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98. Akira Yokoyama, Kazuo Ashida, and Hisashi Tanaka: Studies on the Sulfur-containing Chelating Agents. XIV.[*1] Syntheses of β-Mercaptocinnamamides and their Structures.

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According to the conclusions described in Part XII,[1] concerning the relationship between the chelating abilities and the structures in various types of carbonyl compounds which have a mercapto group at β-position, β-mercaptocinnamamides were expected to be considerably strong chelating agents as well as the esters of β-mercaptothiocinnamic acid.[*1] This paper deals with the syntheses and the structures of β-mercaptocinnamamides. The investigations on their applicabilities as analytical reagents and also on their antimicrobial activities are to be conducted later, in connection with their chelating abilities.

As an attempt to obtain β-mercaptocinnamamides from β-mercaptocinnamic acid[2] or its disulfide[2] through acid chloride was failed, a procedure by the addition of thiourea to phenylpropiolamides was chosen for the purpose. As for the preparations of phenylpropiolamides, Brown[3] reported that ethylamide (Ia) and anilide (Ie) were obtained from

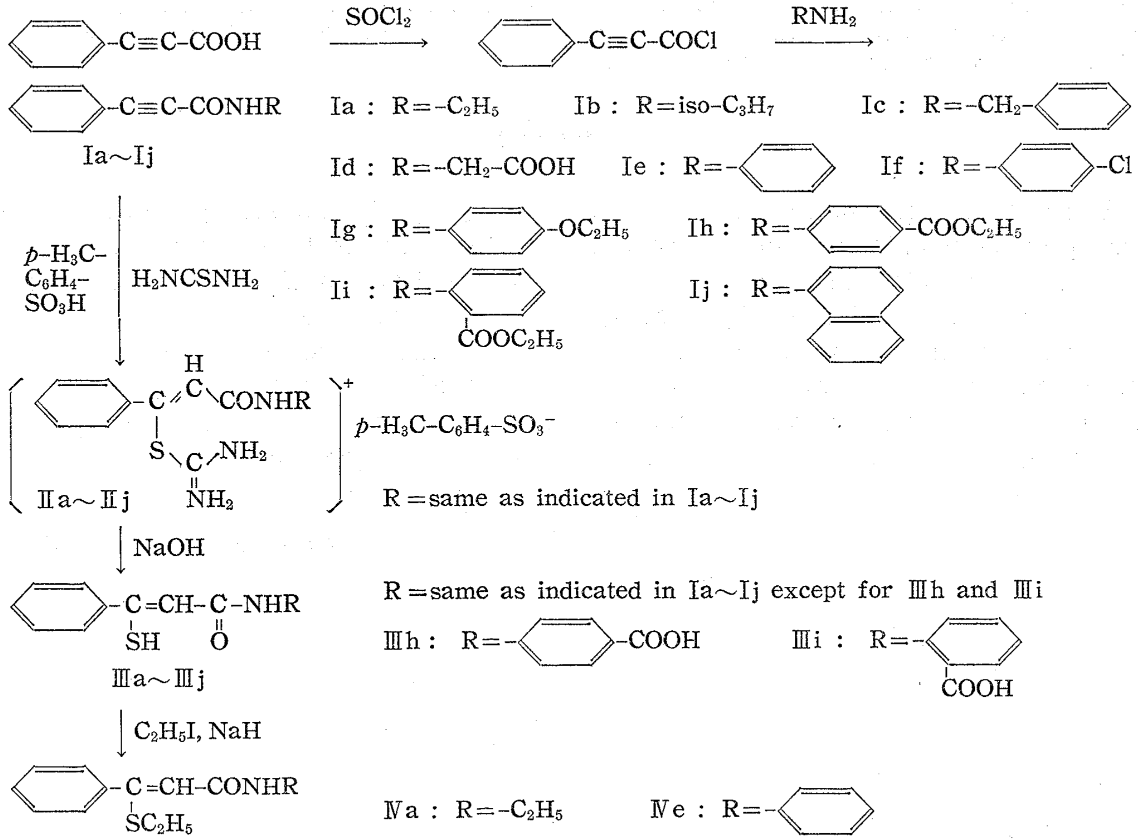

Chart 1.

