[Chem. Pharm. Bull. 22(2) 267—274 (1974)]

UDC 547.496.1.04 : 543.422.6

Decomposition of Dithiocarbamates. VIII.[1] The Decomposition Mechanism of [(4-Amino-2-methyl-5-pyrimidinyl)methyl]-dithiocarbamic Acid and Related Compounds in Alkaline Solutions

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(Received March 26, 1973)

The decomposition of [(4-amino-2-methyl-5-pyrimidinyl)methyl]dithiocarbamic acid (I) in alkaline solution was kinetically studied. The entropy of activation was largely negative compared with that of the corresponding 4-deamino compound (VIII). This result indicates the decomposition pathway should be I→VI→IV (Chart 1). The decomposition of the esters of I showing bell-shaped rate-pH profiles also follows a pathway similar to the above.

It has long been known that [(4-amino-2-methyl-5-pyrimidinyl)methyl]dithiocarbamic acid (I) and its esters (II and III) decompose to 3,4-dihydro-7-methylpyrimido[4,5-*d*]pyrimidine-2-(1H)-thione (IV) in alkaline solutions.[3] The elimination of the decomposition by a conventional method is strongly required, since they are key synthetic intermediates in the thiamine production by so-called "SB_1" method.[4] For the purpose, we attempted to study the mechanism of the decomposition as a part of this series.

Two pathways can be considered for the decomposition of I as shown in Chart 1. One involves an isothiocyanate intermediate V (Route A) and the other does not (Route B). Route A would be a probable one, since the reaction pathway of 1,3-disubstituted thiourea formation from N-monosubstituted dithiocarbamic acid and an appropriate amine has been established to proceed *via* isothiocyanate as an intermediate.[5] For the case of I and its esters, however, the 4-amino group on pyrimidine nucleus situates at a favorable position to react directly with the thiocarbonyl group of the dithiocarbamic acid moiety.

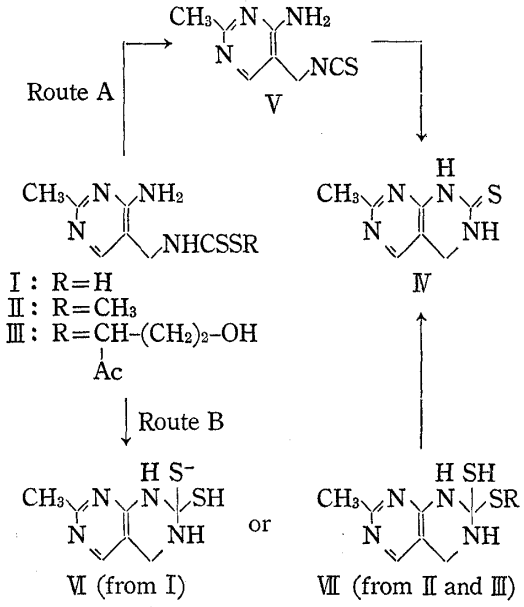
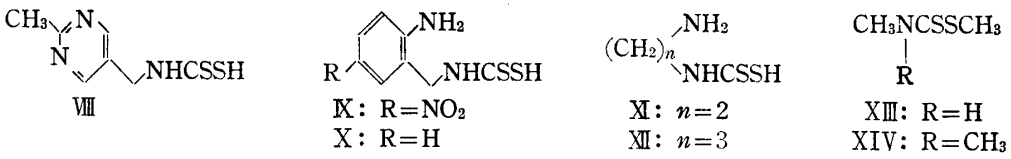


Chart 1

1) *a*) Part VII: F. Takami, K. Tokuyama, S. Wakahara, and T. Maeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1311 (1973); *b*) Pyrimidines. Part XVI, for Part XV: See Ref. 1*a*)
2) Location: *Fukushima-ku, Osaka, 553, Japan.*
3) *a*) K. Sumi, *Yakugaku Zasshi*, **66A**, 62 (1946); M. Tomita, S. Uyeo, H. Inoue, H. Sakurai, and S. Moriguchi, *ibid.*, **68**, 151, 154 (1948); T. Matsukawa and T. Iwatsu, *ibid.*, **72**, 1203 (1952); S. K. Chatterji and N. Anand, *J. Sci. Industr. Res.*, **18B**, 272 (1959); *b*) T. Iwatsu, *Yakugaku Zasshi*, **72**, 358, 362 (1952); *c*) T. Matsukawa and T. Iwatsu, *ibid.*, **71**, 455, 720 (1951); T. Iwatsu, *ibid.*, **72**, 354 (1952).
4) T. Matsukawa and T. Iwatsu, *Yakugaku Zasshi*, **70**, 28 (1950); T. Matsukawa and S. Yuruki, "Bitamin No Shinpo (Advances in Vitaminology)," Vol. 1, ed. by Bitamin Gakkai, Kyoto, 1959, p. 1.
5) D.C. Schroeder, *Chem. Rev.*, **55**, 181 (1955).

