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Studies on the Sulfur-containing Chelating Agents. XLVI.¹⁾ Hydrolysis of Thio- β -diketones and Related Amides in Acetonitrile-Water Mixture

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Thioacetoacetanilide(I) was prepared through β,β -dimercaptobutyranilide by addition of H_2S to acetoacetanilide. The acid dissociation constants (pK_a) of I and thiothenoyltrifluoroacetone(II) were determined spectrophotometrically to be 6.21 ± 0.03 and 4.38 ± 0.09 in 50% acetonitrile, respectively. The pseudo-first order rate constant for the hydrolyses of I and II were $(1.55 \pm 0.28) \times 10^{-2}$ and $(2.92 \pm 0.11) \times 10^{-4} \text{ min}^{-1}$ in 50% acetonitrile, respectively. They depended on the concentration of water, but not on pH over 1-7 and 1-5, respectively. The related compounds, thiobenzoylacetanilide, thiodibenzoylmethane and benzoylthioacetone were also investigated similarly for comparison. The former was hydrolyzed but the latter two were oxidized to form the disulfides. The introduction of phenyl group instead of methyl group into the β -position seems to make the β -thiol group resistant against the hydrolysis or the oxidation.

Keywords—thioacetoacetanilide; thiobenzoylacetanilide; thiodibenzoylmethane; thiothenoyltrifluoroacetone; benzoylthioacetone; hydrolysis of thio- β -diketone

The metal complex formation has been studied extensively on various thio- β -diketones³⁾ and a few of them have been applied as analytical reagent in recent years.^{1,4)} We have extended the similar studies to related amides.⁵⁾

The investigation on the behavior of these chelating agents in solution may be necessary to consider their wide applications as the analytical reagents, because their complicated behavior in solution has been suggested in the survey on the spectral change of the chelating agents with time. We have found that either the hydrolysis or the oxidation occurs preferentially in these chelating agents and reported on the behavior of them in various organic solvents-water mixtures.⁶⁾

The present paper deals with the preparation of thioacetoacetanilide (N-phenyl- β -mercaptoacetoacetamide, Chart 1) (I), and the kinetic study of the hydrolyses of I and thiothenoyltrifluoroacetone (II) in the acetonitrile-water mixture. The related compounds such as thiobenzoylacetanilide (N-phenyl- β -mercaptocinnamamide) (III), thiodibenzoylmethane (IV) and benzoylthioacetone (V) were also studied for comparison. We consider that the

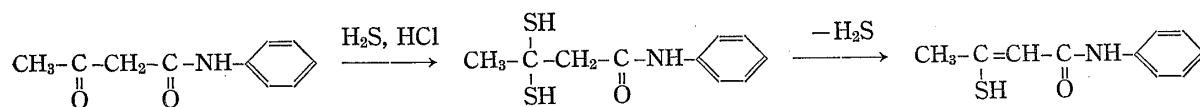


Chart 1

- 1) Part XLV: N. Nakanishi, A. Yokoyama, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **23**, 1684 (1975).
- 2) Location: *Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*
- 3) M. Cox and J. Darken, *Coordination Chem. Rev.*, **7**, 29 (1971); S.E. Livingstone, *ibid.*, **7**, 59 (1971).
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investigation on the solution of appropriate organic solvent-water mixture may be more advantageous for this study than that on aqueous solution, because some of the chelating agents are not readily soluble in water, and the effect of water on the hydrolysis can be detected.

Experimental

Materials— β,β -Dimercaptobutyranilide(VI): A solution of 10 g of acetoacetanilide in 150 ml of abs. EtOH was saturated with dry HCl gas at -5° and placed in a 150 ml pressure-resistant bottle. Dry H_2S was introduced to the solution and liquefied under dry ice-acetone cooling at -70° until the increase of volume became about 15 ml. The bottle was closed and allowed to stand at room temperature until the reaction mixture became reddish brown. The EtOH was evaporated off and the crude product was recrystallized from abs. EtOH to give yellow needles (9.5 g), mp $101-103^\circ$. *Anal.* Calcd. for $C_{10}H_{13}ONS_2$: C, 52.83; H, 5.76; N, 6.16; S, 28.21. Found: C, 53.13; H, 5.76; N, 6.29; S, 27.76. NMR (in $CDCl_3$) δ : 6.66 (2H, C(SH)SH), 7.00 (2H, $-CH_2-$), 1.95 (3H, CH_3). IR ν_{max}^{Nujol} cm^{-1} : 2560 (SH, w).

