CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 8 No. 4 April 1960

UDC 547.569-386 : 546.56

49. **Hisashi Tanaka and Akira Yokoyama:** Studies on the Sulfur-containing Chelating Agents. I. Syntheses of β-Mercaptoketones and their Copper Chelates. (1).

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Many chelating agents whose chelating ability is attributed to the mercapto group are known and not a few of them have been proposed as organic analytical reagents. Most of these compounds are nitrogen-containing compounds, in which the mercapto group and the nitrogen-containing group such as primary, secondary, or tertiary amino or imino group form a chelate ring with metal ions. However, only a few chelating compounds forming chelate rings by the combination of a mercapto group and an oxygen-containing group such as carbonyl or hydroxyl group have been found.

This work was conducted in order to synthesize new types of ligands and examine the relationship between their structure and chelating ability, and also their application as an analytical reagent.

As a first step in this study, compounds involving mercapto and carbonyl groups were chosen, as they were believed to show interesting behavior towards metal ions, in respect to specificity and selectivity.

As it was expected that β-mercaptoketones should be able to form six-membered chelate rings with metals, the synthesis of these compounds was taken up. The general

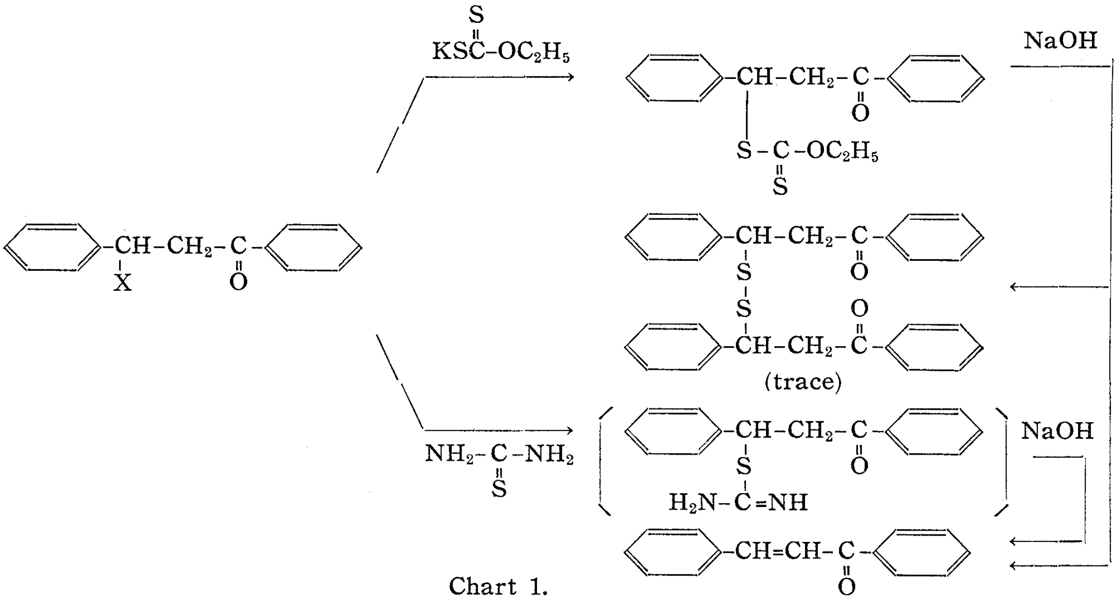

Chart 1.

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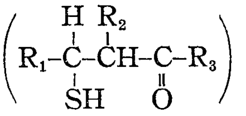
method of introducing a mercapto group, the reaction of potassium ethylxanthate, potassium or sodium hydrogensulfide, sodium hyposulfate, thiourea, or thioacetic acid to the corresponding halides, was considered to be useful for the syntheses of β-mercaptoketones. Asinger, *et al.*[1] synthesized many kinds of mercaptoketones using these methods. Attempt was therefore made with these methods to convert β-chloro-β-phenylpropiophenone, which was obtained by the reaction of hydrogen chloride with α-benzylideneacetophenone, into β-mercapto-β-phenylpropiophenone. Potassium ethylxanthate and thiourea were reacted with β-chloro-β-phenylpropiophenone and intermediate compounds obtained were treated with alkali under various conditions to form a thiol. However, a small amount of the corresponding disulfide was obtained only in the case of the reaction of potassium ethylxanthate, and α-benzylideneacetophenone was recovered and no thiol was obtained in the case of thiourea.

