UDC 547.569–386 : 546.56+546.74

20. **Hisashi Tanaka and Akira Yokoyama** : Studies on the Sulfur-containing Chelating Agents. VI. Syntheses of β-Mercapto-acid Esters and their Copper and Nickel Chelates. (2).[*2]

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In a previous paper,[*2] it was reported that alkyl or aryl β-mercaptohydrocinnamate formed stable chelates with copper and nickel, and that the reaction with nickel was very sensitive. The present paper deals with the synthesis of esters of β-mercaptohydrocinnamic acid with chloro, methoxyl, cyano, and nitro as the substituent and also esters of β-mercapto-β-(1-naphthyl)- and β-mercapto-β-(2-furyl)-propionic acid. Addition of hydrogen sulfide to the esters of substituted cinnamic acid, 1-naphthylacrylic acid, and 2-furylacrylic acid was found to be sufficient for their preparation.

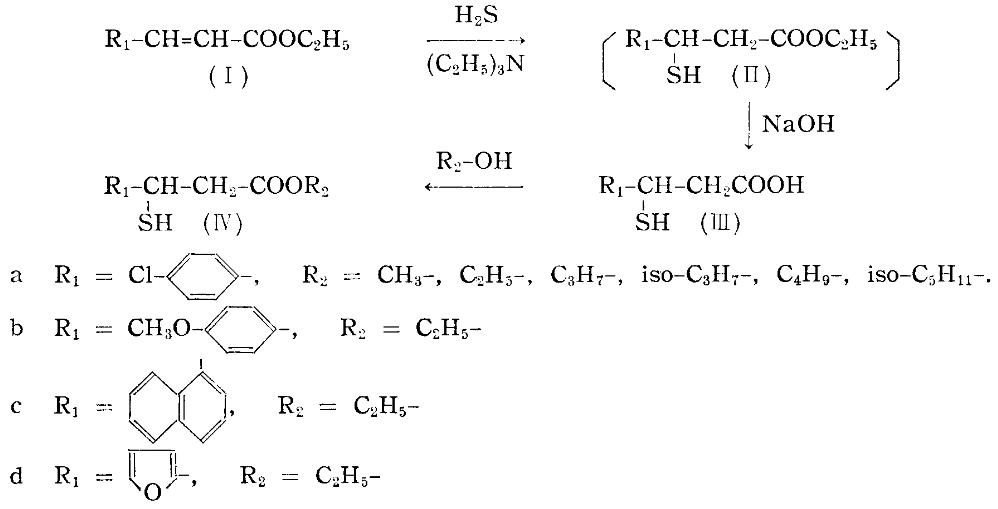


Chart 1.

β-Mercapto-acid esters (Ⅱ) with R_1 of p-chlorophenyl, p-anisyl, 1-naphthyl, and 2-furyl, were prepared by the method analogous to that reported in the previous paper,[*2] as shown in Chart 1, but the procedure had to be changed slightly according to R_1. In all cases, (Ⅱ) could not be separated from the starting material and its hydrolysis to (Ⅲ) was necessary.

(Ⅱa : R_1 = p-chlorophenyl) was more easily hydrolyzed, even at room temperature, than ethyl β-mercaptohydrocinnamate. The starting material (Ia) was also rather easily hydrolyzed and the purification of (Ⅲa) was difficult because of contamination with p-chlorocinnamic acid. (Ⅲa) was purified by repeated recrystallization and esterified to alkyl esters. Hydrolysis of (Ⅱb : R_1 = p-anisyl) to (Ⅲb) required heating and the yield of (Ⅲb) was very poor. The usual esterification of (Ⅲb) was unsuccessful on account of desulfurization. Desulfurization was considered to be due to the effect of the methoxyl group, which facilitates cleavage of the carbon-sulfur bond, analogous to the cleavage of carbon-sulfur bond in vanillyl ethyl sulfide reported by Gierer.[1] However, an oil considered to be ethyl β-mercapto-p-methoxyhydrocinnamate (Ⅱb) was obtained besides (Ⅲb) by the hydrolysis of (Ⅱb) but it could not be purified and confirmed. This oil was positive to the Rheinboldt test[2] and showed coloration with metal ions similar to that of other β-mercapto-acid esters.

[*1] Yoshida, Sakyo-ku, Kyoto (田中 久, 横山 陽).

[*2] Part (1) : This Bulletin, **9**, 66 (1961).

[1] J. Gierer, B. Alfredsson : Chem. Ber., **90**, 1240 (1957).

[2] H. Rheinboldt : *Ibid.*, **59**, 1311 (1926).