Thioacetoacetanilide(I): In a 500 ml flask, 150 ml of a saturated aqueous solution of $NaHCO_3$ was added to a solution of 5 g of VI in 100 ml abs. EtOH with stirring. After the evolution of H_2S had ceased, the mixture was acidified by adding 1N HCl under cooling and extracted with ether. The ether was removed under reduced pressure. The residue was recrystallized from benzene to give light yellow needles (2.5 g), mp $128-130^\circ$. *Anal.* Calcd. for $C_{10}H_{11}ONS$: C, 62.14; H, 5.75; N, 7.25; S, 16.59. Found: C, 62.27; H, 5.73; N, 7.33; S, 16.64. NMR (in $CDCl_3$) δ : 7.00 (H, SH), 5.85 (H, $=CH-$), 2.13 (3H, CH_3). IR ν_{max}^{Nujol} cm^{-1} : 2440 (SH, w), 1600 (C=C, s).

Thiothienyltrifluoroacetone(II)⁷⁾, thiobenzoylacetyl(III),⁸⁾ thiodibenzoylmethane(IV),⁹⁾ benzoylthioacetone(V),⁹⁾ the disulfides of IV(1,3,6,8-tetraphenyl-4,5-dithioocta-2,6-diene-1,8-dione)(VII)¹⁰⁾ and V(3,6-dimethyl-1,8-diphenyl-4,5-dithioocta-2,6-diene-1,8-dione)(VIII)¹⁰⁾ were prepared by the procedures described in the literatures.

Acetonitrile was purified by the procedure of Lewis, *et al.*¹¹⁾

Determination of Acid Dissociation Constant—The acid dissociation constants (pK_a) of I and II were determined spectrophotometrically in a manner as described previously.¹²⁾ The absorbances were measured at 291 (I) and 347 nm (II) respectively immediately after the preparation of the solutions. The absorbances of the solutions were measured at appropriate time intervals to get the absorbance at zero time the extrapolation of the decrease of the absorbances with time.

Kinetic Measurements—The chelating agent in pure acetonitrile was pipetted into a 50 ml measuring flask in which buffer solution has been placed. The sample solution was transferred quickly to a stoppered quartz cell. The decomposition rates were determined at the absorbance at appropriate wavelength employing a Shimadzu spectrophotometer Model QV-50, the cell chamber of which was kept at 30° by means of a thermostating water jacket.

Nuclear Magnetic Resonance(NMR) and Infrared(IR) Spectra Measurements—NMR and IR measurements were made at 60 MHz with a Varian Model A-60 spectrometer and a Hitachi grating IR spectrometer 215, respectively.

Results and Discussion

Determination of pK_a

The absorption maxima of the neutral molecule and the anion of I in 50% acetonitrile were observed at 291 and 327 nm, respectively. Those of II were observed at 362 and 347 nm, respectively. The values of pK_a of I and II were determined to be 6.21 ± 0.03 and 4.38 ± 0.09 , respectively.

Hydrolyses of I and II

No spectral change of I and II in pure acetonitrile was found during 24 hr, and the absorption spectra were not affected by bubbling oxygen. On the contrary, as soon as water was added in the acetonitrile solution, the spectral change occurred as shown in Fig. 1 and 2.