Judging from these results, β-mercapto-β-phenylpropiophenone must be very unstable towards alkali. The separation of this compound was unsuccessful on account of desulfurization caused by alkali. Addition of hydrogen sulfide to the double bond in α-benzylideneacetophenone was examined as a different method of introducing a mercapto group, which does not involve the treatment with alkali. As for the addition of hydrogen sulfide or thiol to the olefines, studies reported by Nicolet,[2] Fromm,[3] and Földi[4] are in the literature. They reported that thiols or alkyl- or arylthio compounds were obtained by the addition of hydrogen sulfide or thiols using small amounts of bases such as potassium hydroxide, piperidine, and triethylamine as a catalyst, and that the addition was found to occur in accordance with Markownikoff's rule.

As β-mercapto-β-phenylpropiophenone was obtained by the method reported by Fromm[3] by the addition of hydrogen sulfide under ice-cooling, this method was applied to many of the substituted α-benzylideneacetophenones. In these cases, however, addition could not be effected and the starting materials were recovered almost completely. A new method for the addition of hydrogen sulfide was applied to these substituted α-benzylideneacetophenones, by introducing hydrogen sulfide into the solution of these α-benzylideneacetophenones in various solvents, under chilling with dry ice-acetone and then heating the mixture under pressure. Using this method, some of the substituted β-mercapto-β-phenylpropiophenones  $\left(R_1-\underset{SH}{\overset{H}{C}}-\overset{R_2}{CH}-\underset{\overset{\|}{O}}{C}-R_3\right)$ were obtained. In some cases corresponding disulfides were also obtained. In the case of α-benzylideneacetophenone, β-mercapto-β-phenylpropiophenone, identical with the substance reported by Fromm,[3] was obtained besides the corresponding disulfide.

It was expected that these mercaptoketones were very unstable towards alkali and actually, desulfurization readily occurred even on treatment with dil. ammonium hydroxide. This was analogous to the fact that desulfurization readily occurred in β-alkylthio-β-phenylpropiophenone reported by Nicolet.[5]

Accordingly, alkali could not be used for the separation of these mercaptoketones, as usually used in the case of common thiols, and separation of thiol from the disulfide, which formed simultaneously, was very difficult. The thiols and the disulfides, listed in Table I, were separated and purified by repeated fractional recrystallization. All of these β-mercaptoketones showed an orange or pink color with nitrous acid (Reinboldt test[6]).

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[1] F. Asinger: Ann., **619**, 169(1957).
[2] B. H. Nicolet: J. Am. Chem. Soc., **57**, 1098(1935).
[3] E. Fromm: Ann., **394**, 301(1912).
[4] Z. Földi, J. Kollonisch: J. Chem. Soc., **1948**, 1683.
[5] B. H. Nicolet: J. Am. Chem. Soc., **53**, 3066(1931).
[6] H. Rheinboldt: Chem. Ber., **59**, 1311(1926).

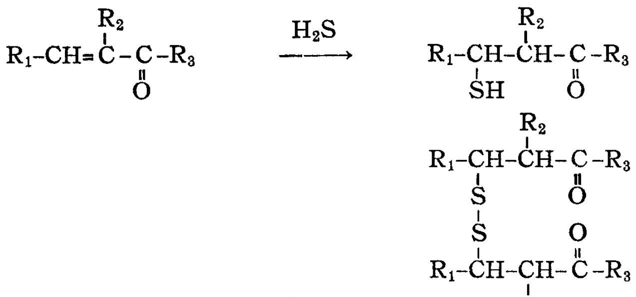


Chart 2.

