UDC 547.569-386

90. **Hisashi Tanaka and Akira Yokoyama :** Studies on Sulfur-containing Chelating Agents. X. Mercapto-acid Amides and their Metal Chelates.[*2]

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In the previous papers,[1~8)][*2] the syntheses and the chelating abilities of various types of compounds involving mercapto group and carbonyl group were reported. These compounds have different chelating abilities due to the difference of their structures, namely differences in the type of carbonyl groups, such as ketone, ester, and thiolester.

In an attempt to investigate the chelating ability of mercaptoamide, and make comparison with that of previously reported mercapto carbonyl compounds, amides of β-mercaptohydrocinnamic acid (I) and amides of *o*-mercaptobenzoic acid (II) were prepared.

As the mercapto-amide, thionalide[9)] has been known and widely used as the analytical reagent. However, the structure of the chelate compounds produced from this reagent has not been investigated.

(I) was prepared by the addition of hydrogen sulfide to various kind of amides of cinnamic acid in almost same manner as described in Part 1.[1)] In the case of aliphatic amides, such as N-ethyl-, N,N-diethyl-, and N-benzyl-amides and N-acylpiperidine, the addition of hydrogen sulfide was unsuccessful throughout various conditions. However, in the case of aromatic amides, mercapto-amides (Ia), (Ib), and (Ic) and the corresponding disulfides (Ia′), (Ib′), and (Ic′) were obtained. The disulfides were reduced to mercapto-amides by zinc and acetic acid. In the case of cinnamamide, only a trace of substance considered to be β-mercaptohydrocinnamamide was obtained, although it was not confirmed. However, this substance was positive in Rheinboldt test[10)] and showed similar coloration with metal ions as other mercapto-amides. *o*-Mercaptobenzamide[11)] (IIa) and 2-mercaptobenzanilide[12)] (IIb) were prepared by the procedure shown in Chart 1. (II) was unstable and more easily oxidized to its disulfide in the air than (I). N,N′-Ethylene-bis(*o*-mercaptobenzamide), which would be considered as quadridentate ligand was also prepared by the same procedure.

The reaction of these compounds with metal ions was investigated by spot test. The results are shown in Table I. The chelate formations were observed with cobalt, nickel, palladium, gold, bismuth, and uranyl, as in the case of other type of ligands involving mercapto and carbonyl group. Comparing the chelating ability of (I) with that of (II), cobalt reacted only with (II) but not with (I). (II) would be stronger chelating agent than (I), due to the presence of conjugated double bond in the chelate ring. The

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

[*2] Part IX : This Bulletin, **10**, 25 (1962).

