformate (0.088 ml) was carried out in the same manner as described for XIIIc. After stirring at 0° for 2.5 hr, the reaction mixture was extracted with ether and evaporation of the dried extract gave an oil. This oily residue was taken up in MeOH and the solution was concentrated to dryness to give a crystalline solid, which was recrystallized from benzene–*n*-hexane to afford 0.02 g (15%) of XVII as colorless needles, mp 156—157°. *Anal.* Calcd. for $C_6H_8O_2N_2S$: C, 41.86; H, 4.68; N, 16.28; S, 18.59. Found: C, 41.55; H, 4.80; N, 16.01; S, 18.63. XVII was shown to be identical with the sample prepared according to the literature[12] by the mixed melting point and comparison of the IR spectra.

ii) A mixture of IIIf (1.00 g) and ethyl chlroformate (6 ml) was stirred at room temperature for 9 hr and *n*-hexane (30 ml) was added to the reaction mixture. The precipitate was collected, washed with *n*-

11) H.E. Westlake, Jr. and G. Dougherty, *J. Am. Chem. Soc.*, **63**, 658 (1941).
12) H.M. Curry and J.P. Mason, *J. Am. Chem. Soc.*, 73, 5043 (1951).

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hexane and cold H_2O and taken up in acetone. The solution was concentrated to 10 ml under reduced pressure at room temperature to give 1.00 g of colorless crystals, mp 93—98°. *Anal.* Calcd. for $C_{15}H_{14}O_3N_2S_2$ (XIIIf): C, 53.89; H, 4.22; N, 8.38; S, 19.14. Found: C, 47.13; H, 4.30; N, 7.28; S, 17.08. IR ν_{max} cm^{-1}: 1730, 1685 (C=O). To a suspension of this crystalline solid in H_2O was added dropwise 5% $NaHCO_3$ on cooling. As 5% $NaHCO_3$ was added to the mixture, the crystalline solid disappeared and an oily layer was separated. After neutralization was complete, the mixture was extracted with $CHCl_3$. Evaporation of the dried extract under reduced pressure gave an oil, which crystallized from MeOH–*n*-hexane. Recrystallization from $CHCl_3$–*n*-hexane afforded 0.31 g (47.2%) of XVII as colorless needles, mp 156—157°.

N-(4-Methyl-2-thiazolyl)-β-(ethoxycarbonylthio)cinnamamide (XIIIg)——The reaction of IIIg (0.05 g) with ethyl chloroformate (0.035 ml) was carried out in the same manner as described for XIIIc. After stirring at 0° for 1.5 hr, the precipitate (0.055 g) was collected and washed with cold H_2O, mp 55—90°. *Anal.* Calcd. for $C_{16}H_{16}O_3N_2S_2$ (XIIIg): C, 55.17; H, 4.63; N, 8.04; S, 18.38. Found: C, 55.60; H, 4.46; N, 8.32; S, 18.92. IR ν_{max} cm^{-1}: 1730, 1690 (C=O). An attempt to recrystallize this crystalline solid from benzene–*n*-hexane was unsuccessful. Evaporation of the benzene solution under reduced pressure gave an oil, from which a crystalline solid was separated after one day and recrystallized from aqueous acetone to give 0.01 g of XVI as colorless needles, mp 97—99°. XVI was shown to be identical with the sample prepared according to the literature[13] by the mixed melting point and comparison of the IR spectra.

N-(3,5-Dimethyl-4-isoxazolyl)-β-(benzoylthio)cinnamamide (XIVc)——To an aqueous solution (5 ml) of IIIc (0.20 g) and 10% NaOH (0.29 ml) at 0° was added dropwise benzoyl chloride (0.17 ml) with stirring. The mixture was stirred at the same temperature for 2 hr and the precipitate was collected and recrystallized from ether to give 0.07 g (25%) of XIVc, colorless needles, mp 129—131°. *Anal.* Calcd. for $C_{21}H_{18}O_3N_2S$: C, 66.66; H, 4.80; N, 7.40; S, 8.46. Found: C, 66.71; H, 4.80; N, 7.34; S, 8.67.