We can postulate Route B containing a tetrahedral intermediate (VI or VII); the existence of such an intermediate is commonly accepted for the aminolysis of carbonic esters.[6] The mechanism should be probable especially for II and III.

In order to decide either of the mechanisms predominant, we investigated the decomposition kinetically using compounds depicted in Chart 2.



Ⅷ

Ⅸ: R=NO2
X: R=H

Ⅺ: n=2
Ⅻ: n=3

XIII: R=H
XIV: R=CH3

Chart 2

Result and Discussion

i) Decomposition of I

The rates of the decomposition of I were spectrophotometrically measured by following the increase of IV; the intensity of the band due to IV at 330 nm increases with the expense of that due to the anion form of I (Ia) at 253 and 285 nm[7] in 0.1N NaOH (see Fig. 1). The pseudo first-order rate constants observed in various alkaline solutions are shown in Table I.

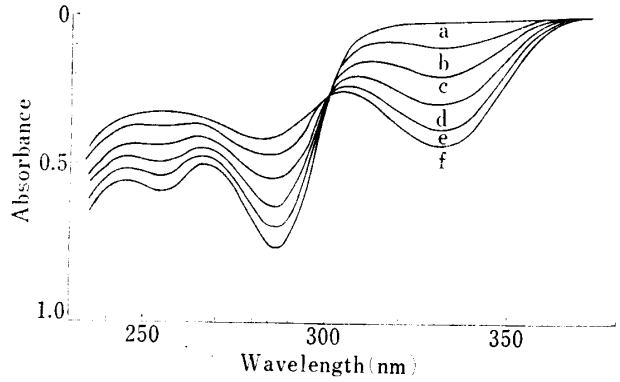


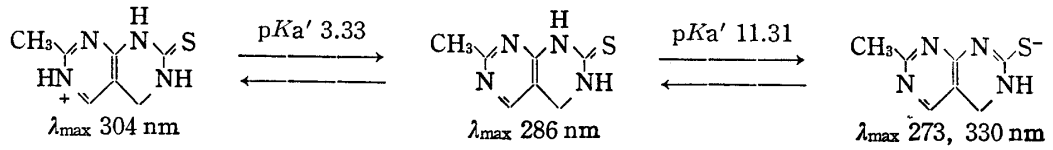
Fig. 1. Changes in UV Spectra of the Decomposition, I→IV, in 0.1N NaOH Solution at 70°

A Perkin-Elmer, 202, Ultraviolet-Visible Spectrophotometer was used; a) spectrum after 1 min, b) spectrum after 50 min, c) spectrum after 113 min, d) spectrum after 204 min, e) spectrum after 310 min, f) spectrum after 410 min.

Table I. Observed First-order Rate Constants (k_{obs}) for the Decomposition, I→IV

$[OH^-]$, N	Reaction temp., °C	$k_{obs} \times 10^3$, min^{-1}
1.0	80.0	7.7_6
1.0×10^{-1}	80.0	8.1_0
	70.0	3.4_3
	60.0	1.3_2
1.0×10^{-2}	80.0	7.8_2
1.0×10^{-3}	80.0	7.7_4

The rate was independent on $[OH^-]$. The presence of an isosbestic point indicated one-to-one transformation between I and IV. The absorption maxima and the isosbestic point altered their positions with the basicity changes of the reaction media due to the dissociation of IV as shown in Chart 3. The spectral feature showed that possible intermediates V and VI



λ_{max} 304 nm

λ_{max} 286 nm

λ_{max} 273, 330 nm

Dissociation of IV

Chart 3

6) A.L.J. Beckwith, "The Chemistry of Amides," ed. by J. Zabicky, Interscience, New York, 1970, p. 96.
7) F. Takami, K. Tokuyama, S. Wakahara, and T. Maeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 329 (1973).

could exist only in a limited extent. The kinetic data on the decomposition of other compounds (IX—XII), having a neighboring amino group to the dithiocarbamic acid moiety, were similarly obtained and are summarized in Table II.

Comparison of the rates of the decompositions of I, IX and X which have a similar steric arrangement indicates the preference of Route B over Route A. The rates increase in the order of X>IX>I. This order must reflect the electronic effect of the substituents on the nitrogen of the dithiocarbamic acid moiety. If they could decompose *via* Route A, an electron-attracting groups should increase the rate as observed for alkyl and aryldithiocarbamic acids.[1] On the other hand, when the decomposition occurs *via* Route B, the increase of electron density of arylamino-nitrogen should facilitate the nucleophilic attack of the nitrogen to thiocarbonyl carbon.