[*1] Part XIII. A. Yokoyama, H. Tanaka: This Bulletin, 12, 683 (1964).

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[1] H. Tanaka, A. Yokoyama: This Bulletin, 10, 1133 (1962).

[2] E. Fischer, W. Brieger: Ber., 47, 2469 (1914); Z. Reyes, R. M. Silverstein: J. Am. Chem. Soc., 80, 6367 (1958).

[3] J. V. Brown, H. Ostermeyer: Ber., 70B, 1002 (1937).

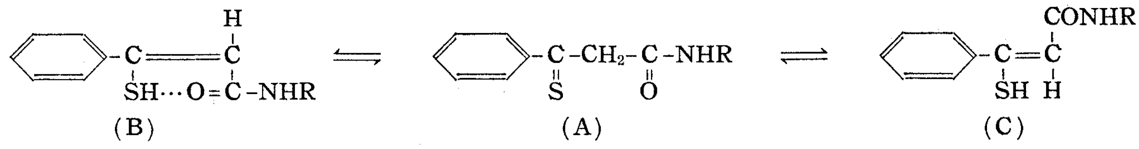

Chart 2.

phenylpropiolic acid through phenylpropioloyl chloride. The preparations of phenylpropiolamides (Ia～Ij) were carried out by the procedure a little modified from Brown's method.[3] The purifications of Ia～Ij were rather difficult and Id could not be purified completely. The additions of thiourea to Ia～Ij were carried out as described in Part XⅢ*[1] and the corresponding isothiuronium salts (Ⅱa～Ⅱj) were obtained with good yield. β-Mercaptocinnamamides (Ⅲa～Ⅲj), except Ⅲc were obtained by hydrolyses of Ⅱa～Ⅱj. A yellowish green solid considered to be Ⅲc, judging from its properties as described in experimental part, was obtained but its purification was not successful. In the procedure of hydrolysis, ester moieties of Ⅱh and Ⅱi were hydrolyzed at the same time and the corresponding carboxylic acids were obtained. The carboxylic acids (Ⅲd, Ⅲh, Ⅲi) were prepared for the purpose of obtaining hydrophylic chelate compounds.

It was found that alkylamides (Ⅲa～Ⅲd) and arylamides (Ⅲe～Ⅲj) showed different properties in the following points. These amides (Ⅲa～Ⅲj) showed the reversible color change (yellowish green～purple) on heating, with or without solvent, as observed in esters of β-mercaptothiocinnamic acid reported in Part XⅢ.*[1] This color change was observed more remarkably even in lower temperature in the cases of alkylamides than in the cases of arylamides. Alkylamides did not crystallize easily even though they were completely pure, while arylamides crystallized easily. The metals which showed color reactions, probably by the chelate-formations, with these ligands were iron, copper, nickel, cobalt, zinc, lead, bismuth, silver, cadmium, platinum, gold, mercury, and uranium. However, as seen in Table V in experimental part, some of the metals reacted with arylamides but not with alkylamides. In the cases of alkylamides, generally the reactions proceeded more slowly, and the yields of metal-chelates were poorer, compared with the cases of arylamides.

In these amides (Ⅲa～Ⅲj), thioxo-thioenol tautomerism shown in Chart 2 should be considered in connection with their structures and their chelating abilities, as well as in the cases of esters of β-mercaptothiocinnamic acid reported in Part XⅢ.*[1] In addition, above-mentioned differences in the chemical properties between alkylamides and arylamides are probably due to the differences of equilibria in the tautomerism. From this point of view, the structures of these amides were investigated by infrared and nuclear magnetic resonance spectroscopy.

