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97. **Akira Yokoyama and Hisashi Tanaka** : Studies on the Sulfur-containing Chelating Agents. XIII.[*1] Syntheses of Esters of β-Mercaptothiocinnamic Acid and their Structures.

(*Faculty of Pharmaceutical Sciences, Kyoto University*[*2])

In Part XI[1] and XII,[*1] relationships between chelating abilities and chemical structures among various types of ligands involving mercapto and carbonyl groups were reported. Depending upon the conclusions described in Part XII,[*1] esters of β-mercaptothiocinnamic acid are expected to have stronger chelating abilities compared with the ligands listed in Part XI.[1] This paper deals with the syntheses of esters of β-mercaptothiocinnamic acid and their structures. The investigations of their applicabilities as the analytical reagent and also on their antimicrobial activities are to be conducted later, in connection with their chelating abilities.

As the addition of hydrogen sulfide or thiourea to the corresponding acetylenic compound was considered to be the most effective method for the introduction of mercapto group, esters of thiophenylpropiolic acid (Ia~Id) were prepared as the intermediates by the procedure shown in Chart 1. These acetylenic compounds were so unstable against heat, that phenylpropioloyl chloride and Ia~Id were used without purification.

Several reports have been found concerning the addition of thiol to the acetylenic linkage,[2] but not that of hydrogen sulfide. Fischer reported[3] that the addition of thiourea to phenylpropiolic acid afforded its addition compound. As shown in Chart 1, the respective additions of hydrogen sulfide and thiourea to Ia afforded ethyl β-mercaptothiohydrocinnamate (II) and 2-amino-6-phenyl-4H-1,3-thiazin-4-one (IV) and these methods were not effective for the purpose. On hydrolysis of II, β-mercaptohydrocinnamic acid (III) yielded, and III and IV were identified with the authentic samples reported in Part V[4] and Part VIII[5] respectively. On the contrary, when the additions of thiourea to Ia~Id were carried out in the presence of p-toluenesulfonic acid, corresponding isothiuronium salts (Va~Vd) were obtained with good yield. Hydrolyses of these isothiuronium salts, exclusive of Vd, afforded the esters of β-mercaptothiocinnamic acid (VIa~VIc). The purifications of VIa~VIc by distillation were difficult and a crystalline solid (VII) separated out from the distillate, in any case, regardless of the kind of alkyl groups. This substance was very stable against acid and alkali and also against the reduction by zinc and acid. Infrared spectrum of VII is shown in Fig. 1 and frequencies of C=O stretching and C=C stretching bands are given in Table I. The data of the elemental analysis and the measurement of molecular weight, and the observation in infrared spectrum suggested that the structure of VII would be as shown in Chart 1. Further investigation on the structure of VII was not conducted. The purifications of VIa~VIc were carried out through their lead salts. The lead salts of VIa~VIc could be purified by reprecipitation using organic solvents such as chloroform and ethanol. The action of hydrogen sulfide to the lead salts yielded VIa~VIc in pure state. The position of the addition of thiourea was confirmed to be β-position because β-mercaptocinnamic acid