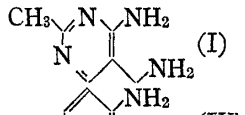
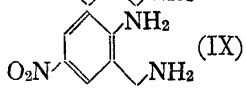
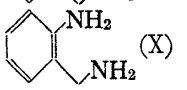
The order of electron density of amino groups is measured by their pKa values;[7] the values of benzyl- and arylamino groups of the starting amines, from which I, IX and X are derivable, should be used for the purpose. These of benzylamines correlate with Route A and of arylamines with Route B. Table III predicts the order of decomposition rate, I>IX>X for Route A and X>IX>I for Route B. Thus, Route A was excluded.

Table II. Observed First-order Rate Constants (k_{obs}) for the Decomposition of VIII—XII[a]

Compound	Reaction temp., °C	k_{obs}, min^{-1}
VIII	60.0	$6.4_1\times10^{-4}$
	70.0	$2.4_5\times10^{-3}$
	80.0	$7.5_1\times10^{-3}$
IX	60.0	$2.7_0\times10^{-3}$
	70.0	$6.2_7\times10^{-3}$
	80.0	$1.2_8\times10^{-2}$
X	25.0	[b]
XI	60.0	$1.7_1\times10^{-3}$
	70.0	$4.6_9\times10^{-3}$
	80.0	$1.1_0\times10^{-2}$
XII	60.0	$2.3_1\times10^{-3}$
	70.0	$5.5_1\times10^{-3}$
	80.0	$1.1_7\times10^{-2}$

a) in 0.1N NaOH solutions
b) The reaction was completed within 1 hr.

Table III. The pK'a Values of Parent Amines of I, IX, and X

Compound[a]	pK'a values	
	Ar-CH_2NH_2	Ar-NH_2
 (I)	8.2_4[b]	-3.9_0
 (IX)	8.3_0	-0.9_6
 (X)	9.4_5	2.4_0

a) The compounds in parentheses are the corresponding dithiocarbamic acids.
b) S. Mizukami and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **14**, 1321 (1966)

The large negative values of entropies of activation for the decompositions of I and IX—XII supported the above idea as compared with the small ones for those of the corresponding deamino compounds, VIII and benzyl-, ethyl- and *n*-propyl-dithiocarbamic acids (see Table IV). The loss of rotational freedom of I and IX—XII to form a tetrahedral inter-

Table IV. Kinetic Parameters

Compound	E, kcal/mole	$\Delta S^{\ddagger}_{353°K}$, eu	Deamino compound		
			Compound	E, kcal/mole	$\Delta S^{\ddagger}_{353°K}$, eu
I	21.2	−18.5	VIII	28.8	+2.8
IX	18.2	−26.1	—	—	—
X	—	—	Bz-DTC[a]	27.8	+0.6
XI	21.8	−16.3	Et-DTC[a]	26.1	−4.0
XII	19.0	−24.1	*n*-Pr-DTC[a]	25.7	−5.4

a) The values are reported in ref. 1; Bz-, Et- and *n*-Pr-DTC mean benzyl-, ethyl- and *n*-propyldithiocarbamic acids, respectively.

mediate such as VI should lead to lower entropies of activation.[8]

ii) Decomposition of II and III

The esters II and III are expected to decompose *via* a mechanism similar to that of I. No evidence was provided for this idea because of the lack of kinetic studies for the alkaline decomposition of N-monosubstituted dithiocarbamic acid esters.

First, the decomposition of simple dithiocarbamic acid esters, XIII and XIV was studied. Kinetic measurements of decomposition of XIII were carried out spectrophotometrically in 0.01—1N NaOH. The rates gradually decreased and deviated from the first-order law as reaction proceeded. The deviation was more clearly observed as with the increase of initial concentration of XIII, ($[XIII]_o$), and/or as with the decrease of $[OH^-]$. Similar results have been observed for the decomposition of methyldithiocarbamic acid into methylisothiocyanate (XV).[1] Thence, an analogous mechanism, containing a parasitic equilibrium between XIII and its conjugate base (XIIIa), shown in Chart 4 can be proposed as a highly probable one.