The infrared spectra of Ⅲa and Ⅲe are shown in Figs. 1 and 2 as the examples of alkylamides and arylamides respectively. Figs. 3 and 4 represent the infrared spectra of the related compounds of Ⅲa and Ⅲe, namely N-ethyl-β-(ethylthio)cinnamamide (Ⅳa)

Table I. Frequencies of ν_{SH}, $\nu_{C=O}$ and $\nu_{C=C}$ (cm^{-1}) in Chloroform

Compd.	ν_{SH}	$\nu_{C=O}$	$\nu_{C=C}$
Ⅲa	2400	1620 1660[a)]	1568
Ⅲe	2400	1630 1685[a)]	1560
Ⅳa		1631	1570
Ⅳe		1650	1562

a) observed as a shoulder.

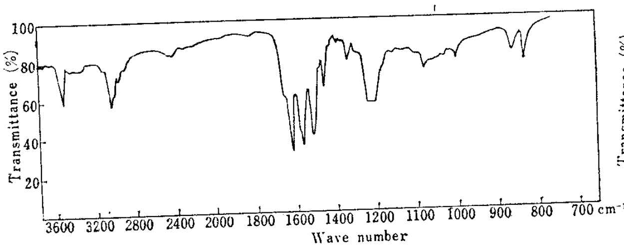

Fig. 1. Infrared Spectrum of N-Ethyl-β-mercaptocinnamamide (Ⅲa) (in $CHCl_3$)

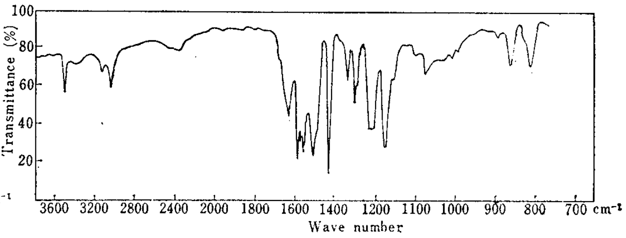

Fig. 2. Infrared Spectrum of N-Phenyl-β-mercaptocinnamamide (Ⅲe) (in $CHCl_3$)

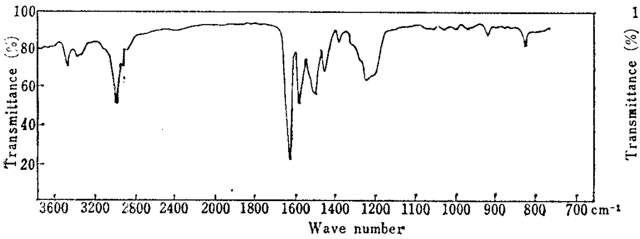

Fig. 3. Infrared Spectrum of N-Ethyl-β-(ethylthio)cinnamamide (Ⅳa) (in $CHCl_3$)

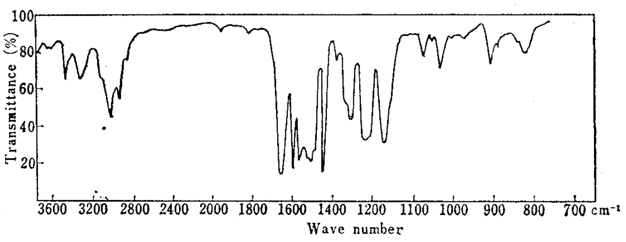

Fig. 4. Infrared Spectrum of N-Phenyl-β-(ethylthio)cinnamamide (Ⅳe) (in $CHCl_3$)

and N-phenyl-β-(ethylthio)cinnamamide (Ⅳe) prepared for the purpose of making comparison, by the procedure shown in Chart 1. As seen in Figs. 1, 2, 3, and 4 and Table I, the stretching bands of SH and C=O were observed in the region of considerably lower frequencies than in the ordinary cases.[4] This fact shows that the mercapto groups and the carbonyl groups are markedly hydrogen-bonded in these amides (Ⅲa～Ⅲj). In other words, the contribution of *cis*-thioenol form (B) is predominant. However, in these amides (Ⅲa～Ⅲj), shoulders which are considered to be based on the carbonyl groups in thioxo form (A) or *trans*-thioenol form (C), were also observed at a little higher frequencies than those where hydrogen-bonded C=O stretching bands were observed. In arylamides an empirical rule concerning the stretching bands of C=C and C=O in *cis-trans* configuration of α,β-unsaturated carbonyl compounds[5] is applicable as the *cis*-thioenol form (B), as in the cases of esters of β-mercaptothiocinnamic acid.[*1] Namely, the intensities of the stretching bands of C=C were always higher than those of the stretching bands of C=O. While, in alkylamides, this relation between the stretching bands of C=C and C=O was not observed clearly.