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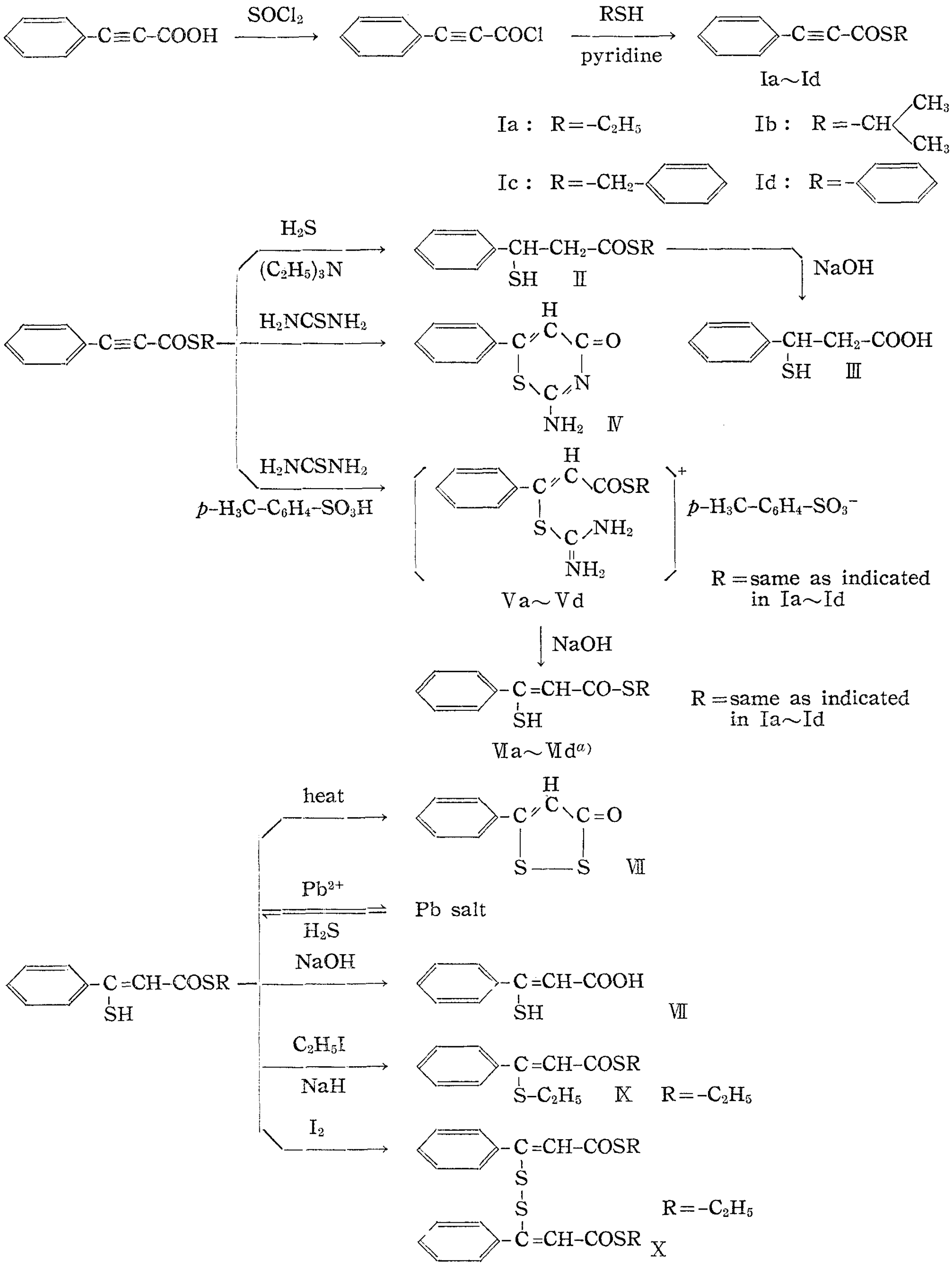
[*1] Part XII. H. Tanaka, A. Yokoyama : This Bulletin, **10**, 1133 (1962).
[*2] Yoshida-konoe-cho, Sakyo-ku, Kyoto (横山 陽, 田中 久).
1) H. Tanaka, A. Yokoyama : This Bulletin, **10**, 1129 (1962).
2) N. Kharash : "Organic Sulfur Compounds" Vol. 1, 112 (1961). Pergamon Press, New York.
3) E. Fischer, W. Brieger : Ber., **47**, 2469 (1914).
4) H. Tanaka, A. Yokoyama : This Bulletin, **9**, 66 (1961).
5) *Ibem* : *Ibid.*, **10**, 19 (1962).



a) The compound (VId) could not be purified completely.

Chart 1.

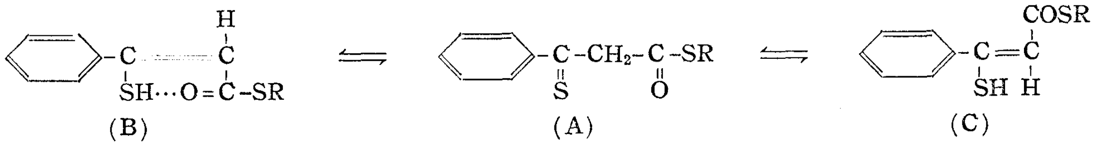


Chart 2.