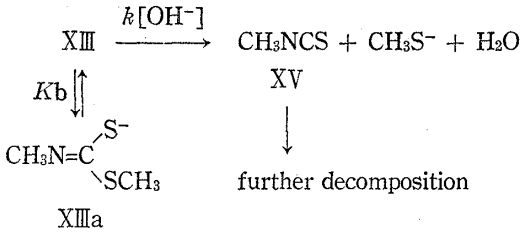


Chart 4

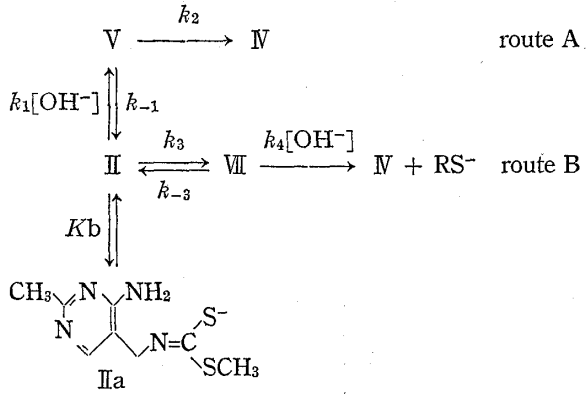


Chart 5

The observed rate constant (k_{obs}) of an infinitely diluted solution is expressed by eq. 1, because the reverse reaction of XV with CH_3S^- is negligible. The constants (k_{obs}) were estimated from the linear relationship between $[XIII]_o$ and half-lives, $\tau_{1/2}$.[1] The data obtained (see Table V) well agreed with eq. 1. The second-order rate constant (k) at 25° was

$$k_{obs} = \frac{Kb}{Kb+[OH^-]} \cdot k[OH^-] \qquad \text{(eq. 1)}$$

calculated to be 1.2×10 l·mole^{-1}·min^{-1} from the values, $\tau_{1/2}$=5.6 min in 1N HaOH solution (see Table V) and $Kb=10^{-2}$M. The latter was obtained spectrophotometrically.

The rate data of XIV gave a further support for the above mechanism. The decomposition of XIV must be the hydrolysis by $B_{Ac}2$ mechanism[9] because XIV is unable to yield isothiocyanate. The rate constant of XIV at 25° was calculated to be 9.5×10^{-5} l·mole^{-1}·min^{-1} by the extrapolation of the data listed in Table VI. The rate ratio of XIII to XIV to be *ca.* 10^5 indicates that the decomposition of XIII proceeds *via* a different pathway from the $B_{Ac}2$ mechanism where the decomposition should be supposed to occur at a rate similar to XIV.

The decomposition of II is expected to proceed *via* a tetrahedral intermediate (VII, R=CH_3) (Route B) in analogy with that of I. However, the possibility of Route A can be still present because there exists the decomposition pathway of dithiocarbamic acid esters into isothiocyanate as seen for XIII. Thus, the two pathways are supposed for the reaction;

8) L.T. Schlager and F.A. Long, "Advance in Physical Organic Chemistry," Vol. 1, ed. by V. Gold, Academic Press, London, 1963, p. 1.
9) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt, 1960, p. 314.

II→V and II→VII (R=CH_3) as shown in Chart 5, containing a parasitic equilibrium between II and its conjugate base (IIa).

The decomposition of II shows a behavior in ultraviolet (UV) spectral changes similar to that of I. The presence of an isosbestic point revealed that a limited extent of possible intermediates, V and VII can exist during the decomposition. The rate obeyed the first-order rate law. The rate expressions, eq. 2 for Route A and eq. 3 for Route B, were derived by assuming the steady-state approximation for V and VII, respectively.

$$\text{rate} = \frac{K\text{b}}{K\text{b}+[\text{OH}^-]} \cdot \frac{k_1 k_2[\text{OH}^-]}{k_{-1}[\text{RS}^-]+k_2}[\text{II}^{\text{total}}] \qquad \text{(eq. 2)}$$

$$\text{rate} = \frac{K\text{b}}{K\text{b}+[\text{OH}^-]} \cdot \frac{k_3 k_4[\text{OH}^-]}{k_{-3}+k_4[\text{OH}^-]}[\text{II}^{\text{total}}] \qquad \text{(eq. 3)}$$

Equation 2 should be simplified to eq. 4 under the observation that the decomposition rates obeyed the first-order law.

$$\text{rate} = \frac{K\text{b}}{K\text{b}+[\text{OH}^-]} \cdot k_1[\text{OH}^-][\text{II}^{\text{total}}] \qquad \text{(eq. 4)}$$

The log k-pH profile, which was obtained as a bell-shape, is accord with eq. 3, but not with eq. 4 (see Fig. 2). The theoretical curve agreed with the experimental points. The value of Kb defined in Chart 5 was approximately equal to that obtained kinetically.