1) Part I : *Ibid.*, 8, 275 (1960).
2) Part II : *Ibid.*, 8, 280 (1960).
3) Part III : *Ibid.*, 8, 1008 (1960).
4) Part IV : *Ibid.*, 8, 1012 (1960).
5) Part V : *Ibid.*, **9**, 66 (1961).
6) Part VI : *Ibid.*, **9**, 110 (1961).
7) Part VII : *Ibid.*, **10**, 13 (1962).
8) Part VIII : *Ibid.*, **10**, 19 (1962).
9) R. Berg, W. Roebling : Chem. Ber., **68**, 403 (1935).
10) H. Reinboldt : Chem. Ber., **59**, 1311 (1931).
11) Farbenfabriken vorm. Friedr. Bayer & Co. : D.R.P. 84666 (Friedr., **4**, 1266 (1894)).
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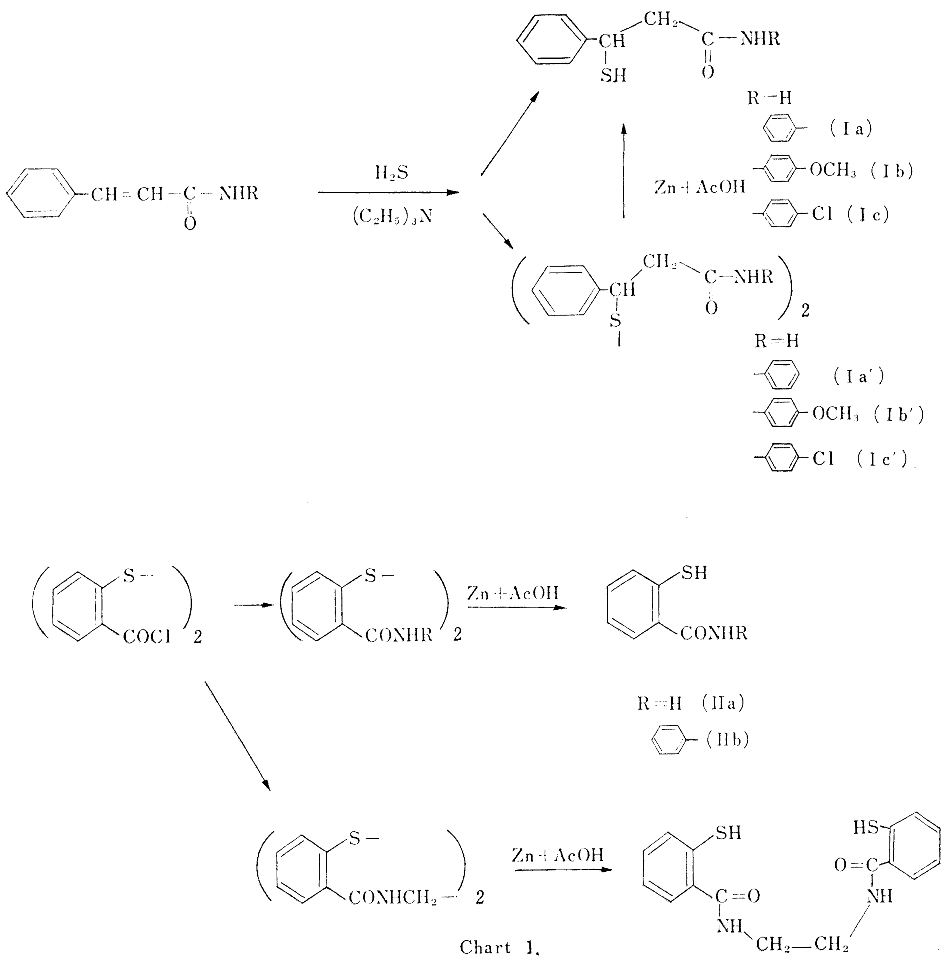


Chart 1.

chelating abilities of these mercapto-amides in connection with those of other ligands involving mercapto and carbonyl group will be discussed in detail in the later paper of this series.

The chelates obtained from (I) and (II) were soluble in chloroform and ethyl acetate, and relatively unstable. Except for palladium chelate, they were decomposed by dilute ammonium hydroxide solution. The reaction of N,N′-ethylenebis(*o*-mercaptobenzamide) was also tested by spot test. In this case, the coloration and precipitation were observed by many kinds of metal ions, in the solution of sodium carbonate, as shown in Table II. However, these colored substances or precipitates were not soluble in the most of organic solvents and did not have melting points or decomposition points. The recognizable limit of cobalt, nickel, copper, palladium and bismuth with these mercapto-amides were measured. As shown in Table III, they were relatively sensitive to palladium but not to other metals.

The structure and formation mechanism of copper, nickel and cobalt chelates of (I) and (II) were investigated.

1) Metal Chelates of (I).

The copper chelates of (I) were separated as yellow crystals, but they were not stable

TABLE I.