(Ⅷ), which was completely identical with an authentic sample prepared by other method,⁶⁾ was obtained by the hydrolysis of Ⅵa. These mercapto compounds (Ⅵa~Ⅵc) were pale yellow oily substances in appearance at room temperature, but color of these compounds turned to purple by heat, and this color change was reversible, These ligands (Ⅵa~Ⅵc) showed color reactions, probably by the chelate-formation, with many kinds of metals, such as iron, copper, nickel, cobalt, zinc, lead, bismuth, silver, cadmium, platinum, gold, mercury, and uranium, as seen in Table Ⅳ, in experimental part.

With respect to the structures of Ⅵa~Ⅵc, tautomerism shown in Chart 2 should be considered and the equilibria among these tautomers are regarded to be closely connected with the chelating abilities of these ligands. In this connection, prior to the study of the metal chelates, the structures of Ⅵa~Ⅵc were investigated by infrared and nuclear magnetic resonance spectroscopy. The keto-enol tautomerism has been investigated by many workers, especially in β-diketones, while tautomerism of thioxo-thioenol has not been studied widely up to the present time. Silverstein⁶⁾ reported that the presence of the same kind of tautomerism as shown in Chart 2 could be considered in ethyl β-mercaptocinnamate from its infrared spectrum. As the infrared spectra of Ⅵa~Ⅵc are similar each other, a spectrum of Ⅵa is shown in Fig. 2 as an example. For the purpose of making comparison, ethyl β-(ethylthio)thiocinnamate (Ⅸ) and diethyl β,β'-dithiobis(thiocinnamate) (Ⅹ) were prepared by the procedure shown in Chart 1 and their infrared spectra are shown in Figs. 3 and 4. The frequencies of the SH, C=O and C=C stretching bands of Ⅵa~Ⅵc, together with those of Ⅸ and Ⅹ are given in Table I. As seen in Table I and Fig. 2, two bands were observed as C=O stretching bands in Ⅵa~Ⅵc. One of these bands in each case, which was very strong, was observed in considerably lower region than in Ⅸ and Ⅹ, and this band was considered to be based on the hydrogen-bonded C=O of *cis*-thioenol form (B). The other one, which was observed as a shoulder, was considered to be based on the non-hydrogen-bonded C=O of thioxo form (A) or *trans*-thioenol form (C). The stretching bands of SH in Ⅵa~Ⅵc were observed in considerably lower region than in ordinary thiols.⁷⁾ These observations suggest the presence of fairy strong hydrogen bond between carbonyl and mercapto groups in Ⅵa~Ⅵc. As for the infrared spectra of the *cis* and *trans* configuration of various kinds of α,β-unsaturated carbonyl compounds, Hirschman⁸⁾ and Winterstein⁹⁾ empirically reported that in *cis* form the frequencies of C=O stretching bands were always more than 75 cm^{-1} higher than those of C=C stretching bands and also the intensities of C=C stretching bands were higher than those of C=O stretching bands. In the case of Ⅵa~Ⅵc, as seen in Table I and Fig. 2, C=O stretching bands were always observed in 70~74 cm^{-1} higher region than C=C stretching bands, and C=C stretching bands were always stronger than C=O stretching bands. On the contrary, in compound (Ⅶ), which should be present as *trans* form, the observations in infrared spectrum were quite different from those of Ⅵa~Ⅵc as shown in Table I and Fig. 1. Judging from above mentioned observations, it was confirmed that Ⅵa~Ⅵc are present mainly as *cis*-thioenol form (B) with a little contribution of thioxo form (A) or *trans*-thioenol form (C) and the double bond character of their carbonyl groups considerably decreases. Concerning the infrared spectra in the region of 1200~800 cm^{-1} of thiolic acid esters, Niquist¹⁰⁾ reported that in many cases two strong characteristic bands, the one in the region of 1100~1200 cm^{-1} the other in the region of 880~1030 cm^{-1}, were observed, and

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6) Z. Reyes, R. M. Silverstein: J. Am. Chem. Soc., **80**, 6367 (1958).

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

8) R. Hirschman: J. Am. Chem. Soc., **76**, 4013 (1954).

9) O. Winterstein, M. Moore: *Ibid.*, **78**, 6193 (1956).