The nuclear magnetic resonance spectra of Ⅲa, Ⅲe, Ⅳa, and Ⅳe are shown in Figs. 5, 6, 7, and 8. As seen in Figs. 5 and 6, signals from mercapto groups are seen in considerably lower field as observed in ethyl β-mercaptothiocinnamate,[*1] than in the ordinary cases.[6] This fact also shows the presence of hydrogen bond between the mercapto and the carbonyl groups, and in other words, *cis*-thioenol form (B) is supported. However, in Ⅲa, the intensities of the signals from the mercapto proton and olefinic proton were found to be a little lower than in Ⅲe. Summarizing above-mentioned discussions, *cis*-thioenol form (B) is predominant, and the double bond character of the carbonyl group considerably decreases, but in alkylamides the contribution of thioxo form (A) or *trans*-thioenol form (C) should be taken into consideration to more extent than in arylamides. These differences might be attributed to the mesomeric

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4) K. J. Bellamy: "The Infrared Spectra of Complex Molecules" 351 (1958). John Wiley & Sons, Inc., New York.

5) R. Hirschman: J. Am. Chem. Soc., **76**, 4013 (1954); O. Winterstein, M. Moore: *Ibid.*, **78**, 6193 (1956).

6) N. F. Chambsrlain: Anal. Chem., **31**, 56 (1959).

effect of the nitrogen atom, which has the tendency to make conjugate system from the benzene ring to the nitrogen atom in arylamides, and hence thioenol form could be taken more easily in arylamides than in alkylamides. In alkylamides and arylamides, the differences in the tautomerism are considered to be corresponding to that seen in the chemical properties, but further investigation would be necessary in this point. Being important in connection with the chelating abilities of these ligands, the above-mentioned tautomerism will be investigated later also with ultraviolet spectroscopy.

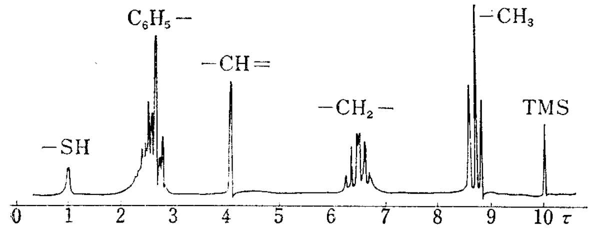

Fig. 5. Nuclear Magnetic Resonance Spectrum of N-Ethyl-β-mercaptocinnamamide (Ⅲa)[*3]

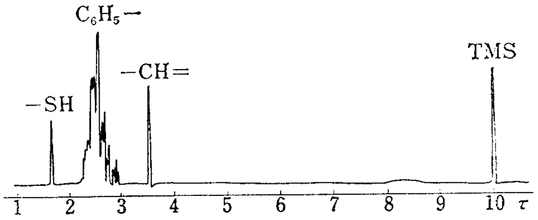

Fig. 6. Nuclear Magnetic Resonance Spectrum of N-Phenyl-β-mercaptocinnamamide (Ⅲe)[*3]

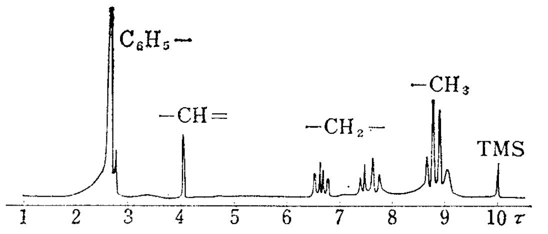

Fig. 7. Nuclear Magnetic Resonance Spectrum of N-Ethyl-β-(ethylthio)cinnamamide (Ⅳa)[*3]