The yield of (IIIc) from (IIc : R_1 = 1-naphthyl) was poor. The esterification of (IIId : R_1 = 2-furyl) was successful only when concentrated sulfuric acid was employed as a dehydrating agent.

Ethyl *p*-nitrocinnamate was reacted with hydrogen sulfide under various conditions, but the addition of hydrogen sulfide did not take place. Ethyl α-cyanocinnamate was also reacted with hydrogen sulfide similarly. In this case, only stilbene was separated from the reaction mixture and other reaction product could not be confirmed.

The reaction of these β-mercapto-acid esters with various kinds of metal ions was examined by the spot test. Results were similar to those obtained with the esters of β-mercaptohydrocinnamic acid[*2] as shown in Table I.

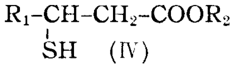
Table I. Spot Test

	Color of precipitate		Color of precipitate
Ni^{2+}	Brick red	Pt^{4+}	Orange
Cu^{2+}	Yellow	Au^{3+}	〃
Pd^{2+}	〃	Hg^{2+}	Yellow
Ag^{+}	White	Pb^{2+}	〃
Sb^{3+}	Yellow	Bi^{3+}	〃

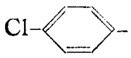
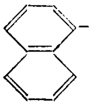
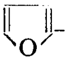
Reagent : 1% EtOH solution of β-mercapto-acid esters.

Copper and nickel chelates of these β-mercapto-acid esters were separated and purified. Their melting points and analytical data are given in Tables IV and V (in the experimental part). The ratio of the ligand to the metal was found to be 1:1 in copper chelates and 2:1 in nickel chelates. Nickel chelates of alkyl β-mercapto-*p*-chlorohydrocinnamate were more soluble in ethyl acetate and chloroform than those of esters of β-mercaptohydrocinnamic acid. Recognizable limit of nickel with these β-mercapto-acid esters was measured and, as shown in Table II, considerable difference was observed according to substituents.

Table II. Recognizable Limit of Nickel by β-Mercapto-acid Esters



$$\underset{\displaystyle SH}{R_1\text{-}CH}\text{-}CH_2\text{-}COOR_2 \quad (IV)$$

R_1	R_2	Recognizable limit (γ/0.05 cc.)
Cl-	CH_3-	1.0
〃	C_2H_5-	1.0
〃	C_3H_7-	0.5
〃	iso-C_3H_7-	0.5
〃	C_4H_9-	0.3
〃	iso-C_5H_{11}-	0.3
	C_2H_5-	5.0
	C_2H_5-	1.0

Reagent : 1% EtOH solution of β-mercapto-acid esters.
Ni : Aqueous solution of $(AcO)_2Ni$.

The absorption spectra of nickel chelates of these β-mercapto-acid esters were measured in the visible region. In all cases, a maximum was observed at about 460 mμ, as shown in Fig. 1. In the case of nickel chelate of ethyl β-mercapto-*p*-methoxyhydrocinnamate, similar type of absorption curve was obtained, although β-mercapto-*p*-methoxyhydrocinnamate and its chelate were not separated in pure state. However, chelate formation was also confirmed in this case from the absorption curve. The absorption spectra of ethyl β-mercapto-*p*-chlorohydrocinnamate and its copper chelate are shown in Fig. 2. Copper chelates of other β-mercapto-acid esters did not show any absorption maximum in the visible or ultraviolet region, although considerable absorption was observed at about 400 mμ.

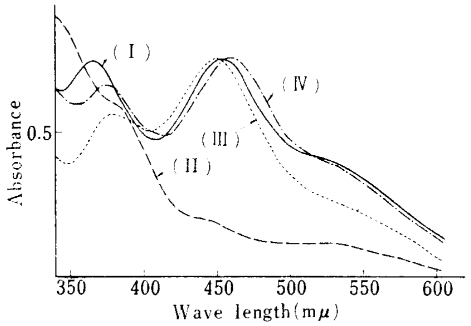
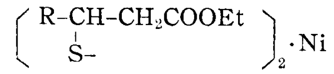


Fig. 1. Absorption Spectra of Nickel Chelates in $CHCl_3$ Solution



$$\left[\begin{array}{c}\text{R-}\underset{\text{S-}}{\text{CH}}\text{-CH}_2\text{COOEt}\end{array}\right]_2\cdot\text{Ni}$$

(I) ———— R=*p*-Chlorophenyl 1×10^{-4} mole
(II) – – – – R=1-Naphthyl 1×10^{-4} mole
(III) ··········· R=2-Furyl 1×10^{-4} mole
(IV) –·–·–· R=*p*-Anisyl *

* The concentration is unknown, because the chelate could not be separated in pure state.