10) R. A. Niquist: Spectrochim. Acta, **7**, 514 (1959).

they should be assigned as the band of $\nu_{-\mathrm{C}-\overset{\|}{\mathrm{C}}-}$ and $\nu_{-\overset{\|}{\mathrm{C}}-\mathrm{S}-}$ respectively. A band observed at 1066 cm^{-1} or 1055 cm^{-1} and another observed at 876 cm^{-1} in Fig. 2, would be assigned as the bands of $\nu_{-\mathrm{C}-\overset{\|}{\mathrm{C}}-}$ and $\nu_{-\overset{\|}{\mathrm{C}}-\mathrm{S}-}$ in the case of Ⅵa respectively, Niquist's assignment being refered. The infrared absorptions based on the linkages of $-\mathrm{C}-\overset{\|}{\mathrm{C}}-$ and $-\overset{\|}{\mathrm{C}}-\mathrm{S}-$ should have connection in some extent with the tautomerism, but a clear correlation could not be derived on this point.

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

Compd.	ν_{SH}	$\nu_{\mathrm{C=O}}$	$\nu_{\mathrm{C=C}}$
Ⅵa[b]	2440	1668[a] 1615	1544
Ⅵb[b]	2400	1670[a] 1613	1542
Ⅵc[b]	2415	1655[a] 1617	1543
Ⅷ[c]		1660 1640	1540
Ⅸ[b]		1650	1545
Ⅹ[c]		1678	1582

a) observed as a shoulder. b) measured as liquid film. c) measured as Nujol mull.

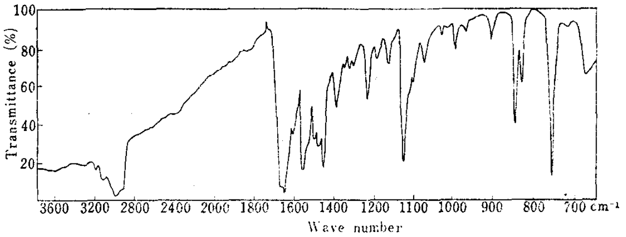

Fig. 1. Infrared Spectrum of 5-Phenyl-3*H*-1,2-dithiol-3-one (Ⅷ) (in Nujol)

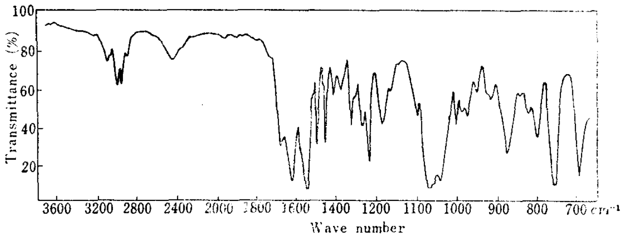

Fig. 2. Infrared Spectrum of Ethyl β-Mercaptothiocinnamate (Ⅵa) (Liquid film)

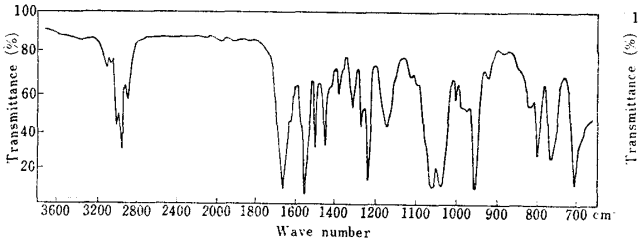

Fig. 3. Infrared Spectrum of Ethyl β-(Ethyl thio)thiocinnamate (Ⅸ) (Liquid film)

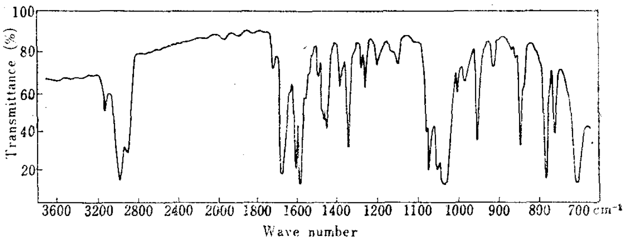

Fig. 4. Infrared Spectrum of Diethyl β,β'-Dithiobis(thiocinnamate) (Ⅹ) (in Nujol)