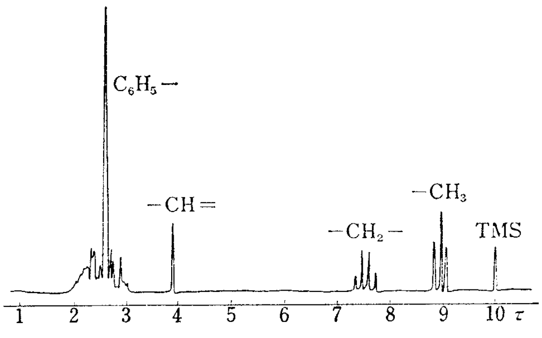

Fig. 8. Nuclear Magnetic Resonance Spectrum of N-Phenyl-β-(ethylthio)cinnamamide (Ⅳe)[*3]

Experimental[*4]

N-Alkyl(or Aryl)propiolamide (Ia~Ij)——A mixture of 0.1 mole of phenylpropiolic acid and 0.12 mole of freshly distilled $SOCl_2$ in 50 ml. of dry benzene was warmed at 60~70° with stirring for 3 hr. and evaporated under reduced pressure. To the residue, 50 ml. of dry benzene was added. To this solution of phenylpropioloyl chloride, 0.2 mole of alkyl- or arylamine in 50 ml. of dry benzene was added dropwise with stirring under ice-cooling and stirring was continued for 1 hr. The reaction mixture was poured into cold H_2O. The benzene layer was separated, washed with 5% HCl, H_2O, 5% Na_2CO_3, and H_2O successively, and dried over Na_2SO_4. After evaporating the solvent, the residual crude crystal of Ia~Ij was collected and recrystallized from the proper solvent to give pale yellow needles. Yield, 60~70%. IR: $\nu_{C\equiv C}$ 2195~2200 cm^{-1} (Nujol). The compounds synthesized are listed in Table Ⅱ.

S-[1-Phenyl-2-(alkyl- or aryl-carbamoyl)vinyl]isothiuronium *p*-Toluenesulfonate (IIa~IIj)——A mixture of 0.05 mole of Ia~Ij, equimolecular thiourea and *p*-toluenesulfonic acid in 100 ml. of EtOH was refluxed for 3 hr. and evaporated to almost half volume. After cooling, Et_2O was added and crystals of Ⅱa~Ⅱj separated out were collected and recrystallized from EtOH-Et_2O to give colorless needles. Yield, 90~95%. The compounds synthesized are listed in Table Ⅲ.

N-Alkyl(or Aryl)-β-mercaptocinnamamide (IIIa~IIIj)——i) Ⅲa~Ⅲg, Ⅲj: A mixture of 0.01 mole of Ⅱa~Ⅱg, Ⅱj and 0.02 mole of NaOH in 100 ml. of 50% EtOH was refluxed for 2 hr. After cooling, the reaction mixture was poured into 100 ml. of H_2O and extracted with Et_2O. Aqueous phase was separated and acidified with conc. HCl under ice-cooling. In the cases of Ⅲa, Ⅲd~Ⅲg, Ⅲj, the precipitate separated out was collected and recrystallized from proper solvent to give yellow~yellowish green needles. Yield, 50~60%. In the case of Ⅲb, the precipitate separated out was dissolved in 5%

[*3] The NMR spectra were measured with a Varian A-60 Spectrometer at 60 Mc.p.s., in $CDCl_3$, using tetramethylsilane as an internal reference.

[*4] All melting points are uncorrected.