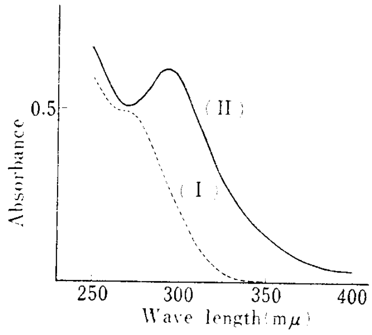


Fig. 2. Absorption Spectra of Ethyl β-Mercapto-*p*-chlorohydrocinnamate and its Copper Chelate in $CHCl_3$ Solution

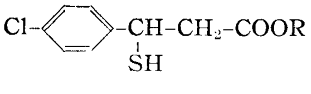
(I) ----- β-Mercapto-acid ester 1×10^{-4} mole
(II) —— Copper chelate 1×10^{-4} mole

Experimental

β-Mercapto-*p*-chlorohydrocinnamic Acid (IIIa)—To a solution of 20 g. of ethyl *p*-chlorocinnamate and 8 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, placed in a pressurized bottle, dry H_2S gas was introduced and liquefied by chilling with dry ice-Me_2CO to −70° to −80° until the increase of volume became 20 cc., and the bottle was closed. The mixture was heated at 40～50° for 2～3 hr. and allowed to stand for 10 days at room temperature. After removal of excess H_2S, the reaction mixture was washed with dil. HCl and H_2O, and extracted with 10% NaOH until $CHCl_3$ layer became negative to the Rheinboldt test. The aqueous layer was acidified with conc. HCl. Crystals of (IIIa) that separated out were collected and repeatedly recrystallized from 70% EtOH to colorless needles, m.p. 128°. Yield, 12 g. Rheinboldt test, red. *Anal.* Calcd. for $C_9H_9O_2ClS$: C, 49.90; H, 4.19. Found : C, 49.60; H, 4.41.

Esterification of (IIIa)—To a solution of 4 g. of (IIIa) in 50～60 cc. of corresponding dehyd. alcohol, dry HCl gas was introduced with ice cooling. After HCl was saturated, the reaction mixture was warmed on a water bath for 1～2 hr. and the alcohol was evaporated. The residual oil was dissolved in Et_2O, washed thoroughly with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residual colorless oil was distilled in a diminished pressure. Rheinboldt test, deep red. Yield, 2.5～3 g. Microanalytical data and boiling points are shown in Table III.

Table III. Esters of β-Mercapto-*p*-chlorohydrocinnamic Acid



$$\text{Cl-C}_6\text{H}_4\text{-}\underset{\text{SH}}{\text{CH}}\text{-CH}_2\text{-COOR}$$

R	b.p. (°C/mm. Hg)	Formula	Analysis (%)			
			Calcd.		Found	
			C	H	C	H
CH_3-	147.5～148/5	$C_{10}H_{11}O_2ClS$	52.06	4.77	52.34	4.99
C_2H_5-	149～150/3	$C_{11}H_{13}O_2ClS$	53.99	5.32	54.15	5.53
C_3H_7-	168/7	$C_{12}H_{15}O_2ClS$	55.71	5.80	55.85	6.02
iso-C_2H_7-	157～158/6	$C_{12}H_{15}O_2ClS$	55.71	5.80	55.55	6.01
C_4H_9-	168/5	$C_{13}H_{17}O_2ClS$	57.25	6.24	57.29	6.47
iso-C_5H_{11}-	172/6	$C_{14}H_{19}O_2ClS$	58.64	6.63	59.01	6.67

β-Mercapto-*p*-methoxyhydrocinnamic Acid (IIIb)—To a solution of 15 g. of ethyl *p*-methoxycinnamate and 10 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, 13~14 cc. of H_2S was introduced as described above. After standing for 1 week, the reaction mixture was washed with dil. HCl and H_2O, and $CHCl_3$ was evaporated. 100 cc. of 10% NaOH solution was added to the residual oil and heated on a water bath for 30 min. After cool, the mixture was extracted with Et_2O and 5 g. of ethyl *p*-methoxycinnamate was recovered from Et_2O layer. The aqueous layer was acidified with conc. HCl and 4 g. of crystals of (IIIb) and 2 g. of oil separated out. The crystals were collected and recrystallized from 50% EtOH to colorless needles, m.p. 96.5°. Rheinboldt test, red. *Anal.* Calcd. for $C_{10}H_{12}O_3S$: C, 56.60; H, 5.70; S, 15.08. Found : C, 56.72; H, 5.94; S, 14.80.