Ligand Metal ion	(Ia)	(Ⅱb)
Co^{2+}	—	green
Ni^{2+}	brown-red	orange
Cu^{2+}	pale yellow	yellow
Pd^{2+}	orange	orange
Ag^{+}	white$^{a)}$	yellow$^{a)}$
Cd^{2+}	—	white$^{a)}$
Pt^{4+}	pale yellow	pale yellow
Au^{3+}	〃	yellow-orange
Hg^{2+}	white$^{a)}$	white$^{a)}$
Pb^{2+}	yellow$^{a)}$	yellow$^{a)}$
Bi^{3+}	yellow	yellow
UO$_2$$^{2+}$	—	brown

a) Insoluble in the organic solvent

TABLE Ⅱ.

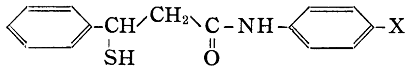
Ligand : N,N′-Ethylenebis(*o*-mercaptobenzamide)

Metal ion	Reaction		
	Acidic (AcOH)$^{a)}$	Neutral$^{a)}$	Alkaline (Na$_2$CO$_3$)
Fe^{3+}	—	green-yellow	yellow
Co^{2+}	—	—	green
Ni^{2+}	—	green	brown
Cu^{2+}	—	grey	grey
Pd^{2+}	—	orange	red
Ag^{+}	—	—	yellow
Cd^{2+}	—	—	white
Sn^{2+}	yellow	—	—
Pt^{4+}	—	pale yellow	—
Au^{3+}	—	—	brown
Hg^{2+}	—	—	white
Tl^{+}	—	—	yellow
Pb^{2+}	—	—	〃
Bi^{3+}	—	pale yellow	〃
UO$_2$$^{2+}$	—	yellow	〃

a) 1% Dioxane solution of the ligand was used

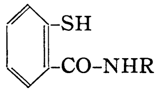
TABLE Ⅲ.

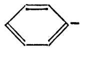
Ligand :



X	Ni	Cu	Pd	Bi
H	5	15	1	5
-Cl	5	15	1	5
-OCH$_3$	3	15	1	3

Ligand :



R	Ni	Cu	Pd	Bi	Co
H	5$^{a)}$	1	0.25	1$^{a)}$	15$^{a)}$
	3	1	0.25	0.5	1

Recognizable limit : γ/0.05 cc.

a) Measured in Na$_2$CO$_3$ solution. Others were measured in neutral solution.

enough to be completely purified. However, their formations were confirmed by their infrared absorption spectra as shown in Table IV. This chelate formation is considered to proceed similarly to the case of β-mercaptoketones reported in Part IV.[4] Namely, cupric ion is reduced to cuprous ion by the ligand and copper-(I) chelate precipitates. Actually, disulfide was obtained on the chelate formation.

The nickel chelate of β-mercapto-*p*-hydrocinnamanisidide (Ib) was separated as a red-brown crystalline powder, with a sharp decomposition point. On the contrary, the chelates of β-mercaptohydrocinnamanilide (Ia) and β-mercapto-4′-chlorohydrocinnamanilide (Ic) could not be obtained in pure state, because of extremely poor yield. This difference is considered to be due to the effect of the substituent such as chloro and methoxy on the chelate formation. The ratio of the ligand to nickel is 2:1.

2) Metal Chelates of (II).

(IIa) is unstable and easily oxidized in the air, so that the chelates of (IIa) could not be separated, although (IIa) showed the color reaction with many kinds of metal ions, as shown in Table I. The copper chelate of (IIb) was separated as a pale yellow crystalline powder, which was soluble in chloroform and had a sharp decomposition point. The ratio of the ligand to copper is 1:1. The chelate formation is considered to proceed as in the case of (I) and also β-mercaptoketones.[4] The nickel chelate of (IIb) was separated as an orange crystalline powder, which was soluble in chloroform and had a sharp decomposition point. The ratio of the ligand to nickel is 2:1. The cobalt chelate of (IIb) was separated as a green crystalline powder, which had a sharp melting point, however this green chelate changed to an insoluble substance during recrystallization from chloroform and could not be completely purified.

