The authors express their deep gratitude to Prof. C. Djerassi for his kind donation of authentic samples of samogenin diacetate and mexogenin. The authors are indebted to Dr. T. Okanishi and Mr. T. Hirata for collecting plant sources, to Mr. N. Maezono for his technical collaboration, to Mr. Y. Matsui for the measurement of infrared absorption spectra, and to the members of analytical section of this laboratory for microanalysis and for measurement of optical rotations.

Summary

Metagenin was derived to samogenin via metagenone or its diacetate by the Huang-Minlon reduction. The possibility of C-6 and C-12 ketone groups in metagenone was excluded from experimental result and thus 5β,25D-spirostane-2β,3β,x-triol (x=7 or 11) was assigned to metagenin.

Partial acetylation of metagenin was carried out by two methods and afforded two diacetates (2,3- and 2,x-) and two monoacetates (2- and x-). The structure of these acetates is discussed.

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168. **Hisashi Tanaka and Akira Yokoyama:** Studies on the Sulfur-containing Chelating Agents. III.[*1] Syntheses of β-Mercaptoketones and their Copper Chelates. (3).

(*Faculty of Pharmacy, Kyoto University*[*2])

In the previous papers,[*1,1)] it was reported that various kinds of β-mercaptoketones formed chelate compounds with copper. This paper deals with the preparation of β-mercaptoketones with a heterocyclic ring, in an attempt to investigate the influence of the heterocyclic ring to chelate formation. The method of preparation is similar to that described in the previous papers,[*1,1)] as shown in Chart 1, by the addition of hydrogen sulfide to corresponding α,β-unsaturated ketones. It was found that in most of the cases, mono- and disulfides were also produced besides the expected mercaptoketones as shown in Table I.

The separation of mercaptoketone from mono- and disulfides was carried out by fractional recrystallization, because mercaptoketone of this series is very unstable towards alkali, so that any kind of alkali could not be used for the separation. In the case of 1,3-di-2-thienyl-2-propen-1-one, bis(1,3-di-2-thienyl-3-oxopropyl) sulfide (VI) was obtained as colorless needles, and only traces of 1,3-di-2-thienyl-3-mercapto-1-propanone (V) were isolated. The yield of (V) was so poor that it could not be purified and analyzed. However, the formation of (V) was confirmed from the results of Rheinboldt test[2)] (red) and copper chelate formation. In the case of 1-(2-furyl)-3-phenyl-2-propen-1-one, besides 1-(2-furyl)-3-mercapto-3-phenyl-1-propanone, traces of needles (m.p. 152°), considered to be a disulfide, were isolated, although it could not be confirmed. In the case of 1,3-di-2-furyl-2-propen-1-one, when the reaction was carried out in ethanol, considerable amount

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[*1] Part II. This Bulletin, 8, 280(1960).
[*2] Yoshida, Sakyo-ku, Kyoto (田中 久, 横山 陽).
1) Part I. This Bulletin, 8, 275(1960).
2) H. Rheinboldt: Chem. Ber., **59**, 1311(1926).

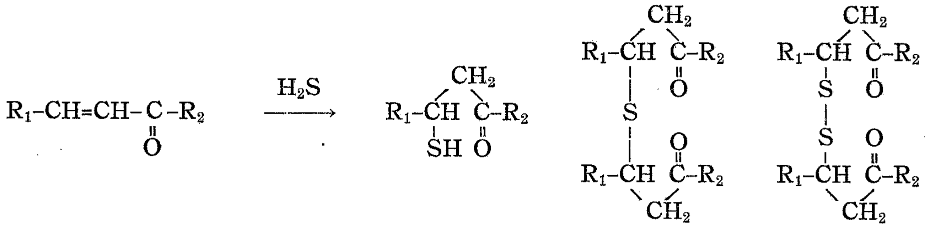
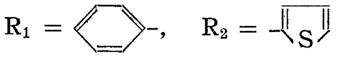
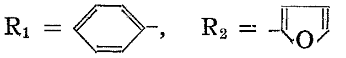


Chart 1.

