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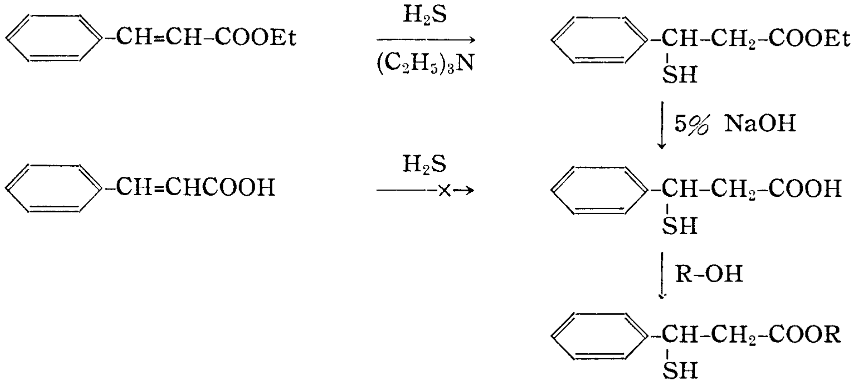
13. **Hisashi Tanaka and Akira Yokoyama** : Studies on the Sulfur-containing Chelating Agents. V. Syntheses of β-Mercapto-acid Esters, and their Copper and Nickel Chelates. (1).

(Faculty of Pharmacy, Kyoto University[*1])

In the previous paper,[1] syntheses of β-mercaptoketones and their metal chelates were reported. The mechanism of the formation of copper chelates and their structure were investigated. The present paper deals with the synthesis of β-mercapto-acid esters and their metal chelates. As in the case of β-mercaptoketones, the chelate formation was attributed to the keto and mercapto group in the case of β-mercapto-acid esters and it was expected that chelate formation would occur through the combination of carbonyl and mercapto group of the ester. In an attempt to compare mercapto-acid esters with mercaptoketones concerning chelate formation, synthesis of various kinds of β-mercapto-acid esters was planned.

Alkyl or aryl β-mercaptohydrocinnamates were prepared as the β-mercapto-acid esters. In the case of β-mercaptoketones, the addition of hydrogen sulfide to α,β-unsaturated ketones was found to be satisfactory for their preparation and this method was applied for the preparation of β-mercapto-acid esters. Addition of hydrogen sulfide to the double bond of alkyl or aryl cinnamate was investigated. As shown in Chart 1, reaction of ethyl cinnamate in chloroform solution with hydrogen sulfide under a high pressure, using triethylamine as a catalyst, was found to produce ethyl β-mercaptohydrocinnamate with a boiling point too close to that of the starting material to be separated by fractional distillation. Therefore, the reaction mixture was treated with 5% sodium hydroxide solution, by which ethyl β-mercaptohydrocinnamate was easily hydrolyzed at room temperature to β-mercaptohydrocinnamic acid, but ethyl cinnamate was not hydrolyzed. β-Mercaptohydrocinnamic acid was obtained with a good yield in a pure state by this method. In order to examine the effect of ester group to chelate formation, methyl, ethyl, propyl, isopropyl, butyl, and isopentyl esters were prepared by the usual esterification of β-mercaptohydrocinnamic acid as shown in Chart 1.

As for the method of preparation of β-mercaptohydrocinnamic acid, E. Fischer[2] re-



R=CH_3-, C_2H_5-, C_3H_7-, iso-C_3H_7-, C_4H_9-, iso-C_5H_{11}-

Chart 1.

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

[1] *a*) Part I : This Bulletin, **8**, 275 (1960). *b*) Part II : *Ibid.*, **8**, 280 (1960). *c*) Part III : *Ibid.*, **8**, 1008 (1960). *d*) Part IV : *Ibid.*, **8**, 1012 (1960).