Only a few reports concerning to nuclear magnetic resonance spectra of mercapto compounds have been found in the literature. It has been reported that τ value of the signal from mercapto group is 8.4~8.8 in ordinary case.[11] The nuclear magnetic resonance spectrum of Ⅵa was measured and each signal was assigned as shown in Fig. 5. An assignment of a signal from the mercapto group was confirmed by the comparison of nuclear magnetic resonance spectrum of Ⅵa with that of Ⅸ (Fig. 6). As seen in Fig. 5, a signal from the mercapto group was observed in extremely lower field than in ordinary case. This fact also shows that the mercapto group and the carbonyl group

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[11] N.F. Chamberlain: Anal. Chem., **31**, 56 (1959).

are markedly hydrogen-bonded, and the presence of the thioxo form could not be suggested from nuclear magnetic resonance spectrum. In addition, the structure of IX was confirmed as shown in Chart 1, from the above mentioned facts, and a possibility that a compound in which the olefinic hydrogen instead of mercapto hydrogen was substituted by ethyl group formed, was deservedly denied.

In order to discuss completely on this tautomerism, further investigations, namely the studies on the ultraviolet spectra are considered to be necessary together with those of the infrared and nuclear magnetic resonance spectra. Especially the effect of solvent and heat should be investigated. The results of these studies will be reported later.

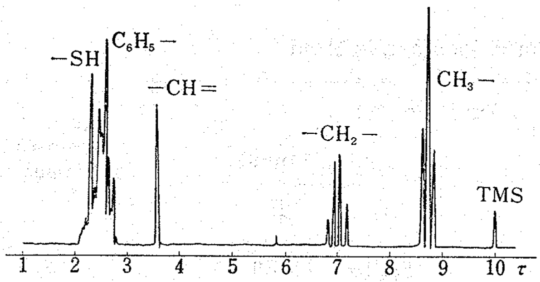

Fig. 5. Nuclear Magnetic Resonance Spectrum of Ethyl β-Mercaptothiocinnamate (VIa)[*3]

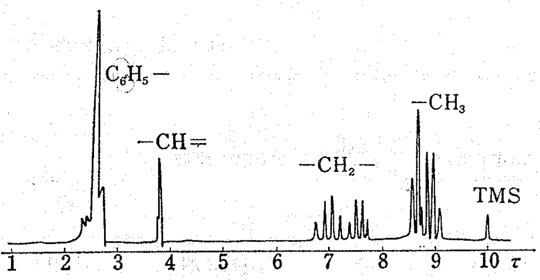

Fig. 6. Nuclear Magnetic Resonance Spectrum of Ethyl β-(Ethylthio)thiocinnamate (IX)[*3]

Experimental[*4]

Alkyl or Aryl Thiophenylpropiolate (Ia∼Id)——A mixture of 0.1 mole of phenylpropiolic acid and 0.12 mole of freshly distilled $SOCl_2$ in 100 ml. of $CHCl_3$ was warmed at 50∼60° with stirring for 3 hr., and evaporated to about 50 ml. under reduced pressure. To the residue, 50 ml. of dry Et_2O was added. This solution of phenylpropioloyl chloride was added dropwise to a mixture of 0.1 mole of thiol and 0.15 mole of pyridine in 50 ml. of dry Et_2O under ice-cooling with stirring. After stirring was continued for 2 hr., and standing overnight at a room temperature, the reaction mixture was poured into 10% H_2SO_4 under ice-cooling with stirring. The ethereal layer was separated and washed with H_2O, 5% Na_2CO_3, and H_2O successively, dried over $CaCl_2$ and the solvent was removed. The residual oil of Ia∼Id was used for the next procedure, without further purification. On distillation, Ia decomposed but small amount of pale yellow oil was obtained, b.p.$_3$ 128∼132°. IR: $\nu_{C\equiv C}$ 2200 cm^{-1} (liquid film).

S-[1-Phenyl-2-(alkyl- or aryl-thiocarbonyl)vinyl] isothiuronium *p*-Toluenesulfonate (Va∼Vd)——A mixture of 0.1 mole of Ia∼Id, equimolecular *p*-toluenesulfonic acid and thiourea in 100 ml. of EtOH was refluxed for 3 hr. Colorless crystals of Va∼Vd separated out during this period. After cooling, Et_2O was added and crystals separated out were collected and washed with Et_2O and recrystallized from EtOH giving colorless needles. Yields (calculated from phenylpropiolic acid), microanalytical data and melting points are given in Table II.