Table I. Result of the Addition of Hydrogen Sulfide to α,β-Unsaturated Ketones

Starting Material	Product
3-(2-Thienyl)acrylophenone 	3-Mercapto-3-(2-thienyl)propiophenone (I)
1-(2-Thienyl)-3-phenyl-2-propen-1-one 	1-(2-Thienyl)-3-mercapto-3-phenyl-1-propanone (II) Bis[1-phenyl-3-(2-thienyl)-3-oxopropyl] sulfide (III) Bis[1-phenyl-3-(2-thienyl)-3-oxopropyl] disulfide (IV)
1,3-Di-2-thienyl-2-propen-1-one 	1,3-Di-2-thienyl-3-mercapto-1-propanone (V) Bis(1,3-di-2-thienyl-3-oxopropyl) sulfide (VI)
3-(2-Furyl)acrylophenone 	3-Mercapto-3-(2-furyl)propiophenone (VII) Bis[1-(2-furyl)-3-phenyl-3-oxopropyl] sulfide (VIII)
1-(2-Furyl)-3-phenyl)-2-penten-1-one 	1-(2-Furyl)-3-mercapto-3-phenyl-propanone (IX)
1,3-Di-2-furyl-2-penten-1-one 	Bis[1,3-di-2-furyl-3-oxopropyl] sulfide (X) Bis[1,3-di-2-furyl-3-oxopropyl] disulfide (XI)

of corresponding monosulfide was obtained and besides, the starting material was recovered. When a mixture of chloroform and ether was used as a solvent, corresponding disulfide was obtained quantitatively. Considering the yields of mono- and disulfides, and recovery of the starting material, expected mercaptoketone was not produced in this case. As 1,3-di(2-furyl)-3-mercapto-1-propanone was not obtained in this case, the reduction of the corresponding disulfide was carried out by zinc and sulfuric acid or acetic acid. In this connection, the reduction of other disulfides was also carried out, but, in all cases, the reduction was unsuccessful and mercaptoketone could not be obtained from the corresponding disulfide.

The preparation of β-mercaptoketones with pyridyl and quinolyl group was also planned. As nitrogen in pyridine and quinoline rings has strong electron-donating property, the combination of nitrogen and mercapto group would be interesting in chelate formation. In fact, it was reported that thioenol form of α-thiopicolinamides had strong chelating ability with various metal ions.[3,4] Considering the combination of mercapto group and nitrogen, the addition of hydrogen sulfide to 4-(2-pyridyl)-3-buten-1-one, 3-(2-pyridyl)acrylophenone, and 3-(2-quinolyl)acrylophenone was investigated. Ether, chloroform, and their mixture were used as a solvent, triethylamine was used as a catalyst, and reaction time and temperature were varied. In all cases, the starting material was recovered almost quantitatively. According to Brown, *et al.*[5] and Kharasch, *et al.*,[6] the

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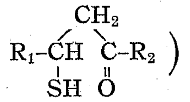
[3] K. V. Martin: J. Am. Chem. Soc., **80**, 233(1958).
[4] F. Lions, K. V. Martin: *Ibid.*, **80**, 1591(1958).
[5] R. Brown, W. E. Jones: J. Chem. Soc., **1951**, 3315.
[6] M. S. Kharasch, C. F. Fucks: J. Org. Chem., **13**, 97(1948).

addition of thiol to olefin is regarded to proceed in the following way. Thiol dissociates and then RS^- and H^+ attack the double bond. The addition of hydrogen sulfide to α,β-unsaturated ketone is considered to be the same type of reaction, namely, an ionic reaction, so that basicity or acidity of the reactant or of the reaction mixture would be a very important factor to the dissociation of hydrogen sulfide. The fact that the starting material was completely recovered in the case of 4-(2-pyridyl)-3-buten-1-one, 3-(2-pyridyl)-acrylophenone, and 3-(2-quinolyl)acrylophenone would be due to the strong basicity of these substances.

Copper chelates were prepared from β-mercaptoketones with thienyl and 2-furyl group by the method described in the previous papers*[1,1)] and they are listed in Table II. The ratio of ligand to copper was found to be 1:1 from the analytical data. The properties of these copper chelates were similar to those reported before and there seems to be no remarkable effect of a heterocyclic ring to the chelate formation with copper. In the spot tests with other metal ions, the results were simiar to those with mercaptoketones reported in Part I,[1)] and no remarkable effect of a heterocyclic ring was observed.