Table I. Results of Addition of Hydrogen Sulfide to Benzylideneacetophenones

Starting Material		Product
α-Benzylideneacetophenone $R_1=C_6H_5-$, $R_2=H$, $R_3=C_6H_5-$	a	β-Mercapto-β-phenylpropiophenone (I).
	b	β-Mercapto-β-phenylpropiophenone (I), bis(1,3-diphenyl-3-oxopropyl) disulfide (II).
α-*p*-Methoxybenzylideneacetophenone $R_1=p-CH_3OC_6H_4-$, $R_2=H$, $R_3=C_6H_5-$	a	Starting material was recovered.
	b	β-Mercapto-β-(*p*-methoxyphenyl)propiophenone (III), bis-(1-*p*-methoxyphenyl-3-phenyl-3-oxopropyl) disulfide (IV).
α-Methyl-α-benzylideneacetophenone $R_1=C_6H_5-$, $R_2=CH_3-$, $R_3=C_6H_5-$	a	Starting material was recovered.
	b	α-Methyl-β-mercapto-β-phenylpropiophenone (V).
α-Phenyl-α-benzylideneacetophenone $R_1=C_6H_5-$, $R_2=C_6H_5-$, $R_3=C_6H_5-$	a	Starting material was recovered.
	b	α,β-Diphenyl-β-mercaptopropiophenone (VI).

a : Fromm's method. b : New method.

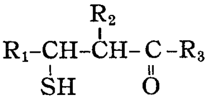
The reaction between these mercaptoketones and many kinds of metal ions was examined by spot tests and results are shown in Table II. The variety of the substituents, R_1, R_2, and R_3, did not show any effect on the color reaction with metal ions.

Table II. Reaction between β-Mercapto-β-phenylpropiophenone and Metal Ions

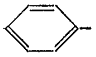
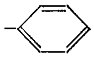
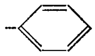
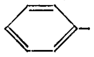
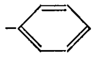
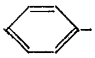
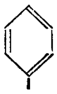
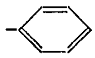
Metal ions	Reaction	
	Neutral	Acid (AcOH)
V^{5+}	yellow-brown ppt.	yellow-brown ppt.
Cu^{2+}	orange ppt.*	orange ppt.*
Pd^{2+}	brown ppt.*	brown ppt.*
Ag^{+}	brown ppt.	white ppt.
Pt^{4+}	brown ppt.*	brown ppt.*
Au^{3+}	〃	〃
Hg^{2+}	yellow-ppt.	yellow-ppt.
Pb^{2+}	〃	〃
Bi^{3+}	yellow ppt.*	yellow ppt.*

* : soluble in AcOEt or $CHCl_3$.

Table III. Copper Chelate of β-Mercaptoketones

Ligand 

$$R_1-\underset{SH}{CH}-\overset{R_2}{CH}-\underset{O}{\overset{\|}{C}}-R_3$$

R_1	R_2	R_3	Cu chelate m.p. (°C)	Recrystn. solvent	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	Cu	C	H	Cu
	H		111	EtOH+$CHCl_3$	$C_{15}H_{13}OSCu$	59.12	4.24	20.86	58.77	4.45	20.23
CH_3O- 	H		116	EtOH+$CHCl_3$	$C_{16}H_{15}O_2SCu$	57.38	4.48	19.08	57.44	4.43	19.08
	H_3C		69~70	EtOH	$C_{16}H_{15}OSCu$	60.47	4.41	20.00	60.16	4.66	20.09
			135	EtOH+$CHCl_3$	$C_{21}H_{17}OSCu$	66.40	4.46	16.58	66.94	4.69	16.55

It was found that these mercaptoketones precipitated yellow-orange substance with Cu^{2+}. The copper compound precipitated at first as an oily substance, became a crystalline powder with a sharp melting point after purification, and was readily soluble in most of the organic solvents, such as ether, chloroform, and ethyl acetate. Considering these properties, copper compounds could be regarded as a kind of chelate compound. The results of analysis indicated that the ratio of the ligand to copper was 1:1. Copper chelates obtained are presented in Table III.