Table II. N-Alkyl(or Aryl)phenylpropiolamide

Compd.	m.p. (°C)	Recryst. solvent	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	N	C	H	N
Ia[a]	63	CCl_4							
Ib	81	$CHCl_3$-petr. ether	$C_{12}H_{13}ON$	76.97	7.00	7.48	76.83	7.10	7.62
Ic	112	$CHCl_3$-petr. ether	$C_{16}H_{13}ON$	81.68	5.57	5.95	81.42	5.49	5.83
Id[b]									
Ie[a]	128	CCl_4							
If	186	EtOH	$C_{15}H_{10}ONCl$	70.45	3.94	5.62	70.26	4.18	5.48
Ig	138	〃	$C_{17}H_{15}O_2N$	76.96	5.70	5.62	76.83	5.96	5.21
Ih	100	70% EtOH	$C_{18}H_{15}O_3N\cdot\frac{1}{2}H_2O$	71.53	5.33	4.63	71.72	5.35	4.68
Ii	113	EtOH	$C_{18}H_{15}O_3N$	73.70	5.15	4.78	73.60	5.06	4.50
Ij	164	50% EtOH	$C_{19}H_{13}ON$	84.11	4.83	5.16	83.91	4.87	5.31

a) The melting points of these compounds were identical with those reported by Brown.[8]
b) This compound was used without purification in next procedure.

Table III. S-[1-Phenyl-2-(alkyl- or aryl-carbamoyl)vinyl]-isothiuronium p-Toluenesulfonate

Compd.	m.p. (decomp.) (°C)	Formula	Analysis (%)					
			Calcd.			Found		
			C	H	N	C	H	N
IIa	193	$C_{19}H_{23}O_4N_3S_2$	54.15	5.50	9.97	54.31	5.43	9.01
IIb	212~213	$C_{20}H_{25}O_4N_3S_2$	55.17	5.79	9.65	55.38	5.79	9.74
IIc	197~198	$C_{24}H_{25}O_4N_3S_2$	59.62	5.21	8.69	59.99	5.46	8.61
IId[a]	186~192							
IIe	204~205	$C_{23}H_{23}O_4N_3S_2$	58.84	4.94	8.95	58.61	4.87	8.98
IIf	202	$C_{23}H_{22}O_4N_3ClS_2$	54.81	4.39	8.34	54.91	4.44	7.83
IIg	198	$C_{25}H_{27}O_5N_3S_2$	58.47	5.30	8.18	58.12	5.43	8.12
IIh	197~198	$C_{26}H_{27}O_6N_3S_2$	57.67	5.03	7.76	57.61	5.22	7.54
IIi	189~190	$C_{26}H_{27}O_6N_3S_2$	57.67	5.03	7.76	57.58	5.13	7.65
IIj	222	$C_{27}H_{25}O_4N_3S_2$	62.42	4.85	8.09	62.15	4.95	8.02

a) This compound was used without purification in next procedure.

Table IV. N-Alkyl(or Aryl)-β-mercaptocinnamamide

Compd.	m.p. (°C)	Recryst. solvent	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	N	C	H	N
IIIa	136~137	EtOH	$C_{11}H_{13}ONS$	63.75	6.32	6.76	63.49	6.61	6.95
IIIb[a]			$C_{12}H_{15}ONS$	65.14	6.83	6.33	65.25	6.80	5.97
IIId	124~125	$CHCl_3$	$C_{11}H_{11}O_3NS$	55.69	4.67	5.91	54.97	4.69	5.73
IIIe	107~108	50% EtOH	$C_{15}H_{13}ONS$	70.58	5.13	5.49	70.31	5.28	5.48
IIIf	119~120	EtOH	$C_{15}H_{12}ONClS$	62.17	4.17	4.83	62.27	4.38	4.61
IIIg	113	〃	$C_{17}H_{17}O_2NS$	68.21	5.73	4.68	67.92	5.87	4.63
IIIh	190	80% EtOH	$C_{16}H_{13}O_3NS\cdot H_2O$	60.56	4.77	4.41	60.73	4.79	4.60
IIIi	156~157	EtOH	$C_{16}H_{13}O_3NS$	64.21	4.38	4.68	64.05	4.50	4.38
IIIj	146~147	70% EtOH	$C_{19}H_{15}ONS$	74.74	4.95	4.56	74.46	5.19	4.35

a) This compound did not crystallize.