A bell-shaped pH-rate profile was also obtained for the decomposition of III into IV (see Table VIII). The decomposition of III into IV should occur by the same mechanism with the case of II, but the rates were by far slow compared to that of II. This difference is caused by the presence of a further parasitic equilibrium of III between cyclic and acyclic forms.[10] As the mole fraction of the acyclic form, from which the decomposition occurs, has been known to be very small,[10] the rate is slower than that of II.

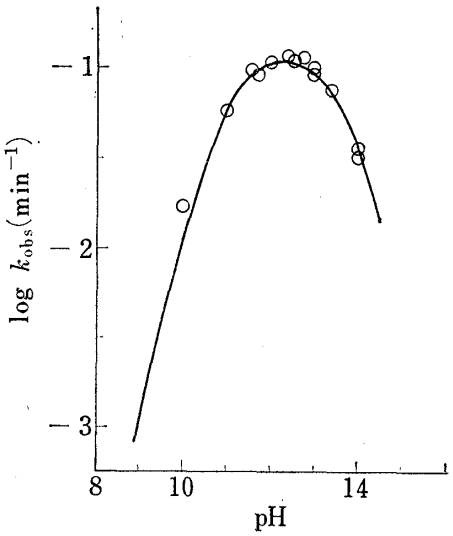


Fig. 2. Rate-pH Profiles for the Decomposition of II at 25°

Solid line was calculated from eq. 3 with $k_3=3.4\times10$ min^{-1}, $K\text{b}'=10^{-8}$M and $k_{-3}/k_4=2.6\times10^{-1}$ mole l^{-1}.

As described above, the decomposition of I proceeds *via* a tetrahedral intermediate, in which the participation of the neighboring amino group to dithiocarbamic acid moiety plays an important role. This mechanism is generally accepted for the compounds, containing a neighboring amino group to the dithiocarbamic acid moiety; the alkaline decomposition pathway of dithiocarbamic acids are changed by the presence or the absence of this kind of amino group.

Experimental[11]

Materials——[(4-Amino-2-methyl-5-pyrimidinyl)methyl]- (I),[12] 2-aminoethyl- (XI) and 3-aminopropyldithiocarbamic acids (XII),[13] 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-4-hydroxy-4-methyl-5-β-

10) S. Yoshida and M. Unoki, *Yakugaku Zasshi*, 73, 627 (1953); R.W. Lamon, W.J. Humphlett, and W.P. Blum, *J. Heterocyclic Chem.*, 4, 349 (1967).
11) All melting points were measured on a hot stage apparatus and uncorrected. Nuclear magnetic resonance (NMR) spectra were measured by Varian A60-A spectrometer, using TMS as an internal reference. Chemical shifts are expressed in δ values (s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet).
12) A. Takamizawa, Y. Sato, S. Nakajima, and T. Ishiba, *Shionogi Kenkyusho Nempo*, 12, 48 (1962).
13) C.F.H. Allen, C.D. Edens and J. Van Allan., "Org. Syntheses," Coll. Vol. 3, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 394.

hydroxyethylthiazolidine-2-thione (III)[3b] and methyl methyl- (XIII) and dimethyl-dithiocarbamates (XIV)[14] were prepared by usual methods. Among them, I, XI, and XII were obtained as inner salts. (2-Aminobenzyl)dithiocarbamic acid (X) was synthesized as a triethylamine salt before use since it was very labile. No satisfactory elementary analysis for the salt was obtained, but its structure was confirmed spectrophotometrically by the decomposition to 3,4-dihydroquinazoline-2-(1H)-thione.[15]

[(2-Methyl-5-pyrimidinyl)methyl]dithiocarbamic Acid (VIII)——VIII was prepared as a sodium salt from the reaction of 5-aminomethyl-2-methylpyrimidine[16] with carbon disulfide by the usual way.[1] *Anal.* Calcd. for $C_7H_8N_3S_2Na \cdot H_2O$: C, 35.14; H, 4.21; N, 17.56; Na, 9.61. Found: C, 35.21; H, 4.44; N, 17.22; Na, 9.89. UV $\lambda_{max}^{0.1N\ NaOH}$ nm (log ε): 252 (4.17), 287 (4.11).

Methyl [(4-Amino-2-methyl-5-pyrimidinyl)methyl]dithiocarbamate (II)——II was prepared as hydrochloride in a manner similar to its ethyl analog.[3c] Colorless needles, mp 282—286° (at *ca.* 240° needles transformed to plates). *Anal.* Calcd. for $C_8H_{13}N_4S_2Cl$: C, 36.29; H, 4.95; N, 21.16; Cl, 13.39. Found: C, 36.27; H, 5.21; N, 21.26; Cl, 13.48.