Absorption spectra in the visible and ultraviolet region of (Ib) and its nickel chelate are shown in Fig. 1, and those of (IIb) and its copper, nickel and cobalt chelate are shown in Fig. 2. In an attempt to investigate the structure of the chelate of mercapto-amides, the infrared absorption spectra of the ligands and the metal chelates were measured in the chloroform. As shown in Table IV, on the chelate formation, the SH stretching band disappeared and considerable shift of amide I band, which is concerned to C-O stretching vibration,[13] was observed. On the contrary, no appreciable shift was observed on amide II and amide III bands, in which vibration of nitrogen atom is involved.[13] In the chelates of (I) and (II), two forms, namely S-O chelating form (A) and S-N chelating form (B) are possibly considered as shown in Chart 2. Judging from the above mentioned observations in infrared absorption spectra, it is confirmed that the chelate formation occurs by the mercapto group with oxygen not with nitrogen of amide group. Therefore, the form (A), namely S-O chelating form is applicable for the chelates of mercapto-amides.

TABLE IV.

Substance	Frequency (cm^{-1})			
	SH	Amide I	Amide II	Amide III
Ligand (Ib)	2590	1675	1520	1250
Cu chelate of (Ib)[a]	—	1660	1520	1250
Ni chelate of (Ib)	—	1660	1515	1250
Ligand (IIb)	2570	1640	1530	1330
Cu chelate of (IIb)	—	1620	1533	1330
Ni chelate of (IIb)	—	1620	1530	1335
Co chelate of (IIb)[a]	—	1615	1530	1330

a) These chelates were separated in almost pure state, but could not be completely purified.

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13) T. Miyazawa, T. Shimanouchi: J. Chem. Phys., **24**, 408 (1956).

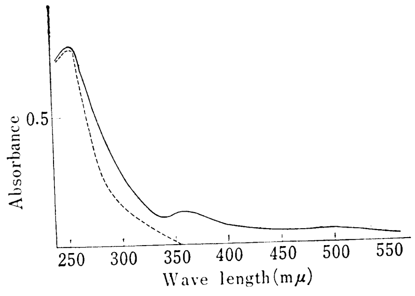

Fig. 1.

········ Ligand (Ib) 5×10^{-5} mole (in $CHCl_3$)

——— Nickel Chelate of (Ib) 2.5×10^{-5} mole (in $CHCl_3$)

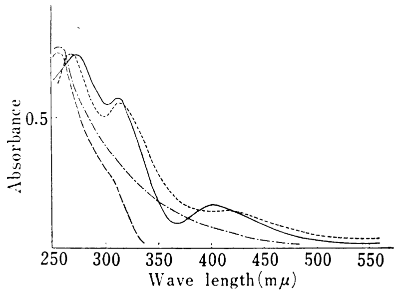

Fig. 2.

------ Ligand (Ⅱb) 5×10^{-5} mole

-·-·- Copper Chelate of (Ⅱb) [a]

——— Nickel Chelate of (Ⅱb) 2.5×10^{-5} mole

········ Cobalt Chelate of (Ⅱb) [a] (in $CHCl_3$)

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

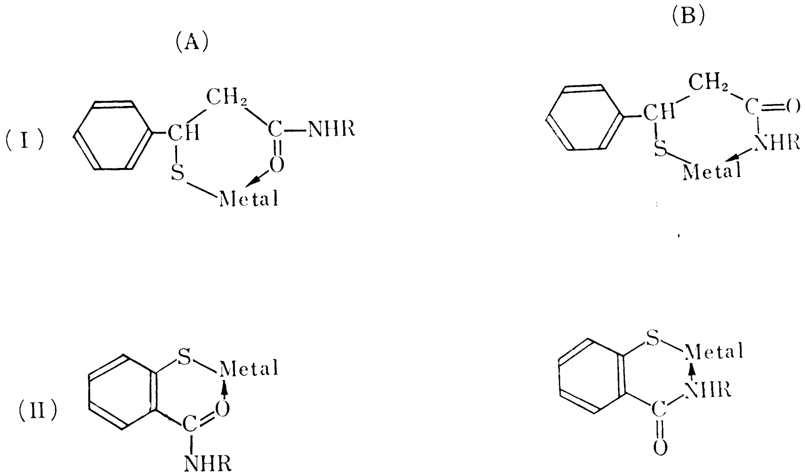

Chart 2.