[2] E. Fischer, W. Brieger : Chem. Ber., **47**, 2469 (1914).

ported a procedure starting from phenylpropiolic acid but the yield from this method is very poor and the procedure is complicated that it is not a very practical method. Another method which is considered to be possible for the preparation of β-mercaptohydrocinnamic acid is the reaction of thiourea and a corresponding halide. In this case, however, Wheeler reported that the ring closure took place and 2-imino-6-phenyl-1,3-thiazan-4-one was obtained.[3] Addition of hydrogen sulfide to cinnamic acid was also investigated under various conditions, but in all cases, the starting material was recovered quantitatively. Therefore, the addition of hydrogen sulfide to ethyl cinnamate seemed to be the most suitable method for the preparation of β-mercaptohydrocinnamic acid.

tert-Butyl β-mercaptohydrocinnamate and phenyl β-mercaptohydrocinnamate were also prepared. As these esters could not be prepared by the procedure shown in Chart 1, thionyl chloride, phosphorus trichloride, or phosphorus pentachloride was reacted respectively with β-mercaptohydrocinnamic acid under mild condition in order to obtain β-mercaptohydrocinnamoyl chloride. In all cases, however, sulfur and cinnamoyl chloride were obtained as the reaction products, and not β-mercaptohydrocinnamoyl chloride. Therefore, hydrogen sulfide was reacted with *tert*-butyl or phenyl cinnamate and the expected β-mercapto-acid esters were purified by repeated fractional distillation, as shown in Chart 2.

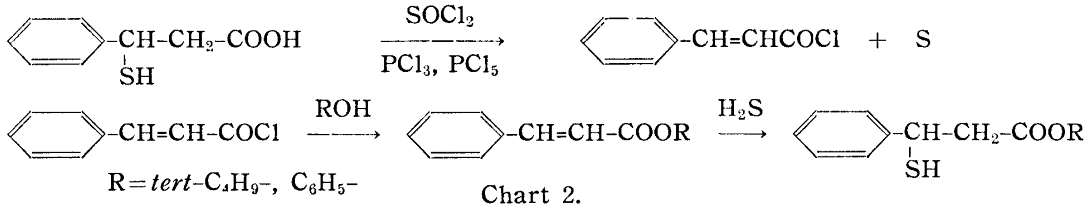


Chart 2.

In the case of the addition of hydrogen sulfide to α,β-unsaturated ketones, mono- and disulfides were often obtained besides mercaptoketones.[1b,c] In the case of esters of cinnamic acid, mono- and disulfides were not obtained except in the case of phenyl cinnamate, from which diphenyl 3,3′-thiobis(3-phenylpropionate) was obtained. In the case of *tert*-butyl cinnamate, fractional distillation of the reaction product was so difficult that the expected *tert*-butyl β-mercaptohydrocinnamate could not be completely purified, although its formation was confirmed by the Rheinboldt test,[4] and copper and nickel chelate formation.

As to the position of newly introduced mercapto group, it is considered to be β-position, analogous to the case of α,β-unsaturated ketones. α-Mercaptohydrocinnamic acid was reported to have $b.p._{12}$ 184∼187° and m.p. 48∼49°, when obtained from α-bromohydrocinnamic acid and potassium ethylxanthate,[5] while the β-mercaptohydrocinnamic acid obtained melted at 109°.

The reaction of β-mercapto-acid esters and β-mercaptohydrocinnamic acid with metal ions was examined by spot tests in acid (acetic acid), neutral, and alkaline (ammonium hydroxide) solutions, and the results are shown in Table I. The same results were obtained from acid and neutral solutions. In the case of β-mercaptohydrocinnamic acid, coloration or precipitation was observed with many kinds of metal ion, but in most cases, this was considered to be due to simple salt-formation. In the case of β-mercapto-acid esters, chelate formation was assumed to have taken place in majority of cases. The difference between alkyl and aryl groups in the esters showed no marked influence towards chelate formation. The reaction with nickel, copper, palladium, platinum, and gold was particularly clear, and resulting precipitate or oil was soluble in ether, ethyl acetate, and chloroform, so that they were considered to be chelate compounds. Copper and nickel chelates

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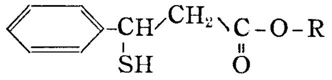
[3] K. W. Wheeler : U. S. Pat. 2,585,064 (1952).
[4] H. Rheinboldt : Chem. Ber., **59**, 1311 (1926).
[5] E. Biilmann, E. H. Madsen : Ann., **402**, 339 (1914).