(2-Amino-5-nitrobenzyl)dithiocarbamic Acid (IX)——a) 2-Acetamidomethyl-4-nitroacetanilide: A mixture of (2-aminobenzyl)amine[15] (13.5 g), acetic anhydride (27 g) and dry pyridine (120 ml) was left overnight at room temperature and then evaporated to dryness. The residue was extracted with chloroform (450 ml) and the chloroform was washed with water (3×160 ml), dried and then evaporated. To a solution of the residue (12.4 g) in sulfuric acid (32.4 g), a mixture of 62% nitric acid (6.3 g) and sulfuric acid (6.3 g) was added under stirring below 0° for 1 hr. The mixture was stirred at 0° for 3 hr and then at 40° for 1 hr. The mixture was added to ice-cold water (120 ml) dropwise under cooling and appeared crystals were collected by filtration, washed with water (2×50 ml) and then recrystallized from methanol. Yield was 10 g, light yellow needles, mp 163—165° (decomp.). *Anal.* Calcd. for $C_{11}H_{13}O_4N_3$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.58; H, 5.36; N, 16.53. NMR (DMSO-d_6): 9.57 (1H, bs, Ar-N<u>H</u>–), 8.45 (1H, d, H_3, J=10 Hz), 8.17—7.95 (2H, m, H_4, H_6), 7.12 (1H, t, –CH_2–N<u>H</u>–, J=7 Hz), 4.45 (2H, d, –C<u>H_2</u>–NH–, J=7 Hz), 2.28 (3H, s), 2.07 (3H, s) (COC<u>H_3</u>). Mass Spectrum *m/e*: 251 (M^+).

b) (2-Amino-5-nitrobenzyl)amine: The above acetanilide (1.5 g) was suspended in 1N NaOH solution (200 ml) and then refluxed until the acetanilide dissolved (about 2 hr was required). The solution was evaporated to dryness and then extracted with benzene (3×100 ml). After the evaporation of the benzene, the residue was recrystallized from ethanol. Yield was 0.25 g, yellow leaflets, mp 156—158° (decomp.). Its *p*-nitroaniline structure was supported by the UV spectral data[17] and the doublet of H_3 ($J_{3,4}$=8.5 Hz) in the NMR. *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.30; H, 5.43; N, 25.14. Found: C, 50.60; H, 5.54; N, 24.99. UV λ_{max}^{MeOH} nm (log ε): 366 (4.16). NMR (DMSO-d_6): 8.03—7.77 (2H, m, H_4, H_6), 6.57 (2H, bs, Ar-N<u>H_2</u>), 6.45 (1H, d, H_3), 3.67 (2H, s, Ar–C<u>H_2</u>–), 2.62 (2H, bs, –CH_2–N<u>H_2</u>). Mass Spectrum *m/e*: 167 (M^+).

c) Triethylammonium (2-Amino-5-nitrobenzyl)dithiocarbamate (IX): Carbon disulfide (150 mg) was added to a solution of the above amine (116 mg) and triethylamine (80 mg) in ethanol (5 ml). The solution was stirred for 10 min at room temperature and for 30 min at 5—10°. Appeared crystals were collected by filtration and washed with ethanol (1 ml). Yield was 205 mg, yellow needles, mp 123—127° (decomp.). *Anal.* Calcd. for $C_{14}H_{24}O_2N_4S_2$: C, 48.80; H, 7.02; N, 16.20; S, 18.60. Found: C, 48.88; H, 7.15; N, 16.37; S, 18.64. UV $\lambda_{max}^{H_2O}$ nm (log ε): 253 (4.17), 286 (4.21), 383 (4.10).

d) 6-Nitro-3,4-dihydroquinazoline-2-(1H)-thione by the Alkaline Decomposition of IX: A solution of IX (246 mg) in 0.1 N NaOH (10 ml) was heated at 80—90° for 3 hr. The yellow crystals appeared. After the solution was neutralized with acetic acid, crystals were collected by filtration and washed with water (2 ml). Recrystallization from water containing a small amount of DMF gave yellow needles, mp>290° (decomp.). Yield was 120 mg. *Anal.* Calcd. for $C_8H_7O_2N_3S$: C, 45.92; H, 3.39; N, 20.08; S, 15.32. Found: C, 46.20; H, 3.69; N, 20.30; S, 15.16. UV $\lambda_{max}^{1N\ NaOH}$ nm (log ε): 423 (4.15) (shifted to 350 nm in dilute acidic solution). NMR (DMSO-d_6): 10.88 (1H, bs), 9.00 (1H, bs) (–N<u>H</u>), 8.18—7.98 (2H, m, H_5 and H_7), 7.08 (1H, d, H_8, J=9 Hz), 4.50 (2H, s, H_4). Mass Spectrum *m/e*: 209 (M^+).