Table II. S-[1-Phenyl-2-(alkyl- or aryl-thiocarbonyl)vinyl]-isothiuronium *p*-Toluenesulfonate

Compd.	m.p. (decomp.) (°C)	Yield (%)	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	N	C	H	N
Va	222	60	$C_{19}H_{22}O_4N_2S_3$	52.05	5.06	6.39	52.21	5.50	6.30
Vb	235	50	$C_{20}H_{24}O_4N_2S_3$	53.09	5.35	6.16	53.29	5.50	5.87
Vc	204	50	$C_{24}H_{24}O_4N_2S_3$	57.60	4.83	5.60	57.30	4.99	5.44
Vd	214	30	$C_{23}H_{22}O_4N_2S_3$	56.79	4.56	5.76	56.77	4.73	5.97

[*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.

Alkyl or Aryl β-Mercaptothiocinnamate (VIa~VId)——A solution of 0.05 mole of Va~Vc in 100 ml. of 3% NaOH was stirred for 2 hr. at a room temperature, and the reaction mixture was filtered and the filtrate was acidified with conc. HCl under ice-cooling with stirring. Purple oil of VIa~VIc separated out was extracted with Et_2O, washed with H_2O and dried over Na_2SO_4, and the solvent was evaporated. Residual oil was dissolved in EtOH and added to EtOH solution of $Pb(OAc)_2$ and the mixture was allowed to stand overnight, after stirring of 5 hr. The Pb-salt precipitated was collected, washed with EtOH and reprecipitated from $CHCl_3$ by EtOH, Passing of H_2S through a suspension of Pb-salt in Et_2O regenerated VIa~VIc. After PbS was removed, the solvent was evaporated to obtain VIa~VIc in pure state. Yields, microanalytical data and melting points of Pb-salt are given in Table III. On hydrolysis of Vd as described above, a yellow oil was obtained, which was positive to Rheinboldt test[12] and showed similar coloration with metal ions to that of VIa~VIc. However, its purification was unsuccessful, because its Pb-salt was not soluble in any organic solvent.

Table III. Esters of β-Mercaptothiocinnamic Acid

Compd.	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S	m.p. (decomp.) of Pb-salt (°C)
VIa	50	$C_{11}H_{12}OS_2$	58.92	5.40		59.14	5.66		163
VIb	55	$C_{12}H_{14}OS_2$	60.50	5.92	26.86	60.98	6.21	26.44	127
VIc	45	$C_{16}H_{14}OS_2$	67.12	4.93		66.98	5.05		150

5-Phenyl-3*H*-1,2-dithiol-3-one (VII)——One gram of VIa~VIc was distilled under reduced pressure. From the distillate (b.p$_1$ 142°), colorless crystals of VII that separated out, were collected and recrystallized from EtOH to give 0.5 g. of colorless needles, m.p. 115°. *Anal.* Calcd. for $C_9H_6OS_2$: C, 55.68; H, 3.12; S, 32.96; mol. wt., 194. Found: C, 55.76; H, 3.18; S, 32.70; mol. wt., (Rast) 198.

Hydrolysis of Ethyl β-Mercaptothiocinnamate (VIa)——To a solution of 1 g. of VIa in 20 ml. of Et_2O, 10 ml. of 10% NaOH solution was added and the mixture was refluxed for 4 hr. After cooling, the mixture was acidified with dil. HCl and extracted with Et_2O, washed with H_2O and dried over Na_2SO_4 and the solvent was evaporated. The residue (VIII) was repeatedly recrystallized from CCl_4-petr. ether to give yellow needles, m.p. 112~113°. Yield, 50 mg. The identity of VIII and β-mercaptocinnamic acid was confirmed by a mixed fusion and the comparison of IR spectrum with an authentic sample.[6]

Addition of Hydrogen Sulfide to Ethyl Thiophenylpropiolate (Ia)——To a mixture of 10 g. of Ia and 3 g. of Et_3N in 100 ml. of dry Et_2O, 10~12 ml. of H_2S was added at −80° as described in the preceding paper.[13] After standing for a week at a room temperature, under pressure, the reaction mixture was washed with dil. HCl and H_2O and dried over Na_2SO_4. The solvent was evaporated and the residual oil was distilled under reduced pressure to give 5 g. of pale yellow oil (II), b.p$_4$ 156°. The identity of II and ethyl β-mercaptothiohydrocinnamate was confirmed by the comparison of IR spectrum with an authentic sample.[14] Hydrolysis of II by NaOH solution yielded colorless needles (III), m.p. 108°. The identity of III and β-mercaptohydrocinnamic acid was confirmed by a mixed fusion, and the comparison of IR spectrum with an authentic sample.[4]

