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Thermal Decomposition of 1,1-Disubstituted-3-aryl-3-(aryloxythiocarbonyl)-2-thioureas*[1]

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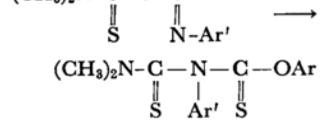
1,1-Disubstituted-3-(4-chlorophenyl)-3-(phenoxythiocarbonyl)-2-thioureas of the formula $R,R'N\text{–}C^1(\text{=}S)\text{–}N(p\text{-}Cl\text{–}C_6H_4\text{–})\text{–}C'(\text{=}S)\text{–}OC_6H_5$ (II), when kept at an elevated temperature without any solvent, decomposed into the corresponding thionocarbamates of the formula $R,R'N\text{–}C(\text{=}S)\text{–}OC_6H_5$ (III), while *p*-chlorophenyl isothiocyanate was eliminated. A carbon-14-labeling experiment showed that the decomposition proceeded only through the following path:

$$\text{II} \longrightarrow R,R'N\text{–}C^2(\text{=}S)\text{–}OC_6H_5 + p\text{-}Cl\text{–}C_6H_4\text{–}N{=}C^1{=}S$$

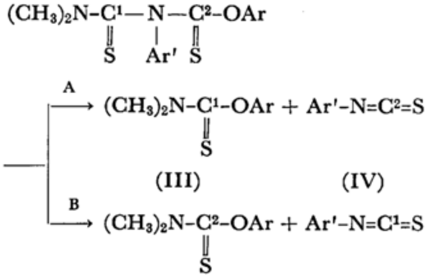
Kinetic studies of the various II showed that the decompositions were strictly first order. The rate constant at 175°C increased in the order: $R,R' = (CH_3)_2 > (C_2H_5)_2 > CH_3$,4-methylbenzyl $\gtrsim (n\text{-}C_3H_7)_2 > CH_3$, benzyl $> CH_3$, 4-chlorobenzyl. Neither the products nor the rate of the decomposition reaction was influenced by the presence of a radical scavenger. Furthermore, a crossover decomposition reaction did not give any crossover products. On the basis of these results, a possible intramolecular mechanism of the decomposition involving a four-membered cyclic intermediate structure was proposed.

In an earlier paper,[1] it was shown that *O*-aryl-*S*-(*N,N*-dimethylthiocarbamoyl)-*N*-(aryl)thiolimido carbonates with the formula I, when kept at a temperature higher than their melting points, rearranged within a few minutes into the corresponding 1, 1-dimethyl-3-aryl-3-(aryloxythiocarbonyl)-2-thioureas with the formula II (Eq. (1)).



$$(CH_3)_2N\text{-}\underset{\underset{S}{\|}}{C}\text{-}S\text{-}\underset{\underset{N\text{-}Ar'}{\|}}{C}\text{-}OAr \longrightarrow (CH_3)_2N\text{-}\underset{\underset{S}{\|}}{C}\text{—}\underset{\underset{Ar'}{|}}{N}\text{—}\underset{\underset{S}{\|}}{C}\text{—}OAr \qquad (1)$$

During the course of a continuous investigation of the rearrangement of I to II, it has been found that II gradually decomposed, when the reaction time was prolonged, into the aryl *N,N*-dimethylthionocarbamate (III), while aryl isothiocyanate (IV) was eliminated. It can easily be considered, however, that IV can be split off in the two ways shown in Eq. (2):



$$(CH_3)_2N\text{-}\underset{\underset{S}{\|}}{C^1}\text{—}\underset{\underset{Ar'}{|}}{N}\text{—}\underset{\underset{S}{\|}}{C^2}\text{-}OAr \begin{cases} \xrightarrow{A} (CH_3)_2N\text{-}\underset{\underset{S}{\|}}{C^1}\text{-}OAr + Ar'\text{-}N{=}C^2{=}S \\ \qquad\qquad (III) \qquad\qquad\qquad (IV) \\ \xrightarrow{B} (CH_3)_2N\text{-}\underset{\underset{S}{\|}}{C^2}\text{-}OAr + Ar'\text{-}N{=}C^1{=}S \end{cases} \qquad (2)$$

In the present paper, a carbon-14-labeling experiment and the kinetics of the decomposition have been studied for a series of 1,1-disubstituted-3-(4-chlorophenyl)-3-(phenoxythiocarbonyl)-2-thioureas in order to clarify the decomposition mechanism.

Results and Discussion

The compounds II studied here were prepared by the reaction of an appropriate 1,1-disubstituted-3-(4-chlorophenyl)-2-thiourea with a proper aryl chlorothionoformate, as has been reported previously.[1] The data are shown in Table 1. On being heated at 175°C without any solvent and under a slow stream of nitrogen, the compounds II underwent a gradual decomposition, with the elimination

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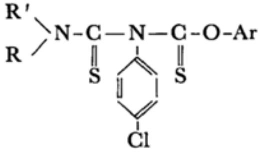
*[1] Presented in part at the 19th Annual Meeting of the Chemical Society of Japan, Yokohama, April, 1966.

[1] A. Kaji and K. Miyazaki, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **87**, 727 (1966).