Apparatus——A Towa-Dempa pH-meter, model HM-8, was used for the measurement of pH with a glass electrode in a thermostatted vessel. UV spectroscopic data were recorded on a Hitachi two-wave length/double-beam spectrophotometer, model 356, with a thermostat cell compartment unless otherwise stated. Temperature control was within 0.1° with a Haake FT thermostat. A Metrohm Herisau Potentiograph, E436, equipped with glass and calomel (Metrohm, EA 120) electrodes was used for potentiometric titration.

Kinetic Measurements——The rates of the decomposition of all the compounds examined were measured spectrophotometrically by following the increase in absorbance due to product IV for the decompositions of I—III, and by following the decrease in absorbance due to starting dithiocarbamate for the decompositions of VIII—XIV by the methods similar to the previous report.[1] The reactions were monitored at least 60% completion. The kinetics were analyzed using a plot of ln $|A_\infty - A_t|$ *vs.* time, where A_∞ employed were

14) Y. Ueno, T. Nakai, and M. Okawara, *Bull. Chem. Soc. Japan*, **44**, 1933 (1971).
15) R.E. Orth and J.W. Jones, *J. Pharm. Sci.*, **50**, 866 (1961).
16) This compound was kindly provided by Drs. A. Takamizawa and H. Harada of this laboratory.
17) C.N.R. Rao, "Ultra-violet and Visible Spectroscopy," Butterworth, London, 1961, Chapter 5.

obtained in either of two ways; (1) A_∞ was estimated from the extinction coefficience of IV determined in the same alkaline solutions as those of the reactions of I—III; or (2) the absorbance at $t=\infty$(after 10 half-lives) was used for VIII—XIV. The first-order rate constants obtained for the decompositions of I—III, and VIII—XIV are listed in Tables I, II, and V—VIII. Initial concentrations were about 5×10^{-5} M except IX unless otherwise stated. Decomposition of IX were run at initial concentrations of about 5×10^{-4} M of IX in strictly deairated condition because IX was rapidly oxidized in the presence of oxygen.[18] The spectral measurements were performed immediately after rapid cooling of an aliquot with ice-cold water and diluting the aliquot 10 times with well-deairated water. At the initial concentration of XIII above 5×10^{-5} M, the measurements were followed by diluting an aliquot to a value near 5×10^{-5} M with acetate buffer solution of pH 7.

Table V. Observed Half-lives ($\tau_{1/2}$) for the Decomposition of XIII[a]

[OH⁻], N	Initial concentration, M	$\tau_{1/2}$, min[b]
1.0		(5.6)
	$7.0_4\times10^{-4}$	7.1
	$3.5_9\times10^{-3}$	11.8
	$6.6_9\times10^{-3}$	18.7
1.0×10^{-1}		(5.8)
	$6.1_7\times10^{-5}$	7.0
	$7.4_5\times10^{-5}$	4.9
	$2.3_8\times10^{-4}$	8.2
	$7.1_5\times10^{-4}$	21.3
	$3.6_4\times10^{-3}$	78
	$4.8_7\times10^{-3}$	94
	$7.1_0\times10^{-3}$	134
1.0×10^{-2}		(−20)
	$1.5_5\times10^{-4}$	99
	$3.6_8\times10^{-4}$	178
	$7.2_1\times10^{-4}$	306

a) at 25°, b) The values in parentheses were those obtained by extrapolation to zero initial concentration.

Table VI. Observed First-order Rate Constants (k_{obs}) for the Decomposition of XIV

[OH⁻], N	Reaction temp., °C	k_{obs}, min⁻¹
1.0	80.0	$1.0_9\times10^{-2}$
	80.0	$1.0_7\times10^{-2}$
3.0	80.0	$4.0_7\times10^{-2}$
5.0	80.0	$1.0_3\times10^{-1}$
	70.0	$4.7_3\times10^{-2}$
	60.0	$2.1_6\times10^{-2}$

Table VII. Observed First-order Rate Constants (k_{obs}) for the Decomposition of II[a]

[OH⁻], N	k_{obs}, min⁻¹
(pH, 9.9_9)[b]	($1.7_1\times10^{-2}$)[b]
(pH, 10.9_9)[b]	($5.7_6\times10^{-2}$)[b]
3.4×10^{-3}	$9.7_9\times10^{-2}$
5.8×10^{-3}	$8.8_5\times10^{-2}$
1.0×10^{-2}	$1.0_6\times10^{-1}$
2.5×10^{-2}	$1.1_5\times10^{-1}$
3.6×10^{-2}	$1.1_0\times10^{-1}$
5.1×10^{-2}	$1.1_3\times10^{-1}$
1.0×10^{-1}	$9.6_0\times10^{-2}$
	$9.6_9\times10^{-2}$
	$8.9_2\times10^{-2}$
2.4×10^{-1}	$7.7_9\times10^{-2}$
1.0	$3.5_6\times10^{-2}$
	$3.0_4\times10^{-2}$

a) at 25°, b) Values in parentheses were obtained in Sörensön buffer solutions of pH cited.