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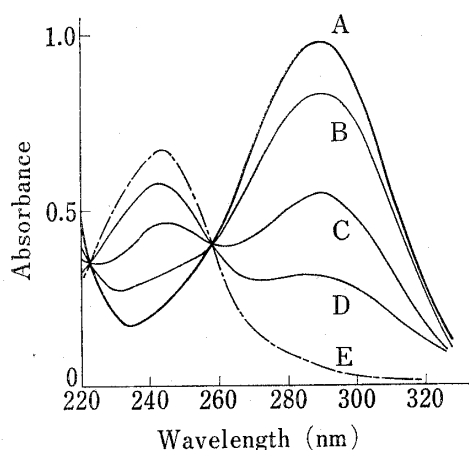


Fig. 1. Hydrolysis of Thioacetacetanilide (I) in 50% Acetonitrile-Water Mixture

I: $5 \times 10^{-5}M$, pH 1.5
 A: immediately after reaction
 B: 10 min
 C: 50 min
 D: 90 min
 E: acetoacetanilide, $5 \times 10^{-5}M$

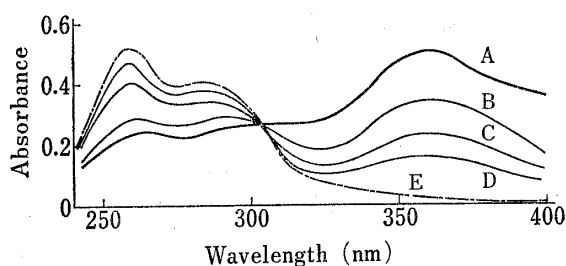


Fig. 2. Hydrolysis of Thiothenoyltrifluoroacetone (II) in 50% Acetonitrile-Water Mixture

II: $5 \times 10^{-5}M$, pH 1.5
 A: immediately after reaction
 B: 24 hr
 C: 48 hr
 D: 72 hr
 E: thenoyltrifluoroacetone, $5 \times 10^{-5}M$

The absorbance at 291 nm decreased continuously, while that near 244 nm increased in the case of I. Two isosbestic points were found at 223 and 258 nm. In the case of II, the absorbance at 362 nm decreased continuously, while that near 263 and 290 nm increased. An isosbestic point was found at 304 nm. The spectra of decomposition products of I and II were similar to those of the oxygen homologues, acetoacetanilide and thenoyltrifluoroacetone, respectively.

The NMR spectra of I and II in deuteroacetonitrile- D_2O mixture were measured. After adding D_2O to the deuteroacetonitrile solution of I, the intensities of the signals at 2.13 ($-CH_3$) and 5.85 ppm ($=CH-$) decreased gradually, while new signals appeared at 2.24 and 3.55 ppm, which were identical with those of CH_3 and CH_2 groups of acetoacetanilide, respectively. In the case of II, the intensity of the signal at 7.17 ppm ($=CH-$) decreased slowly, while a new signal appeared at 6.70 ppm, which was identical to that of thenoyltrifluoroacetone.

The final products formed from I and II reacted with Fe^{3+} to form purple and red complexes, respectively and they could be extracted into chloroform and ethyl acetate.

The above-mentioned results on the electronic spectra, NMR and the reactivities with Fe^{3+} show that both I and II were hydrolyzed to form the corresponding oxygen homologues.

Kinetics of the Hydrolysis

Since no spectral change of I and II in 50% acetonitrile- H_2O mixture at pH 9.0 occurred within first several hours after preparation, the contribution of the anion form of the chelating agent to the hydrolysis process is negligible. Therefore, the pseudo-first order reactions are shown in equations (1) and (2).

$$-\frac{d[RSH]}{dt} = k[RSH]_{\text{neutral}} \quad (1)$$

$$= k(1 + Ka[H]^{-1})^{-1}[RSH]_{\text{initial}} \quad (2)$$

In equations (1) and (2), k , RSH, H and the suffixes "neutral" and "initial" denote the pseudo-first order rate constant, chelating agent, hydrogen ion, neutral molecule of chelating agent and initial concentration, respectively. The data shown in Table I indicate that the rate constants are independent of both the concentration of hydrogen ion and the components of the buffer solutions within experimental errors under these conditions. It may be allowed

to assume that the hydrolysis rate depends on the concentration of water under these conditions, because the rate constant is independent of the concentration of the hydrogen ion. Thus, equation (2) is rewritten as equation (4), because the concentration of water is constant apparently.

$$-\frac{d[\text{RSH}]}{dt} = k'(1 + K_a[\text{H}^+]^{-1})^{-1}[\text{H}_2\text{O}]_{\text{initial}}^n[\text{RSH}]_{\text{initial}} \quad (3)$$

In equation (3), k' is equal to $k[\text{H}_2\text{O}]_{\text{initial}}^{-n}$. The results shown in Fig. 3 support the validity of equation (3) and the value of n is found to be 1.