Reaction of Thiourea and Ethyl Thiophenylpropiolate (Ia)——A mixture of 3.5 g. of Ia and 1.5 g. of thiourea in 30 ml. of Me_2CO was refluxed for 25 hr. and the solvent was evaporated. Recrystallization of the residue from EtOH yielded 2 g. of colorless needles (IV), m.p. 215°. The identity of IV and 2-amino-6-phenyl-4*H*-1,3-thiazin-4-one was confirmed by a mixed fusion and the comparison of IR spectrum with an authentic sample.[5]

Ethyl β-(Ethylthio)thiocinnamate (IX)——To a solution of 0.16 g. of NaH in 5 ml. of benzene, a solution of 1.5 g. of VIa in 10 ml. of benzene was added dropwise under cooling with H_2O. After the evolution of gas ceased, a solution of 1.1 g. of EtI in 5 ml. of benzene was added and the mixture was refluxed for 3 hr., cooled and filtered, and the solvent was evaporated. The residual oil was distilled under reduced pressure. After a small amount of forerun of purple oil, a yellow oil of IX was collected and redistillation yielded 0.5 g. of pure IX, b.p$_{0.07}$ 135~136°. *Anal.* Calcd. for $C_{13}H_{16}OS_2$: C, 61.89; H, 6.39. Found: C, 61.60; H, 6.55.

Diethyl β,β'-Dithiobis(thiocinnamate) (X)——To a solution of 0.65 g. of VIa in 5 ml. of EtOH, a solution of 0.37 g. of I_2 in 5 ml. of EtOH was added dropwise with stirring at a room temperature and

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[12] H. Rheinboldt: Ber., **59**, 1311 (1926).
[13] H. Tanaka, A. Yokoyama: This Bulletin, 8, 275 (1960).
[14] *Idem*: *Ibid.*, **10**, 13 (1962).

the stirring was continued for additional 10 hr. After removing the excess I_2 by adding cold solution of 5% $Na_2S_2O_3$, the reaction mixture was poured into H_2O and extracted with Et_2O, washed with H_2O and dried over Na_2SO_4. After evaporating the solvent, the oily residue solidified by addition of petr. ether. Recrystallization from EtOH yielded 500 mg. of colorless needles, m.p. 156.5°. *Anal.* Calcd. for $C_{22}H_{22}O_2S_4$: C, 59.19; H, 4.97. Found : C, 59.30; H, 5.24.

Reactions of VIa~VIc with Metal Ions——The reactions of Ⅵa~Ⅵc with metal ions were examined by spot tests. The results are shown in Table Ⅳ.

TABLE Ⅳ. Spot Test (in neutral solution)

Metal	Reaction	Metal	Reaction
Fe^{3+}	green ppt.	Bi^{3+}	yellow ppt.
Cu^{2+}	orange yellow ppt.	Ag^{+}	〃
Ni^{2+}	dark red ppt.	Cd^{2+}	〃
Co^{2+}	yellow green ppt.	Pt^{4+}	pale yellow
Zn^{2+}	pale yellow ppt.	Au^{3+}	orange ppt.
Pd^{2+}	orange ppt.	Hg^{2+}	yellow ppt.
Pb^{2+}	yellow ppt.	$UO_2{}^{2+}$	〃

Reagent : 1%EtOH solution

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Summary

Esters of β-mercaptothiocinnamic acid were prepared as strong chelating agents. Phenylpropioloyl chloride was converted into alkyl or aryl phenylthiopropiolate and thiourea was reacted in the presence of *p*-toluenesulfonic acid to obtain corresponding isothiuronium salts. Esters of β-mercaptothiocinnamic acid were obtained by the hydrolyses of the isothiuronium salts. Thioxo-thioenol tautomerism in the esters of β-mercaptothiocinnamic acid was investigated by infrared and nuclear magnetic resonance spectroscopy. It was found that *cis*-thioenol form is predominant and hence the mercapto group and the carbonyl group are markedly hydrogen-bonded.

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