N-(3,4-Dimethyl-5-isoxazolyl)-β-(benzoylthio)cinnamamide (XIVd)——The reaction of IIId (0.70 g) with benzoyl chloride (0.5 ml) was carried out in the same manner as described for XIVc. After stirring at 0° for 2 hr, the reaction mixture was extracted with $CHCl_3$. Evaporation of the dried extract under reduced pressure afforded 0.84 g (87%) of XIVd. Recrystallization from aqueous acetone gave colorless needles, mp 137—139° (decomp.). *Anal.* Calcd. for $C_{21}H_{18}O_3N_2S$: C, 66.66; H, 4.80; N, 7.40; S, 8.46. Found: C, 66.44; H, 4.59; N, 7.18; S, 8.70.

N-(2-Thiazolyl)-β-(benzoylthio)cinnamamide (XIVf)——The reaction of IIIf (0.30 g) with benzoyl chloride (0.20 ml) was carried out in the same manner as described for XIVc. Recrystallization from $CHCl_3$–*n*-hexane gave 0.30 g (72%) of XIVf, slightly yellow needles, mp 142—144° (decomp.). *Anal.* Calcd. for $C_{19}H_{14}O_2N_2S_2$: C, 62.29; H, 3.85; N, 7.65; S, 17.47. Found: C, 62.43; H, 3.90; N, 7.54; S, 17.52.

N-(4-Methyl-2-thiazolyl)-β-(benzoylthio)cinnamamide (XIVg)——The reaction of IIIg (0.30 g) with benzoyl chloride (0.20 ml) was carried out in the same manner as described for XIVc. Recrystallization from acetone–*n*-hexane yielded slightly yellow needles (XIVg), mp 134—135° (decomp.). *Anal.* Calcd. for $C_{20}H_{16}O_2N_2S_2$: C, 63.15; H, 4.24; N, 7.37; S, 16.83. Found: C, 63.09; H, 4.32; N, 7.09; S, 16.60.

Treatment of XIVg with Boiling Acetone——A solution of XIVg (0.25 g) in acetone (20 ml) was refluxed for 1 hr and concentrated under reduced pressure to give a crystalline solid, which was recrystallized from acetone to afford colorless needles (XVIII), mp 112—114° (decomp.). *Anal.* Calcd. for $C_{20}H_{16}O_2N_2S_2 \cdot H_2O$ (XVIII): C, 60.30; H, 4.55; N, 7.03; S, 16.07. Found: C, 60.50; H, 4.75; N, 6.73; S, 15.90.

A methanolic solution of XVIII was allowed to reflux for 3 hr and evaporated to dryness under reduced pressure to give an oil which crystallized from EtOH. Recrystallization from acetone–*n*-hexane gave XIX as colorless prisms, mp 151—152°. XIX was shown to be identical with the sample prepared according to the literature[14] by the mixed melting point and comparison of the IR spectra.

Bis[N-(2-thiazolyl)-β-mercaptocinnamamidato]zincum (II) (XVf)——To a stirred solution of IIIf (0.40 g) in EtOH (40 ml) was added an aqueous solution (20 ml) of $Zn(OAc)_2 \cdot 2H_2O$ (0.50 g). Immediately after the addition a yellow crystalline solid was precipitated. After stirring at room temperature for 2 hr, the reaction mixture was diluted with H_2O (10 ml). The precipitate was collected and recrystallized from DMF-H_2O to give 0.46 g (a quantitative yield) of XVf as yellow powder, mp 265—266° (decomp.). *Anal.* Calcd. for $C_{24}H_{18}O_2N_4S_4Zn$: C, 49.02; H, 3.09; N, 9.53; S, 21.81; Zn, 11.12. Found: C, 48.82; H, 3.32; N, 9.55; S, 21.50; Zn, 10.87. IR ν_{max} cm^{-1}: 1610 (C=O).