The overall hydrolysis reaction is shown as equation (4).

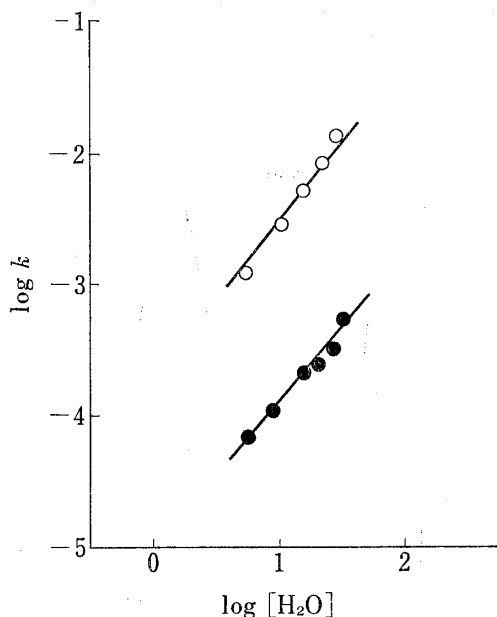
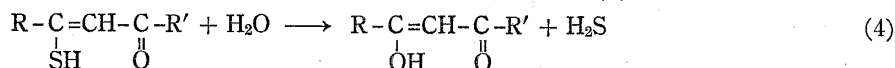


Fig. 3. Effect of the Concentration of Water on the Pseudo-First Order Rate Constant for the Hydrolysis of Thioacetoacetanilide (I) and Thiothenoyl-trifluoroacetone (II)

○: I
●: II
pH 1.50 ($\mu=0.3$)

TABLE I. Effect of pH on the Pseudo-First Order Rate Constants at 30° and $\mu=0.3$ with NaClO_4

I		II	
pH	$10^2 k$ (min^{-1})	pH	$10^4 k$ (min^{-1})
0.95 ^a	1.33	1.02 ^a	2.87
1.48 ^a	1.27	1.47 ^a	2.90
2.04 ^a	1.34	2.01 ^a	2.87
5.40 ^b	1.65	3.98 ^b	3.04
5.79 ^b	1.71	4.02 ^b	3.02
5.82 ^b	1.70	4.41 ^b	3.05
6.18 ^b	1.69	4.83 ^b	2.99
6.77 ^b	1.70	4.99 ^b	3.00

a) buffer; $\text{CH}_3\text{COONa}-\text{HCl}$

b) buffer; $\text{KH}_2\text{PO}_4-\text{NaHPO}_4$

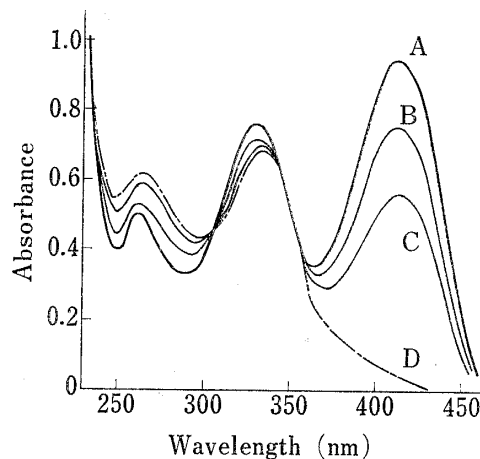


Fig. 4. Oxidation Reaction of Thiodibenzoylmethane (III) in 50% Acetonitrile-Water Mixture

III: $5 \times 10^{-5} \text{M}$
A: 4 min
B: 120 min
C: 210 min
D: 24 hr

TABLE II. Apparent Decomposition Rate Constants in 50% Acetonitrile-Water Mixture^a

Compound	$10^3 k$ (min^{-1})
Thioacetoacetanilide	12.7
Thiothenoyl-trifluoroacetone	0.290
Thiobenzoylacetanilide	0.75
Thiodibenzoylmethane	0.78
Benzoylthioacetone	3.04

a) pH 1.48 ($\text{HCl}-\text{NaClO}_4$), $\mu=0.3$, 30°

The thion-enthion tautomer has been found in many thio- β -diketones and the related compounds.³⁾ The NMR spectra of I and II suggest that the tautomerism leans to enthion side.