TABLE II. Copper Chelate of β-Mercaptoketone (Ligand:



$R_1\text{-}\underset{SH}{CH}\text{-}CH_2\text{-}\underset{O}{\overset{\|}{C}}\text{-}R_2$)

R_1	R_2	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	Cu	Found C	H	Cu
2-Thienyl	Phenyl	78~79	$C_{13}H_{11}OS_2Cu$	50.24	3.54	20.45	50.36	3.82	21.05
Phenyl	2-Thienyl	115	$C_{13}H_{11}OS_2Cu$	50.24	3.54	20.45	49.64	3.70	20.81
2-Thienyl	2-Thienyl	112	$C_{11}H_9OS_3Cu$	41.71	2.84	20.06	41.88	3.02	19.83
2-Furyl	Phenyl	100~102	$C_{13}H_{11}O_2SCu$	52.97	3.76	21.57	52.74	3.91	22.02
Phenyl	2-Furyl	142~143	$C_{13}H_{11}O_2SCu$	52.97	3.76	21.57	52.60	3.71	21.45

Experimental

3-Mercapto-3-(2-thienyl)propiophenone (I)—A solution of 3-(2-thienyl)acrylophenone (2.5 g.) and triethylamine (1g.) in dry Et_2O (50 cc.) was placed in a pressurized bottle and dry H_2S gas was introduced and liquefied under dry ice-Me_2CO chilling at −70° to −80° until the increase of volume became 9~10 cc. and the bottle was closed. After standing overnight, the mixture was heated at 40° for 3 hr. and allowed to stand overnight at room temperature under pressure. The reaction mixture was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. Yellowish oily residue was dissolved in hot 50% EtOH and crystals of (I) were obtained, after cooling, as colorless plates, m.p. 55~55.5°. Yield, 0.5 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{13}H_{12}OS_2$: C, 62.90; H, 4.87. Found : C, 63.18; H, 5.10.

1-(2-Thienyl)-3-mercapto-3-phenyl-1-propanone (II), Bis[1-phenyl-3-(2-thienyl)-3-oxopropyl] Sulfide (III), and Bis[1-phenyl-3-(2-thienyl)-3-oxopropyl] Disulfide (IV)—To a solution of 1-(2-thienyl)-3-phenyl-2-propen-1-one (5 g.) and triethylamine (2 g.) in dry Et_2O (80 cc.), dry H_2S (14 cc.) was added as described above. After standing overnight, the reaction mixture was heated at 40° to 50° for 3 hr. and allowed to stand for 4 days at room temperature under pressure. A mixture of (III) and (IV) separated out was collected and fractionally recrystallized from $CHCl_3$-EtOH. Crystals of (III) (1 g.) and a small amount of (IV) were obtained. (III) was recrystallized from EtOH to colorless needles, m.p. 136°, Yield, 1 g. *Anal.* Calcd. for $C_{26}H_{22}O_2S_3$: C, 67.52; H, 4.80; S, 20.77. Found : C, 67.39; H, 5.06; S, 20.59.

(IV) was recrystallized from $CHCl_3$-EtOH to colorless needles, m.p. 125°. Rheinboldt test, negative. *Anal.* Calcd. for $C_{26}H_{22}O_2S_4$: C, 63.15; H, 4.49; mol. wt., 494. Found : C, 63.09; H, 4.46; mol. wt. (Rast), 521.

Filtrate was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. An oily residue was extracted with hot EtOH and crude crystals of (II) were obtained after removal of EtOH. (II) was recrystallized from 50% EtOH to colorless plates, m.p. 47°. Yield, 1 g. Rheinboldt test, orange. *Anal.* Calcd. for $C_{13}H_{12}OS_2$: C, 62.90; H, 4.87; S, 25.81. Found : C, 62.86; H, 5.15; S, 26.12.