The oil was positive to the Rheinboldt test and was considered to be (IIb) but could not be purified by distillation.

Esterification of (IIIb)—To a solution of 3 g. of (IIIb) in 50 cc. of dehyd. EtOH, dry HCl gas was introduced with ice cooling. After HCl was saturated, the mixture was allowed to stand overnight at room temperature and the solvent was evaporated. The residual oil was extracted with Et_2O, which was washed with H_2O and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled in a diminished pressure and a turbid oil distilled at $b.p_8$ 168~175°, from which 0.5 g. of crystals separated out, which showed no melting point depression on admixture with the authentic specimen of *p*-anisylacrylic acid.

β-Mercapto-β-(1-naphthyl)propionic Acid (IIIc)—To a solution of 7 g. of ethyl β-(1-naphthyl)-acrylate and 2 g. of triethylamine in 60 cc. of dehyd. $CHCl_3$, 15 cc. of H_2S was introduced as described above. (IIIc) was recrystallized from EtOH to colorless needles, m.p. 140°. Yield, 4 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{13}H_{12}O_2S$: C, 67.23; H, 5.21; S, 13.78. Found : C, 67.04; H, 5.24; S, 14.08.

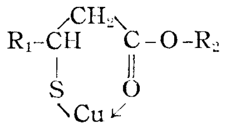
Ethyl β-Mercapto-β-(1-naphthyl)propionate (IVc)—A mixture of 1 g. of (IIIc) and 3 cc. of conc. H_2SO_4 in 20 cc. of dehyd. EtOH was refluxed for 5 hr. After EtOH was evaporated, the residue was poured into about 100 cc. of ice-water, extracted with Et_2O, washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residual crude oil was distilled, $b.p_5$ 178°. Yield, 0.5 g. Rheinboldt test, deep red. *Anal.* Calcd. for $C_{15}H_{16}O_2S$: C, 69.21; H, 6.20; S, 12.29. Found : C, 69.67; H, 6.55; S, 11.90.

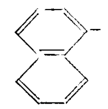
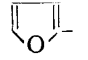
β-Mercapto-β-(2-furyl)propionic Acid (IIId)—To a solution of 20 g. of ethyl β-(2-furyl)acrylate and 10 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, 20 cc. of H_2S was introduced as described above. (IIId) was recrystallized from H_2O to colorless plates, m.p. 89°. Yield, 10 g. Rheinboldt test, deep red. *Anal.* Calcd. for $C_7H_8O_3S$: C, 48.84; H, 4.68; S, 18.60. Found : C, 49.03; H, 4.80; S, 18.40.

Ethyl β-Mercapto-β-(2-furyl)propionate (IVd)—A mixture of 3 g. of (IIId) and 4 cc. of conc. H_2SO_4 in 30 cc. of dehyd. EtOH was refluxed for 5 hr., poured into about 100 cc. of ice-water, and extracted with Et_2O. The extract was washed with H_2O and dried over Na_2SO_4. After evaporation of Et_2O, the residue was distilled, $b.p_{13}$ 123°. Yield, 2 g. Rheinboldt test, deep red. *Anal.* Calcd. for $C_9H_{12}O_3S$: C, 53.99; H, 6.04. Found : C, 54.39; H, 6.20.

Addition of H_2S to Ethyl α-Cyanocinnamate—To a solution of 10 g. of ethyl α-cyanocinnamate

Table IV. Copper Chelates of β-Merapto-acid Esters



R_1	R_2	m.p. (°C)	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	Cu	C	H	Cu
	CH_3-	131	$C_{10}H_{10}O_2ClCuS$	40.96	3.75	21.67	40.91	3.51	21.92
〃	C_2H_5-	122~122.5	$C_{11}H_{12}O_2ClCuS$	43.00	3.91	20.68	44.23	4.37	19.65
〃	C_3H_7-	100~100.5	$C_{12}H_{14}O_2ClCuS$	44.86	4.36	19.78	44.68	4.16	20.30
〃	iso-C_3H_7-	82~83	$C_{12}H_{14}O_2ClCuS$	44.86	4.36	19.78	44.39	4.49	18.62
〃	C_4H_9-	92~93	$C_{13}H_{16}O_2ClCuS$	46.57	4.77	18.96	46.52	4.73	19.14
〃	iso-C_5H_{11}-	115~116	$C_{14}H_{18}O_2ClCuS$	48.14	5.16	18.19	47.60	5.28	18.99
	C_2H_5-	89~90	$C_{15}H_{15}O_2CuS$	55.81	4.65	19.69	54.98	4.80	20.46
	C_2H_5-	119	$C_9H_{11}O_3CuS$	41.14	4.19	24.21	41.35	4.40	24.69