Experimental

Reaction of β-Chloro-β-phenylpropiophenone with Potassium Ethylxanthate—To a solution of 6.1 g. of β-chloro-β-phenylpropiophenone in 40 cc. of dimethylformamide, a solution of 4 g. of K ethylxanthate in 10 cc. of dimethylformamide was added dropwise with stirring at room temperature. Stirring was continued for 10 hr. The reaction mixture was poured into 100 cc. of H_2O and extracted with Et_2O. A small amount of bis(1,3-diphenyl-3-oxopropyl) disulfide separated out and was recrystallized from $CHCl_3$-EtOH to colorless needles, m.p. 156°. *Anal.* Calcd. for $C_{30}H_{26}O_2S_2$: C, 74.67; H, 5.43. Found : C, 74.88; H, 5.60.

Ether layer was dried over Na_2SO_4, evaporated, 100 cc. of 10% NaOH was added to the residue, and heated in a water bath for 4 hr. After cool, the mixture was extracted with Et_2O which was dried over Na_2SO_4 and evaporated. The residue was identified as α-benzylideneacetophenone, m.p. 55°. Yield, 4.0 g. The mixed m.p. did not show any depression.

The aqueous layer was acidified with dil. HCl, by which a trace of S separated out and evolution of H_2S was observed.

Reaction of β-Chloro-β-phenylpropiophenone with Thiourea—A solution of 6.1 g. of β-chloro-β-phenylpropiophenone and 1.8 g. of thiourea dissolved in 100 cc. of EtOH was refluxed for 12 hr., 20 cc. of 10% NaOH was added, and again refluxed for 4 hr. After removing the solvent under reduced pressure, the reaction mixture was poured into 100 cc. of H_2O and extracted with Et_2O, which was dried over Na_2SO_4 and evaporated. About 5 g. of α-benzylideneacetophenone (m.p. 55°) was obtained. The mixed m.p. did not show any depression. The aqueous layer was acidified with dil. HCl, traces of S separated out, and evolution of H_2S was observed.

β-Mercapto-β-phenylpropiophenone (I) and Bis(1,3-diphenyl-3-oxopropyl) Disulfide (II)—i) Fromm's Method : Dry H_2S gas was passed into a solution of 7 g. of benzylideneacetophenone in dehyd. EtOH with stirring under ice-salt cooling. After H_2S was saturated, 0.5 cc. of 50% KOH was added. Colorless crystals began to separate out. H_2S gas was introduced continuously for 2 hr. with stirring. The product was collected and recrystallized from EtOH-$CHCl_3$ to colorless plates, m.p. 102~103°. Yield, 7 g. (β-mercapto-β-phenylpropiophenone). The data agreed with the result reported by Fromm.

ii) New Method : A solution of 10 g. of benzylideneacetophenone in 60 cc. of dehyd. Et_2O and 1 g. of triethylamine was placed in a pressurized bottle, dry H_2S gas was introduced, and liquefied under dry ice-acetone cooling at −70° to −80° until the increase of volume became 15~16 cc. The bottle was closed, allowed to stand over night, and the mixture was heated at 40~50° for 2 hr. Crystals of (II) separated out, which were collected and recrystallized from $CHCl_3$ to colorless needles, m.p. 156.5°. Yield, 1.0 g. Rheinboldt test, negative. *Anal.* Calcd. for $C_{30}H_{26}O_2S_2$: C, 74.67; H, 5.43; S, 13.21. Found : C, 74.31; H, 5.65; S, 13.58.