NaOH and reprecipitated with 5% HCl and reprecipitation was repeated to give yellowish purple viscous solid. Yield, 45%. In the case of Ⅲc, yellowish purple precipitate was obtained which was positive to Rheinboldt test[7] and showed similar colorations with metal ions to those of other ligands. This substance was considered to be Ⅲc, but its purification was unsuccessful.

ii) Ⅲh, Ⅲi : A mixture of 0.01 mole of Ⅱh, Ⅱi and 0.03 mole of NaOH in 50% EtOH was treated as described above, and the precipitate separated out was collected and recrystallized from proper solvent to give yellow needles. Yield, 55∼60%. The compounds synthesized are listed in Table Ⅳ.

N-Ethyl-β-(ethylthio)cinnamamide (IVa)——To a solution of 0.17 g. of NaH in 10 ml. of dry benzene, a solution of 1g. of Ⅲa in 10 ml. of dry benzene was added dropwise under cooling with H_2O. After the evolution of gas ceased, a solution of 0.8 g. of EtI in 5 ml. of dry benzene was added and the mixture was refluxed for 3 hr., cooled and filtered and the solvent was evaporated. The residual solid of Ⅳa was recrystallized from benzene to give 0.75 g. of colorless needles, m.p. 168°. *Anal.* Calcd. for $C_{13}H_{17}ONS$: C, 66.36; H, 7.28; N, 5.95. Found : C, 66.65; H, 7.52; N, 6.24.

N-Phenyl-β-(ethylthio)cinnamamide (IVe)——To a solution of 0.15 g. of NaH in 10 ml. of dry benzene, a solution of 1 g. of Ⅲe in 10 ml. of dry benzene was added dropwise under cooling with H_2O and a solution of 0.7 g. of EtI in 5 ml. of dry benzene was treated as described above. After the solvent was evaporated, the residual solid of Ⅳe was collected and recrystallized from EtOH to give 0.9 g. of colorless needles, m.p. 84°. *Anal.* Calcd. for $C_{17}H_{17}ONS$: C, 72.06; H, 6.05; N, 4.94. Found : C, 71.36; H, 6.29; N, 4.49.

Reactions of IIIa∼IIIj with Metal Ions——The reactions of Ⅲa∼Ⅲj with metal ions were examined by spot tests. The results are shown in Table V.

TABLE V. Spot Test (in neutral solution)

Ligand Metal	Reaction	
	Ⅲa∼Ⅲd	Ⅲe∼Ⅲj
Fe^{3+}	green ppt.	blue
Cu^{2+}	brown ppt.	brown ppt.
Ni^{2+}	orange ppt.	orange ppt.
Zn^{2+}	pale yellow	
Pb^{2+}	orange ppt.	orange ppt.
Bi^{3+}	yellow ppt.	
Ag^{+}	pale yellow ppt.	pale yellow
Cd^{2+}	yellow ppt.	
Pt^{4+}	pale yellow	
Au^{3+}	yellow ppt.	yellow ppt.
Hg^{2+}	〃	〃
UO_2^{2+}	orange ppt.	

Reagent : 1% EtOH solution.

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Summary

β-Mercaptocinnamamides were prepared as strong chelating agents. Phenylpropioloyl chloride was converted into alkyl- or arylamides, and thiourea was reacted in the presence of *p*-toluenesulfonic acid to obtain corresponding isothiuronium salts. β-Mercaptocinnamamides were obtained by the hydrolyses of the isothiuronium salts. Thioxo-thioenol tautomerism in the β-mercaptocinnamamides was investigated by infrared and nuclear magnetic resonance spectroscopy. It was found that *cis*-thioenol form is predominant in these amides but some differences were observed between alkylamides and arylamides. The arylamides were considered to have stronger chelating abilities than the alkylamides judging from their chemical properties, and this difference would be attributed to the difference in thioxo-thioenol tautomerism.

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7) H. Rheinboldt : Ber., **59**, 1311 (1926).