Experimental

β-Mercaptohydrocinnamanilide (Ia) and β,β'-Dithiobishydrocinnamanilide (Ia')——To a solution of 3 g. of cinnamanilide and 3 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 10 cc., and the bottle was closed. After standing for 10 days at room temperature, the reaction mixture was washed with dil. HCl and H_2O and dried over Na_2SO_4. After the solvent was distilled off to almost dryness, 5 cc. of dehyd. Et_2O was added to the residue. 1 g. of (Ia') separated out as colorless needles, m.p. 182°. Rheinboldt test, negative. *Anal.* Calcd. for $C_{30}H_{28}O_2N_2S_2$: C, 70.30; H, 5.51; N, 5.47; S, 12.48. Found : C, 70.25; H, 5.50; N, 5.63; S, 12.33.

After (Ia') was collected, the residual Et_2O solution was extracted with 10% NaOH solution and the aqueous layer was acidified by dil. H_2SO_4. Traces of crystals of (Ia) separated out, m.p. 123°. Rheinboldt test, red. The mixed meltiong point with (Ia) obtained by the following experiment, did not show any depression.

Reduction of (Ia') to (Ia)——A mixture of 1 g. of (Ia'), 1 g. of Zn powder and 40 cc. of AcOH was heated at 70° to 80° on a water bath with stirring. Precipitates separated out were collected and 30 cc. of dil. H_2SO_4 was added to them and extracted with Et_2O. After the Et_2O layer was washed with H_2O, Et_2O was distilled off. The residue was recrystallized from 50% EtOH to colorless needles, m.p. 124°. Yield, 0.5 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{15}H_{15}ONS$: C, 70.02; H, 5.88; N, 5.44; S, 12.44. Found: C, 70.07; H, 6.08; N, 5.28; S. 12.39.

β-Mercapto-*p*-hydrocinnamanisidide (Ib) and β,β′-Dithiobis(*p*-hydrocinnamanisidide) (Ib′)——To a solution of 11 g. of *p*-cinnamanisidide, 3 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, 15 cc. of H_2S was added as described above. After heating at 50° for 3 hr., the reaction mixture was allowed to stand for 7 days at room temperature under pressure. The reaction mixture was extracted with 10% NaOH solution and the NaOH layer was acidified with conc. HCl. Colorless plates that separated out were recrystallized from 70% EtOH to obtain 4 g. of (Ib), m.p. 105°. Rheinboldt test, red. *Anal.* Calcd. for $C_{16}H_{17}O_2NS$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.60; H, 6.03; N, 4.72.

After the extraction with 10% NaOH, the $CHCl_3$ layer was washed with H_2O, dil. HCl and H_2O successively, and dried over Na_2SO_4. After the solvent was distilled off to almost dryness, 20 cc. of Et_2O was added. Crystals of (Ib′) that separated out were recrystallized from EtOH to colorless needles, m.p. 184°. Yield, 7.5 g. Rheinboldt test, negative. *Anal.* Calcd. for $C_{32}H_{32}O_4N_2S_2$: C, 67.12; H, 5.63; N, 4.89. Found: C, 67.30; H, 5.88; N, 4.79.

Reduction of (Ib′) to (Ib)——A mixture of 7 g. of (Ib′), 7.5 g. of Zn powder and 250 cc. of AcOH was treated as described in the experiment of the reduction of (Ia′) to (Ia). 3.5 g. of (Ib) was obtained, m.p. 105°. Rheinboldt test, red. The mixed melting point with (Ib) obtained by the addition of H_2S, did not show any depression.