Table I. Color in Spot Test

	β-Mercaptohydrocinnamic acid	β-Mercapto-acid esters	
	Neutral	Acid (AcOH) and neutral	Alkaline (NH_4OH)
Fe^{3+}	Blue	—	—
Ni^{2+}	—	Brick red ppt.	Brick red ppt.
Cu^{2+}	Green ppt.	Yellow ppt.	—
Pd^{2+}	Orange ppt.	〃	Orange ppt.
Ag^{+}	White ppt.	Grey ppt.	—
Sb^{3+}	〃	Yellow oil	—
Pt^{4+}	〃	Orange oil	—
Au^{3+}	〃	〃	—
Hg^{2+}	Pale yellow ppt.	Yellow ppt.	—
Pb^{2+}	White ppt.	〃	—
Bi^{3+}	Yellow ppt.	Yellow oil	—

were respectively separated and purified as pale yellow and brick-red crystalline powder. In the case of copper chelate, the ratio of ligand to metal was found to be 1:1 and in nickel chelate, the ratio was found to be 2:1, both from microanalytical data. The reaction with Ni^{2+} is considerably sensitive as shown in Table II. Higher alkyl esters were slightly more sensitive than lower alkyl esters. The reaction with Cu^{2+} was not sensitive. The recognizable limit was about 15 γ/0.05 cc. with all of the esters.

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



$C_6H_5\text{-}CH(SH)\text{-}CH_2\text{-}C(=O)\text{-}O\text{-}R$

R	Recognizable limit (γ/0.05 cc.)	R	Recognizable limit (γ/0.05 cc.)
CH_3	0.5	C_4H_9	0.3
C_2H_5	0.5	iso-C_5H_{11}	0.3
C_3H_7	1.0	C_6H_5	1.0
iso-C_3H_7	0.3		

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

Absorption spectra of these mercapto-acid esters and their copper and nickel chelates were measured in visible and infrared region. Absorption spectra of β-mercapto-acid esters and their nickel chelates in visible region are shown in Fig. 1. Absorption maximum was observed at 460 mμ in the case of nickel chelates, but β-mercapto-acid esters did not absorb in this region and this fact offers a clear sign of chelate formation. In the case of copper chelates, absorption maximum was not observed in visible region, but a considerable absorption was observed at about 400 mμ. In infrared region, an absorption maximum due to mercapto group was observed at 2580 cm^{-1} in the case of β-mercapto-acid esters, but this maximum was not observed in their copper and nickel chelates. The structure of copper and nickel chelates is considered to be as shown in Tables IV and V, respectively. The formation mechanism of copper chelate is considered to be analogous to that

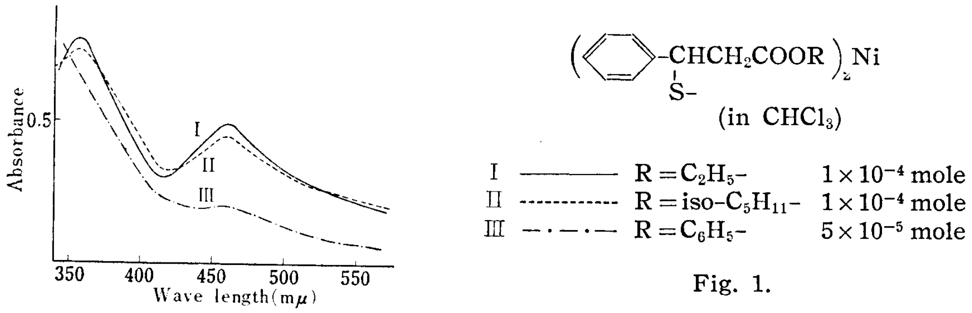


Fig. 1.

of β-mercaptoketones as reported in the preceding paper,1a) Cu^{2+} being reduced to Cu^{+} by β-mercapto-acid ester and Cu^{+} forming chelate with β-mercapto-acid ester in 1:1 ratio.

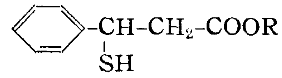
Comparing the β-mercapto-acid esters with β-mercaptoketones and their respective chelates, it was found that β-mercapto-acid esters are stable towards alkali and gave nickel chelates even from ammonium hydroxide solution, while β-mercaptoketones are unstable towards ammonium hydroxide and decomposed to release sulfur, not forming a nickel chelate from neutral and acid solution.