The filtrate was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from EtOH to colorless plates (I), m.p. 101°. Yield, 10 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{15}H_{14}OS$: C, 74.36; H, 5.83. Found : C, 74.10; H, 5.91.

β-Mercapto-β-(*p*-methoxyphenyl)propiophenone (III) and Bis(1-*p*-methoxyphenyl-3-phenyl-3-oxopropyl) Disulfide (IV)—To a mixture of 3 g. of α-*p*-methoxybenzylideneacetophenone and 3 g. of triethylamine in 120 cc. of dehyd. Et_2O, 10 cc. of H_2S was added as described above. After standing over night, the mixture was heated at 50° for 4 hr. under pressure. Crystals of (IV) sepapated out, which were collected and recrystallized from $CHCl_3$ to colorless needles, m.p. 125~126°. Yield, 0.5 g. Rheinboldt test, negative. *Anal.* Calcd. for $C_{32}H_{30}O_4S_2$: C, 70.83; H, 5.57. Found : C, 70.25; H, 5.39.

The filtrate was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. The oily residue was extracted with EtOH. On removal of EtOH, crude crystals of (III) were obtained and were recrystallized from EtOH to colorless plates, m.p. 59~60°. Yield, 0.5 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{16}H_{16}O_2S$: C, 70.57; H, 5.92. Found : C, 70.53; H, 6.04.

α-Methyl-β-mercapto-β-phenylpropiophenone (V)—To a mixture of 11.5 g. of α-methyl-α-benzylideneacetophenone and 3 g. of triethylamine in 50 cc. of dehyd. Et_2O, 10 cc. of H_2S was added, as described in the case of (I). The mixture was heated for 6 hr. at 40~50° under pressure. The reaction mixture was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. The residue was distilled under reduced pressure. b.p$_4$ 180°. Yield, 11 g. The distillate solidified after standing for several days. m.p. 29~30°. Rheinboldt test, red. *Anal.* Calcd. for $C_{16}H_{16}OS$: C, 74.98; H, 6.29. Found : C, 74.70; H, 6.24.

α,β-Diphenyl-β-mercaptopropiophenone (VI)—To a mixture of 3 g. of α-phenyl-α-benzylideneacetophenone and 0.5 g. of triethylamine in 50 cc. of dehyd. Et_2O, 7 cc. of H_2S was added as described in the case of (I) and the mixture was heated for 2 hr. at 40~60° under pressure. After cool, a trace of S that separated out was filtered off, the filtrate was washed with dil. HCl and H_2O, and evaporated. The residue was recrystallized from $CHCl_3$-EtOH to colorless plates, m.p. 126°. Yield, 0.5 g. Rheinboldt test, pink. *Anal.* Calcd. for $C_{21}H_{18}OS$: C, 79.22; H, 5.70. Found : C, 79.40; H, 5.76.

Preparation of Cu Complexes—EtOH solution of thiol and aqueous solution of equimolar $Cu(NO_3)_2$ or $Cu(AcO)_2$ were mixed, and warmed in a water bath with stirring for a few min. An orange-red viscous oil separated out and solidified while standing in the air. The solvent was decanted off and the crude complex was purified from a suitable solvent as shown in Table III. 50~60 mg. of Cu complex was obtained from 100 mg. of thiol.

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

Summary

β-Mercaptoketones were prepared as a new type of chelating agent in which the mercapto and keto groups take part in chelate formation. β-Mercapto-β-phenylpropiophenone was prepared by the addition of hydrogen sulfide to α-benzylideneacetophenone under pressure. This method was applied to the syntheses of β-mercapto-β-(*p*-methoxyphenyl)-, α-methyl-β-mercapto-β-phenyl-, and α,β-diphenyl-β-mercaptopropiophenones. In most cases, corresponding disulfides were also obtained as a result of the addition of hydrogen sulfide. These mercaptoketones formed orange-yellow chelates with copper and the ratio of ligand to copper was found to be 1:1.

(Received August 25, 1959)