β-Mercapto-4′-chlorohydrocinnamanilide (Ic) and β,β′-Dithiobis(4′-chlorohydrocinnamanilide) (Ic′)——To a solution of 5 g. of 4′-chlorocinnamanilide, 2 g. of triethylamine in 100 cc. of dehyd. $CHCl_3$, 10 cc. of H_2S was added as described above. After heating at 50° for 3 hr., the reaction mixture was allowed to stand for 7 days, at room temperature, under pressure. Colorless crystals that separated out were collected and the solvent was distilled off. The residue and the crystals collected were mixed and extracted with 10% NaOH solution. The crystals of (Ic′), insoluble in NaOH solution were recrystallized from EtOH-H_2O to colorless needles, m.p. 217°. Yield, 4 g. Rheinboldt test, negative. *Anal.* Calcd. for $C_{30}H_{26}O_2N_2Cl_2S_2$: C, 61.96; H, 4.48; N, 4.89. Found: C, 61.72; H, 4.79; N, 5.17.

After separation of (Ic′), the NaOH solution was acidified with eonc. HCl. Colorless crystals that separated out were extracted with Et_2O and Et_2O was distilled off. The residual crystals of (Ic) were recrystallized from $CHCl_3$ to colorless plates, m.p. 145°. Yield, 1 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{15}H_{14}ONClS$: C, 61.75; H, 4.80; N, 4.80 Found: C, 61.46; H, 4.75; N, 4.71.

Reduction of (Ic′) to (Ic)——A mixture of 4 g. of (Ic′), 5 g. of Zn powder and 180 cc. of AcOH was treated as described in the experiment of the reduction of (Ia′) to (Ia). 1.8 g. of (Ic) was obtained, m.p. 145°. Rheinboldt test, red. The mixed melting point with (Ic) obtained by the addition of H_2S, did not show any depression.

N,N′-Ethylenebis(*o*-mercaptobenzamide)——To a solution of 3.8 g. of 2,2′-dithiodi(benzoyl chloride) in 50 cc. of dehyd. benzene 0.6 g. of ethylenediamine was gradually added. Crystals considered to be of 13,14-dihydrodibenzo[*b,j*][1,2,6,9]dithiodiazacyclododecine-11(12*H*), 16(15*H*) dione that separated out were collected. Yield, 1.5 g. A mixture of 1.5 g. of these crystals, 0.5 g. of Zn powder and 50 cc. of AcOH was refluxed for 5 hr. After AcOH was distilled off, 20 cc. of 5% NaOH solution was added to the residue. Insoluble substance was filtered off and the filtrate was acidified with dil. H_2SO_4. White precipitates that separated out were collected and dissolved in 5% NaOH solution and reprecipitated with dil. H_2SO_4, m.p. 189°. Yield, 0.5 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{16}H_{16}O_2N_2S_2$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.59; H, 5.05; N, 8.71.

Nickel Chelate of (Ib)——To a solution of 1.3 g. of $(AcO)_2Ni \cdot 4H_2O$ in 10 cc. of H_2O, 2.9 g. of (Ib) in 20 cc. of EtOH was added gradually. Red-brown crystalline powders that separated out were collected and washed with H_2O, EtOH and Et_2O, m.p. 132~134° (decomp.). Yield, 2.8 g. *Anal.* Calcd. for $C_{32}H_{32}O_4N_2NiS_2$: C, 61.07; H, 4.81; Ni, 9.33. Found: C, 60.87; H, 5.01; Ni, 9.11.