1,3-Di-2-thienyl-3-mercapto-1-propanone (V) and Bis(1,3-di-2-thienyl-3-oxopropyl) Sulfide (VI)—To a solution of 1,3-di-2-thienyl-2-propen-1-one (5 g.) and triethylamine (1 g.) in dry Et_2O (100 cc.), dry H_2S (10 cc.) was added as described above. The mixture was allowed to stand for a week at room temperature under pressure. Crystals of (Ⅵ) separated out were collected and recrystallized from $CHCl_3$-EtOH to colorless needles, m.p. 144°. Yield, 2 g. *Anal.* Calcd. for $C_{22}H_{18}O_2S_5$: C, 55.70; H, 3.80; S, 33.76. Found : C, 55.53; H, 3.97; S, 33.61.

Filtrate was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. An oily residue was extracted with hot 50% EtOH. After cooling, a trace of (V) separated out, m.p. 102°. Rheinboldt test, red.

3-Mercapto-3-(2-furyl)propiophenone (VII) and Bis[1-(2-furyl)-3-phenyl-3-oxopropyl] Sulfide (VIII)—To a solution of 3-(2-furyl)acrylophenone (10 g.) and triethylamine (2 g.) in dry Et_2O (100 cc.), dry H_2S (13 cc.) was added as described above. After heating at 40°~50° for 3 hr. the mixture was allowed to stand for 2 days. Crystals of (Ⅷ) that separated out were collected and recrystallized from $CHCl_3$-EtOH to colorless needles, m.p. 127°. Yield, 2 g. *Anal.* Calcd. for $C_{26}H_{22}O_4S$: C, 72.54; H, 5.15. Found : C, 72.43; H, 5.29.

Filtrate was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. An oily residue was distilled under a diminished pressure. A pale yellow oil was obtained and it solidified after standing for several days, b.p$_6$ 160~163°, m.p. 45° (from petr. ether). Yield, 4 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{13}H_{12}O_2S$: C, 67.23; H, 5.21. Found : C, 67.60; H, 5.47.

1-(2-Furyl)-3-mercapto-3-phenyl-1-propanone (IX)—To a solution of 1-(2-furyl)-3-phenyl-2-propen-1-one (2 g.) and triethylamine (1 g.) in dry Et_2O (70 cc.), dry H_2S was added as described above. The mixture was allowed to stand for 3 days at room temperature under pressure. Traces of needles (m.p. 152°) separated out were filtered. Filtrate was washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. Residue was recrystallized from petr. ether to colorless needles (Ⅸ), m.p. 53°. Yield, 1.5 g. Rheinboldt test, red. *Anal.* Calcd. for $C_{13}H_{12}O_2S$: C, 67.23; H, 5.21; S, 13.79. Found : C, 67.42; H, 5.41; S, 13.72.

Bis(1,3-di-2-furyl-3-oxopropyl) Sulfide (X) and Bis(1,3-di-2-furyl-3-oxopropyl) Disulfide (XI)—i) To a solution of 1,3-di-2-furyl-2-propen-1-one (5 g.) and triethylamine (2 g.) in dehyd. EtOH (60 cc.), dry H_2S (15 cc.) was added as described above. After heating at 70°~80° for 5 hr., the mixture was allowed to stand for 2 days under pressure. Crystals of (X) separated out were collected and recrystallized from $CHCl_3$-EtOH to colorless needles, m.p. 122°. Yield, 4.5 g. *Anal.* Calcd. for $C_{22}H_{18}O_6S$: C, 64.39; H, 4.42; S, 8.08. Found : C, 64.24; H, 4.67; S, 7.51.

Filtrate was evaporated and dissolved in Et_2O, washed with dil. HCl and H_2O, dried over Na_2SO_4, and evaporated. Residue was dissolved in benzene and passed through Al_2O_3 column and 1,3-di-2-furyl-2-propen-1-one (0.4 g.) was recovered.

ii) To a solution of 1,3-di-2-furyl-2-propen-1-one (5 g.) and triethylamine (2 g.) in dry $CHCl_3$-Et_2O (60 cc.), H_2S (10 cc.) was added as described above. The solvent was removed and the residue was dissolved in Et_2O. After cooling, crystals of (Ⅺ) that separated were collected and recrystallized from $CHCl_3$ to colorless needles, m.p. 142°. Yield, 4 g. Rheinboldt test, negative. *Anal.* Calcd. for $C_{22}H_{18}O_6S_2$: C, 59.73; H, 4.10; mol. wt., 442. Found : C, 60.22; H, 4.32; mol. wt. (Rast), 428.