Bis[N-(4-methyl-2-thiazolyl)-β-mercaptocinnamamidato]zincum (II) (XVg)——The reaction was carried out in the same manner as described for XVf. Recrystallization from DMF–EtOH gave an almost quantitative yield of yellow powder (XVg), mp 248—249° (decomp.). *Anal.* Calcd. for $C_{26}H_{22}O_2N_4S_4Zn$: C, 50.68; H, 3.60; N, 9.09; S, 20.82; Zn, 10.61. Found: C, 50.52; H, 3.82; N, 8,81; S, 21.11; Zn, 10.63. IR ν_{max} cm^{-1}: 1604 (C=O).

N-Methyl-N-(2-thiazolyl)phenylpropiolamide (XX)——A mixture of If (2.48 g) and 10% methanolic KOH (6.7 ml) in EtOH (20 ml) was refluxed on a steam bath for 30 min and concentrated to 10 ml. After cooling, 2.84 g (98.0%) of the potassium salt of If was obtained as a precipitate. A mixture of this potas-

13) K. Takatori and S. Asano, *Yakugaku Zasshi*, **80**, 789 (1960).
14) M. Ohta, *Yakugaku Zasshi*, **71**, 1428 (1951).

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sium salt (2.84 g) and methyl iodide (30 ml) was refluxed with stirring for 3 hr. After removing KI, the filtrate was concentrated to give a crystalline solid, which was recrystallized from ligroin to yield 1.73 g (66.7%) of XX, colorless needles, mp 120—121°. *Anal.* Calcd. for $C_{13}H_{10}ON_2S$: C, 64.46; H, 4.16; N, 11.57; S, 13.21. Found: C, 64.48; H, 4.13; N, 11.32; S, 13.22. IR ν_{max} cm^{-1}: 2230, 1630. UV λ_{max}^{EtOH} mμ (log ε): 236 (3.91), 247.5 (3.93), 261 (4.00), 271 (4.03), 304 (4.18). NMR (in $CDCl_3$) δ: 3.97 (3H, singlet, NCH_3).

S-[2-(Methyl-2-thiazolyl)carbamoyl-1-phenylvinyl]isothiourea *p*-Toluenesulfonate (XXI)——A mixture of XX (0.50 g), thiourea (0.16 g) and *p*-toluenesulfonic acid (0.43 g) in absolute EtOH (20 ml) was refluxed on a steam bath for 1 hr. After cooling, the precipitate was collected and recrystallized from EtOH to give 0.69 g (68%) of XXI, slightly greenish needles, mp 179—180° (decomp.). *Anal.* Calcd. for $C_{21}H_{22}O_4N_4S_3$: C, 51.43; H, 4.52; N, 11.43; S, 19.58. Found: C, 51.59; H, 4.60; N, 10.97; S, 19.82.

N-Methyl-N-(2-thiazolyl)-*β*-mercaptocinnamamide (XXII)——The reaction of XXI (0.24 g) with NaOH was carried out in the same manner as described for III. After stirring at room temperature for 1 hr, the solution was neutralized with 20% AcOH to give a gum, which was extracted with $CHCl_3$. Evaporation of the dried extract under reduced pressure afforded an oil, which crystallized from aqueous EtOH to yield 0.13 g (93%) of XXII, greenish needles, mp 104—105°. *Anal.* Calcd. for $C_{13}H_{12}ON_2S_2$: C, 56.52; H, 4.38; N, 10.14; S, 23.17. Found: C, 56.29; H, 4.31; N, 10.01; S, 22.93.

Bis[N-methyl-N-(2-thiazolyl)-*β*-mercaptocinnamamidato]zincum (II) (XXIII)——The reaction was carried out in the same manner as described for XVf. Recrystallization from DMF–EtOH–H_2O gave an almost quantitative yield of XXIII, yellow scales, mp 224—226°. *Anal.* Calcd. for $C_{26}H_{22}O_2N_4S_4Zn$: C, 50.68; H, 3.60; N, 9.09; S, 20.82; Zn, 10.61. Found: C, 50.83; H, 3.69; N, 9.34; S, 21.00; Zn, 10.68. IR ν_{max} cm^{-1}: 1575 (sh), 1560.

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