Copper Chelate of (IIb)——To a solution of 1.0 g. of $(AcO)_2Cu \cdot H_2O$ in 10 cc. of H_2O, 1.5 g. of (Ⅱb) in 20 cc. of EtOH was added gradually. The mixture was heated on a water bath for a few min. Pale yellow precipitates that seperated out were collected and dissolved in a mixture of Et_2O and $CHCl_3$. Insoluble substance was collected and confirmed to be 2,2′-dithiobisbenzanilide (m.p. 232°) by the mixed melting point with an authentic specimen. Yield, 0.7 g. The Et_2O-$CHCl_3$ solution was evaporated to obtain 1.0 g. of copper chelate. The copper chelate was dissolved in $CHCl_3$ and reprecipitated by Et_2O to pale yellow crystalline powders, m.p. 183~185°. *Anal.* Calcd. for $C_{13}H_{10}ONCuS$: C, 53.52; H, 3.43; Cu, 21.78. Found: C, 54.02; H, 3.66; Cu, 21.19.

Nickel Chelate of (IIb)——To a solution of 1.3 g. of $(AcO)_2Ni \cdot 4H_2O$ in 10 cc. of H_2O, 1.5 g. of (Ⅱb) in 20 cc. of EtOH was added gradually. Orange crystalline powders that separated out were collected and washed with H_2O, EtOH and Et_2O, m.p. 208~209° (decomp.). Yield, 1.4 g. *Anal.* Calcd. for $C_{26}H_{20}O_2N_2NiS_2$: C, 60.62; H, 3.89; Ni, 11.40. Found: C, 60.08; H, 4.19; Ni, 11.65.

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 the analytical data. The infrared spectra were determined by Mr. K. Machida and Mrs. I. Hamanaka of Kyoto University, to whom the authors are also grateful.

Summary

Amides of β-mercaptohydrocinnamic acid were prepared by the addition of hydrogen sulfide to amides of cinnamic acid. Amides of thiosalicylic acid were also prepared. Some of these mercapto-amides formed stable chelates with copper and nickel. Cobalt chelate was not stable enough to be separated in pure state. The ratio of the ligand to the metal was 1:1 in copper chelate and 2:1 in nickel chelate. It was found that these chelate compounds were S-O chelating compounds from the infrared spectra.

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91. **Masuo Akagi, Setsuzo Tejima, and Masanobu Haga :** Biochemical Studies on Thiosugars. III.[*1] Synthesis of 6-Deoxy-6-mercapto-D-glucose.

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Thiosugars in which the primary hydroxyl group of sugars is substituted by the thiol group are not found in nature, however, it seems to be sure that they heve some biological activities on the basis of the rationale of structural analogue. From this point of view, the present work deals with the synthesis and characterization of 6-deoxy-6-mercapto-D-glucose (I).

Previously in 1935, Ohle and Mertens[1)] reported that 6-deoxy-6-mercapto-D-glucose (I) was obtained as syrup by the addition of hydrogen sulfide to 1,2-O-isopropylidene-5,6-anhydro-α-D-glucofuranose (II) in barium hydroxide solution and acid-hydrolysis of isopropylidene group of 1,2-O-isopropylidene-6-mercapto-α-D-glucofuranose (III).

In addition, they described that (I) did not react with carbonyl reagents, such as phenylhydrazine, and that β-pentaacetate of (I) did not form corresponding glycosyl halide derivative.

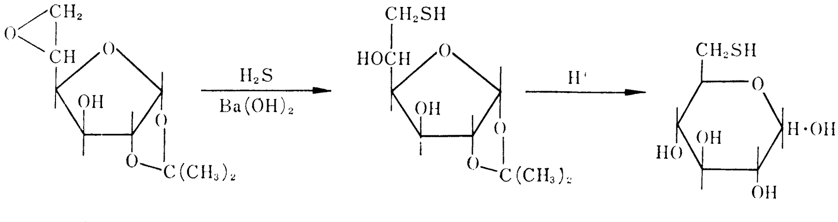

Chart 1.

[*1] Part II : This Bulletin, 9, 360 (1961).

[*2] Nishi 5-chome, Kita 12-jo, Sapporo, Hokkaido (赤木満洲雄, 手島節三, 羽賀正信).

1) H. Ohle, W. Mertens : Ber., 68, 2176 (1935).