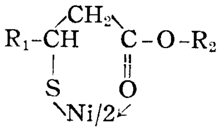
and 5 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, 15 cc. of H_2S was introduced as described above. After standing for 1 week at room temperature, the mixture was washed with dil. HCl and H_2O, and extracted with 10% NaOH. The aqueous layer was acidified with conc. HCl, extracted with Et_2O, and Et_2O was evaporated. Sulfur that separated out was removed and residual oil was distilled in a diminished pressure (b.p$_6$ 122°) but this product could not be identified. From the $CHCl_3$ layer, 3 g. of an oil was obtained by distillation, b.p$_7$ 163° or m.p. 124°. This substance was identified as stilbene. *Anal.* Calcd. for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found : C, 93.59; H, 6.74.

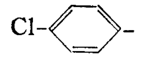
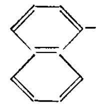
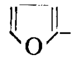
Preparation of Copper Chelates—EtOH solution of β-mercapto-acid ester and equimolar amount of aqueous solution of $(AcO)_2Cu$ were mixed and warmed on a water bath with shaking for a few min. Yellow-colored oil separated. The solvent was decanted off, the crude product was washed with H_2O, and purified by a suitable method for each compound.

Chelates of Compounds (IV) with R_1=*p*-chloropheny, R_2=methyl to isopentyl, recrystallized from EtOH; R_1=1-naphthyl, R_2=ethyl, dissolved in $CHCl_3$ and reprecipitated with EtOH; R_1=2-furyl, R_2=ethyl, dissolved in $CHCl_3$-EtOH and reprecipitated with petr. ether. Microanalytical data and melting points are listed in Table IV.

Preparation of Nickel Chelates—EtOH solution of β-mercapto-acid ester and equimolar amount of EtOH solution of $(AcO)_2Ni$ were mixed and shaken for a few min. Brick red Ni chelate that precipitated was collected and washed with dil. EtOH. Microanalytical data and melting points are given in Table V. They are very soluble in $CHCl_3$ and benzene, slightly soluble in Et_2O, EtOH, AcOEt, and Me_2CO, and insoluble in H_2O.

TABLE V. Nickel Chelates of β-Mercapto-acid Esters



R_1	R_2	m.p. (°C)	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	Cu	C	H	Cu
	CH_3-	174.5	$C_{20}H_{20}O_4Cl_2NiS_2$	46.42	4.25	11.34	47.35	4.35	10.89
〃	C_2H_5-	174～175	$C_{22}H_{24}O_4Cl_2NiS_2$	48.38	4.40	10.76	48.89	4.73	11.06
〃	C_3H_7-	172	$C_{24}H_{28}O_4Cl_2NiS_2$	50.20	4.88	10.23	49.93	4.99	10.38
〃	iso-C_3H_7-	177～178	$C_{24}H_{28}O_4Cl_2NiS_2$	50.20	4.88	10.23	50.88	5.22	9.97
〃	C_4H_9-	175～176.5	$C_{26}H_{32}O_4Cl_2NiS_2$	51.85	5.65	9.76	51.55	5.41	9.82
〃	iso-C_5H_{11}-	175～176	$C_{28}H_{36}O_4Cl_2NiS_2$	53.36	5.72	9.32	53.29	5.90	9.53
	C_2H_5-	165	$C_{30}H_{30}O_4NiS_2$	62.42	5.24	10.17	62.86	5.34	9.97
	C_2H_5-	151	$C_{18}H_{22}O_6NiS_2$	47.29	4.82	12.87	47.44	5.22	13.17

The authors extend their gratitude to Prof. T. Uno for his helpful advices. They are also indebted to the members of the Microanalytical Center of the Kyoto University for analytical data.

Summary

β-Mercapto-*p*-chlorohydrocinnamic acid, β-mercapto-*p*-methoxyhydrocinnamic acid, β-mercapto-β-(1-naphthyl)propionic acid, and β-mercapto-β-(2-furyl)propionic acid and their alkyl esters were prepared. These β-mercapto-acid esters formed stable chelates with copper and nickel. The ratio of ligand to the metal was 1:1 in copper chelates and 2:1 in nickel chelates. The reaction with nickel was particularly sensitive.

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