4-(2-Pyridyl)-3-buten-2-one—A mixture of picolinaldehyde (8 g.), Me_2CO (15 cc.), and 1*N* KOH (15 cc.) was stirred for 12 hr. under ice-cooling and allowed to stand for 2 weeks at room temperature. Precipitates separated were collected, dissolved in $CHCl_3$, and passed through Al_2O_3 column. Crystals obtained were recrystallized from EtOH-Et_2O to yellow needles, m.p. 55°. Yield, 4 g. *Anal.* Calcd. for C_9H_9ON : C, 73.45; H, 6.10. Found : C, 72.89; H, 6.40.

4-(2-Quinolyl)-3-buten-2-one—To a solution of quinolinaldehyde (3.5 g.) and acetophenone (2.7 g.) in MeOH (60 cc.), 50% KOH (1 cc.) was added dropwise under ice-cooling with stirring. Stirring was continued for 5 hr. and the mixture was allowed to stand overnight at room temperature. Crystals that separated were collected and recrystallized from EtOH to pale yellow needles, m.p. 116.5°. Yield, 5 g. *Anal.* Calcd. for $C_{18}H_{13}ON$: C, 83.37; H, 5.05; N, 5.40. Found : C, 83.11; H, 5.30; N, 5.38.

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 Kyoto University for the analytical data.

Summary

The following β-mercaptoketones were prepared : 1-Phenyl-3-mercapto-3-(2-thienyl)-, 1-(2-thienyl)-3-mercapto-3-phenyl-, 1,3-di-2-thienyl-3-mercapto-, 1-phenyl-3-mercapto-3-(2-furyl)-, and 1-(2-furyl)-3-mercapto-3-phenyl-1-propanone were prepared by the addition of hydrogen sulfide to the corresponding α,β-unsaturated ketones. These mercaptoketones formed chelate compounds with copper and the ratio of ligand to copper was found to be 1:1.

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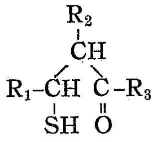
169. **Hisashi Tanaka and Akira Yokoyama** : Studies on the Sulfur-containing Chelating Agents. IV.[*1] Structure of Copper Chelate of β-Mercaptoketones.

(*Faculty of Pharmacy, Kyoto University*[*2])

In the previous papers,[1,2][*1] it was reported that β-mercaptoketones, represented by the general formula (A), formed a stable copper chelates.



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

$R_1 = R_3 =$ aryl

$R_2 =$ H, alkyl, or aryl

This paper deals with the structure of these copper chelates. The ratio of ligand to copper was expected to be one to one or two to one, and, from the result of microanalysis, the ratio was found to be one to one.

In the course of preparation of the copper chelate, after the copper chelate was separated, colorless crystals appeared from the residual solution. In the case of $R_1=R_3=$phenyl, $R_2=$H, namely, 3-mercapto-3-phenylpropiophenone, colorless needles which melted at 156° were obtained. This substance was identified with the corresponding disulfide, reported in Part I.[1] Moreover, when 3-mercapto-3-phenylpropiophenone was oxidized with hydrogen peroxide, the same substance was also obtained. Molecular weight was measured and the value found agreed with the calculated value for the disulfide. Accordingly, formation of a disulfide with the chelate formation was confirmed.

As a result of above-mentioned experiments, formation of copper chelate was considered to proceed according to Chart 1, namely, Cu^{2+} was reduced to Cu^{+} by the mercaptoketone and the mercaptoketone was oxidized to disulfide simultaneously, Cu^{+} forming a chelate with the mercaptoketone.[3] About 1/2 mole of copper chelate was obtained from 1 mole of mercaptoketone, as shown in Table Ⅲ in the Experimental part. In

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[*1] Part Ⅲ : This Bulletin, 8, 1008(1960).

[*2] Sakyo-ku, Kyoto (田中 久, 横山 陽).

1) Part Ⅰ : This Bulletin, 8, 275(1960).

2) Part Ⅱ : *Ibid.*, 8, 280(1960).

3) H. Tanaka, A. Yokoyama : Paper read at the 12th Annual Meeting of the Pharmaceutical Society of Japan, April, 1959.