Table VIII. Observed First-order Rate Constants (k_{obs}) for the Decomposition of III[a]

pH[b]	k_{obs}, min⁻¹
7.0_1	$1.0_6\times10^{-2}$
7.8_8	$6.9_5\times10^{-2}$
8.1_2	$8.4_9\times10^{-2}$
9.0_5	$4.0_7\times10^{-1}$
9.1_3	$3.3_5\times10^{-1}$
9.4_8	$4.2_2\times10^{-1}$
9.8_6	$4.4_0\times10^{-1}$
10.0_7	$3.2_4\times10^{-1}$
10.1_7	$2.6_6\times10^{-1}$
10.5_3	$2.1_2\times10^{-1}$
10.6_3	$2.1_3\times10^{-1}$
10.9_0	$9.2_8\times10^{-2}$
11.0_2	$8.1_9\times10^{-2}$
11.4_0	$5.3_4\times10^{-2}$

a) at 60°, b) Borate buffer was used.

The activation energies and frequency factors for the decomposition of I and VIII—XII were calculated from the data in 0.1 N NaOH by the usual method.[1]

18) F. Takami, K. Tokuyama, S. Wakahara, and T. Maeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 594 (1973).

The observed first-order rate constants of XIV listed n Table VI are proportional to the acidity function H_-.[19] The second-order rate constant was calculated from the following equation;

$$\log k_{obs} = -2.299 + 0.8316H_- - \frac{3.98_6 \times 10^3}{T} \qquad \text{(eq. 5)}$$

p*Ka* Determination——a) Potentiometric Titration: The p*Ka*′ values of benzylamino group of (2-aminobenzyl)amine and (2-amino-5-nitrobenzyl)amine were determined at 25° to be 9.4_5 and 8.3_0, respectively. An aqueous solution (100 ml) containing *ca.* 10^{-3} mole of the amine was titrated at 25° with 0.1 N HCl solution. The p*Ka*′ was determined by reading the pH value at half-equivalence point.[20]

b) Spectrophotometric Titration: All p*Ka*′ values were determined at 25° and calculated in a manner similar to a previous paper.[7] The p*Ka*′ values of arylamino group of (2-aminobenzyl)amine and (2-amino-5-nitrobenzyl)amine were determined to be 2.4_0 and -0.9_6 by using the changes of absorbances at 231 and 370 nm, respectively. The buffer solutions[21] of pH 2—4 were used for the former and 1—5 N HCl solutions were employed for the latter. The absorbance of un-ionized form was determined in water. The p*Ka*′ values of IIand XIII were determined to be 10.6 and 12.0, respectively, by following the change of absorbance at 270 nm. The Britton–Robinson buffer solutions of pH 8.0—11.5 were used for II and the borate buffer solutions of pH 11—12 and 0.01 N NaOH solution were done for XIII. The absorbance of ionized form of II and un-ionized form of XIII were observed in the solutions of 5 N NaOH and pH 7, respectively. Since II decomposed slowly under the conditions employed, the absorbance was extraporated to zero time. The two values of p*Ka*′ of IV were measured in Britton–Robinson buffer solutions of pH 7.1—12.2 and 1 N NaOH solution or those of pH 3.0—7.0 and 0.01—0.1 N HCl solutions. The values were determined to be 11.3, and 3.3_3 by using the changes of absorbances at 330 and 304 nm, respectively. The absorbance of conjugate base of IV were determined in 1 N NaOH solution and that of IV were done in water. The p*Ka*′ of 4-amino group of 4-amino-5-aminomethyl-2-methylpyrimidine was determined to be −3.9, using the change of absorbance at 255 nm in 30—70 w/w % H_2SO_4 solutions.

Acknowledgement We are grateful to Professor Y. Inubushi, University of Kyoto, who has read and criticized the manuscript. We also thank Dr. K. Ikawa, Assistant Manager of the Production Department of this company, for his interest.

19) G. Yagil, *J. Phys. Chem.*, **71**, 1034 (1967).
20) J.J. Lingane, "Electroanalytical Chemistry," Interscience, Inc., New York, 1953, Chapter V.
21) D.D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).