The hydrolysis reaction is regarded as a reverse reaction to the formation of thio- β -diketones, in which gem-olthion type compound was suggested as an intermediate.³⁾ Further, the presences of gem-dithion type compound such as VI and hydrated thenoyltrifluoroacetone¹³⁾ which is a kind of gem-diol type compound suggest the presence of the gem-olthion type as an intermediate, although it was unsuccessful to verify its presence by means of NMR and UV.

Investigation on the Related Chelating Agents

On related compounds III, IV and V, the pseudo-first order rate constants of the decomposition in 50% acetonitrile were shown in Table II. III was hydrolyzed to form benzoyl-acetanilide and the rate constant was smaller than that of I. IV and V were found to be oxidized to form their disulfides (Fig. 4, 5 and 6). The decompositions of IV and V at the initial state obeyed first order kinetics and the half-lives were 892 and 228 min, respectively.

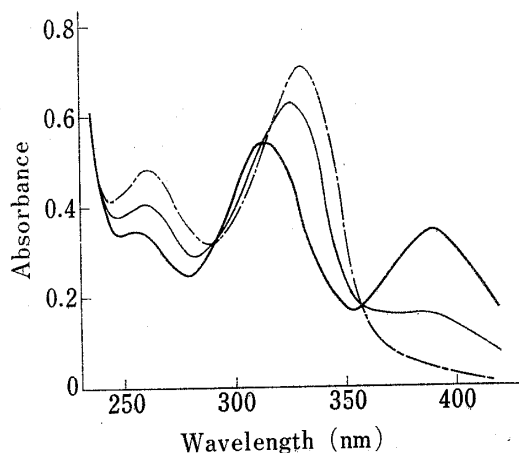


Fig. 5. Oxidation Reaction of Benzoylthioacetone (IV) in 50% Acetonitrile-Water Mixture

IV: $4 \times 10^{-5} M$
 —: 15 min
 - - - : 200 min
 ···· : 600 min

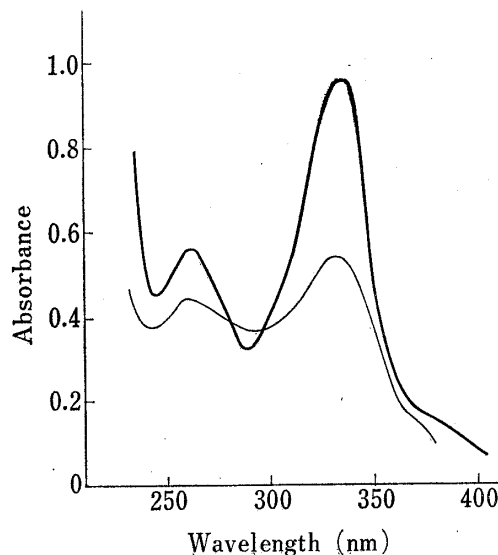


Fig. 6. Absorption Spectra of 1,3,6,8-Tetraphenyl-4,5-dithioocta-2,6-diene-1,8-dione (VII) and 3,6-Dimethyl-1,8-diphenyl-4,5-dithioocta-2,6-diene-1,8-dione (VIII) in 50% Acetonitrile-Water Mixture

—: VII, $2 \times 10^{-5} M$
 - - - : VIII, $2.5 \times 10^{-5} M$

In dioxane- H_2O mixture, I, II and III were also hydrolyzed, while IV and V were oxidized to form the disulfides, respectively.¹²⁾ However, acetonitrile was chosen instead of dioxane in this study, because dioxane was easily decomposed to form an oxidizing substance.

The factors which control the readiness of the hydrolysis and the oxidation in these chelating agents are unknown. However, it is apparent that the presence of phenyl group instead of methyl group at β -position may make the β -thiol group resistant against the hydrolysis or the oxidation. Thiodibenzoylmethane (IV) has been recommended as the analytical reagent based on its stability.^{4b)}

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