Experimental

β-Mercaptohydrocinnamic Acid—To a solution of 20 g. of ethyl cinnamate and 10 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 in volume became 15~20 cc., and the bottle was closed. After standing overnight, the mixture was heated at 40~50° for 4~5 hr. and allowed to stand for 1 week at room temperature. After removing excess H_2S, the reaction mixture was washed with dil. HCl and H_2O, and extracted with 5% NaOH until $CHCl_3$ layer became negative to Rheinboldt test. The aqueous layer was acidified with conc. HCl, crystals that separated out were collected, and recrystallized from H_2O to colorless needles, m.p. 109°. Yield, 16 g. *Anal.* Calcd. for $C_9H_{10}O_2S$: C, 59.33; H, 5.53. Found : C, 59.69; H, 5.69. From the $CHCl_3$ layer, 3 g. of ethyl cinnamate was recovered.

Esterification of β-Mercaptohydrocinnamic Acid—To a solution of 3 g. of β-mercaptohydrocinnamic acid in 50 cc. of corresponding dehyd. alcohol, dry HCl gas was introduced under ice cooling. After HCl was saturated, the reaction mixture was warmed on a water bath for 1~2 hr. and alcohol was evaporated. Residual oil was dissolved in Et_2O, washed thoroughly with H_2O, and dried over Na_2SO_4. The solvent was evaporated and residual colorless oil was distilled under a diminished pressure. Rheinboldt test, deep red. Yield, 1.5~2 g. Microanalytical data and b.p. are shown in Table III.

Table III. Esters of β-Mercaptohydrocinnamic Acid



R	b.p. (°C/mm. Hg)	Formula	Analysis (%)					
			Calcd.			Found		
			C	H	S	C	H	S
CH_3	124/8	$C_{10}H_{12}O_2S$	61.21	6.17	16.31	61.41	6.21	16.04
C_2H_5	157/16	$C_{11}H_{14}O_2S$	62.84	6.71	15.22	63.05	6.94	15.17
C_3H_7	130~132/3	$C_{12}H_{16}O_2S$	64.27	7.19	14.27	64.77	7.34	14.20
iso-C_3H_7	138/6	$C_{12}H_{16}O_2S$	64.27	7.19	14.27	64.11	7.17	14.36
C_4H_9	149~150/5	$C_{13}H_{18}O_2S$	65.53	7.61	13.43	65.68	7.75	13.21
iso-C_5H_{11}	155/5	$C_{14}H_{20}O_2S$	66.64	7.99	12.69	66.90	8.27	12.58

Phenyl β-Mercaptohydrocinnamate (I) **and Diphenyl 3,3′-Thiobis(3-phenylpropionate)** (II)—To a solution of 5 g. of phenyl cinnamate and 2 g. of triethylamine in 60 cc. of dehyd. $CHCl_3$, 15 cc. of H_2S was introduced as described above. After standing for 10 days at room temperature under pressure, the reaction mixture was washed with dil. HCl and H_2O, and dried over Na_2SO_4. After removal of the solvent, the residual oil was distilled using a fractionating column. After a small forerun of phenol, 2 g. of (I), $b.p_5$ 146~150°, was collected and purified by redistillation. Rheinboldt test, red. *Anal.* Calcd. for $C_{15}H_{14}O_2S$: C, 69.75; H, 5.46; S, 12.39. Found : C, 69.68; H, 5.59; S, 12.35.

Distillation of the residue gave (II), $b.p_5$ 160~165°. Yield, 0.5 g. The oil solidified after standing for a few days, m.p. 60°. *Anal.* Calcd. for $C_{30}H_{26}O_4S$: C, 74.67; H, 5.43. Found : C, 74.48; H, 5.59.

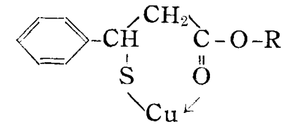
Addition of H_2S to *tert*-Butyl Cinnamate—To a solution of 18 g. of *tert*-butyl cinnamate and 5 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, 15 cc. of H_2S was introduced as described above. After standing for 1 week at room temperature under pressure, the reaction mixture was washed with dil. HCl and H_2O, and dried over Na_2SO_4. After removal of the solvent, the residual oil was distilled using a fractionating column. Colorless oil, $b.p_5$ 110~114°, which showed red color in the Rheinboldt test, was obtained. *Anal.* Calcd. for $C_{13}H_{18}O_2S$: C, 65.53; H, 7.61; S, 13.43. Found : C, 68.24; H, 7.635; S, 9.51.

The analytical data showed that this substance is not a pure *tert*-butyl β-mercaptohydrocinnamate, but it gave Cu and Ni chelates as shown in Tables IV and V.

Preparation of Copper Chelates—A mixture of EtOH solution of β-mercapto-acid ester and equimolar aqueous solution of $(AcO)_2Cu$ was warmed in a water bath with occasional shaking. Yellow-colored viscous oil separated out, which was extracted with Et_2O. The extract was washed thoroughly with H_2O and evaporated. The residual crude product was purified in the following manner.

Purification of Copper Chelates—(I) with $R=CH_3$ and iso-C_3H_7 were dissolved in Et_2O and reprecipitated with petr. ether. (I) with $R=C_2H_5$ and C_3H_7 were recrystallized from EtOH-petr. ether. (I) with $R=C_4H_9$, *tert*-C_4H_9, and iso-C_5H_{11} were recrystallized from 50% EtOH. (I) with $R=C_6H_5$ was dissolved in $CHCl_3$ and reprecipitated with EtOH. Microanalytical data and m.p. are shown in Table IV.

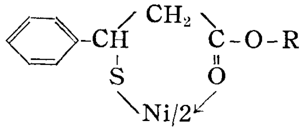
Table IV. Copper Chelates of β-Mercapto-acid Esters


(I)

R	m.p. (°C)	Formula	Analysis (%)					
			Calcd.			Found		
			C	H	Cu	C	H	Cu
CH_3	112	$C_{10}H_{11}O_2CuS$	46.41	4.26	24.79	46.42	4.25	24.56
C_2H_5	68~70	$C_{11}H_{13}O_2CuS$	48.44	4.77	23.30	48.37	4.92	23.11
C_3H_7	50	$C_{12}H_{15}O_2CuS$	50.25	5.23	22.17	50.45	5.20	22.43
iso-C_3H_7	132	$C_{12}H_{15}O_2CuS$	50.25	5.23	22.17	49.86	5.25	22.55
C_4H_9	45~50	$C_{13}H_{17}O_2CuS$	51.91	5.66	21.13	52.30	5.88	20.94
tert-C_4H_9	94~95	$C_{13}H_{17}O_2CuS$	51.91	5.66	21.13	51.63	5.66	21.41
iso-C_5H_{11}	oil	$C_{14}H_{19}O_2CuS$	53.42	6.04	20.19	54.97	6.69	19.99
C_6H_5	111~112	$C_{15}H_{13}O_2CuS$	56.16	4.06	19.81	55.55	3.94	20.57

Preparation of Nickel Chelates—A mixture of EtOH solution of β-mercapto-acid ester and equimolar EtOH solution of $(AcO)_2Ni$ was shaken for a few min. Brick red Ni chelate that precipitated was collected and washed with dil. EtOH. Microanalytical data and m.p. are shown in Table V.

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


(II)

R	m.p. (decomp.) (°C)	Formula	Analysis (%)					
			Calcd.			Found		
			C	H	Ni	C	H	Ni
CH_3	184~185	$C_{20}H_{22}O_4NiS_2$	53.49	4.91	13.08	53.35	5.03	12.91
C_2H_5	190~192	$C_{22}H_{26}O_4NiS_2$	55.33	5.45	12.30	55.73	5.65	12.81
C_3H_7	189~190	$C_{24}H_{30}O_4NiS_2$	57.06	5.94	11.63	57.19	6.14	11.88
iso-C_3H_7	184~185	$C_{24}H_{30}O_4NiS_2$	57.06	5.94	11.63	57.09	6.23	11.63
C_4H_9	182	$C_{26}H_{34}O_4NiS_2$	58.56	6.43	11.01	58.44	6.68	11.23
tert-C_4H_9	185~186	$C_{26}H_{34}O_4NiS_2$	58.56	6.43	11.01	58.76	6.37	11.69
iso-C_5H_{11}	178~180	$C_{28}H_{38}O_4NiS_2$	59.93	6.78	10.47	60.20	6.95	10.19
C_6H_5	137	$C_{30}H_{26}O_4NiS_2$	62.86	4.54	10.25	62.66	5.00	10.68

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Summary

β-Mercaptohydrocinnamic acid was prepared by the addition of hydrogen sulfide to ethyl cinnamate and hydrolysis. The acid was esterified by the usual method to form methyl, ethyl, propyl, isopropyl, butyl, and isopentyl β-mercaptohydrocinnamate. *tert*-Butyl and phenyl β-mercaptohydrocinnmates were also prepared by the direct addition of hydrogen sulfide to *tert*-butyl and phenyl cinnamates. 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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