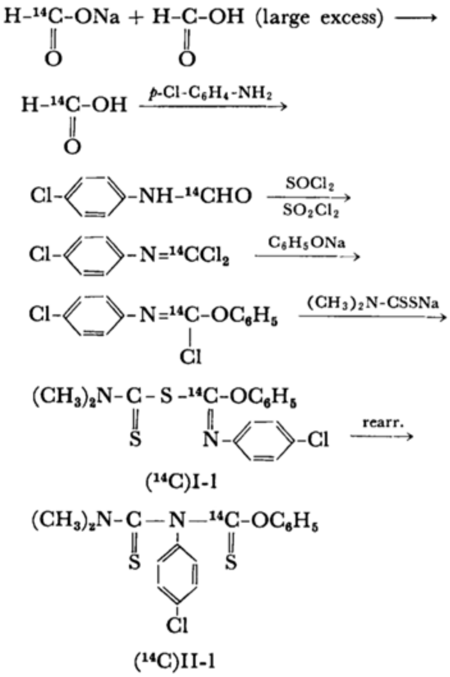
TABLE 1. 1,1-DISUBSTITUTED-3-(4-CHLOROPHENYL)-3-ARYLOXYTHIOCARBONYL-2-THIOUREAS



Compd. No	R R'	Ar	Appearance	Mp[a) °C	Yield[b) %	Formula	Anal. C(%) Found (Calcd)	Anal. H(%) Found (Calcd)	Anal. N(%) Found (Calcd)
II-1	CH_3 CH_3	phenyl	Colorless prisms[c)	169—170	74.5	$C_{16}H_{15}ClNO_2S_2$[e)	—	—	—
II-2	C_2H_5 C_2H_5	phenyl	Colorless needles[c)	112—113	71	$C_{18}H_{19}ClN_2OS_2$	56.70 (56.70)	5.07 (9.02)	7.42 (7.40)
II-3	n-C_3H_7 n-C_3H_7	phenyl	Colorless prisms[d)	90— 91	71	$C_{20}H_{23}ClN_2OS_2$	59.00 (59.05)	5.42 (5.66)	7.09 (6.90)
II-4	C_2H_5 C_2H_5	4-tolyl	Colorless needles[c)	157—158	68	$C_{19}H_{21}ClN_2OS_2$	57.70 (58.09)	5.55 (5.35)	6.97 (7.15)
II-5	CH_3 4-Methylbenzyl	phenyl	Colorless needles[c)	110—111.5	66	$C_{23}H_{21}ClN_2OS_2$	62.30 (62.66)	4.93 (4.77)	6.11 (6.36)
II-6	CH_3 Benzyl	phenyl	Colorless needles[c)	121.5—122.5	65	$C_{22}H_{19}ClN_2OS_2$	61.70 (61.90)	4.52 (4.45)	6.43 (6.57)
II-7	CH_3 4-Chlorobenzyl	phenyl	Colorless needles[c)	131—132	68	$C_{22}H_{18}Cl_2N_2OS_2$	57.20 (57.27)	4.03 (3.90)	6.33 (6.07)

a) All melting points are uncorrected. b) Yields recorded are those of recrystallized products. c) From ethanol - acetone.
d) From methanol. e) Reported previously (lit. 1).

of *p*-chlorophenyl isothiocyanate (IVa); the corresponding aryl *N*,*N*-disubstituted-thionocarbamates could be detected as the other major decomposition products. The compounds IVa and the thionocarbamates isolated by a chromatograph were identified by a mixed-melting-point test and/or by the agreement of the IR spectra with those of the corresponding authentic samples. It will easily be seen that there are two possible ways to split off the compound IVa, as has been expressed in Eq. (2). In order to ascertain which way was preferable, the thermal decomposition of II-1, but with the C^2 atom (in Eq. (2)) labeled with a radioactive carbon, was studied; the radioactive II-1 was prepared by the method shown in the following scheme.



As a result of the experiment, it was found that the compound, IVa, formed by the decomposition of (^{14}C)II-1 did not have any radioactivity, while phenyl *N*,*N*-dimethylthionocarbamate (IIIa) still retained its radioactivity, with almost the same specific activity as that of the starting material, (^{14}C) II-1. These results show that the decomposition proceeds exclusively through the path B in Eq. (2).

In order to investigate the influence of the substituent (R, R′) on the rate of decomposition, the kinetics of the decomposition were investigated on three compounds (II-1—II-3). The decomposition rates were determined by measuring the amount of the product IVa by spectrophotometry. As a result, it was found that the decomposition reactions followed good first-order kinetics (Fig. 1). The first-order rate constants, which were derived from the slopes of the straight lines in Fig. 1, are listed in Table 2.

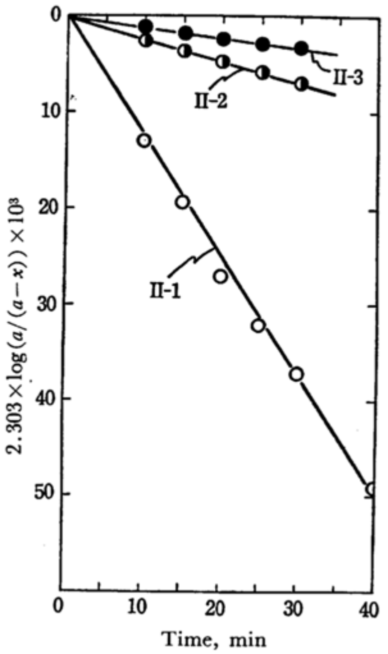


Fig. 1. First-order plots of kinetic data for II-1—II-3 at 175±0.5°C.

TABLE 2. FIRST-ORDER RATE CONSTANTS (k_1) OF THE DECOMPOSITION REACTIONS AT 175±0.5°C FOR II-1—II-3

Compd. No.	$k_1\times10^3$ (min^{-1})	Relative rate
II-1	12.80	(1)
II-2	2.32	0.18
II-3	1.04	0.08

In order to examine whether the decomposition, which followed the path B in Eq. (2), proceeded by an intermolecular route or by an intramolecular route, a crossover experiment was performed with two compounds of II. That is, an equimolecular mixture of II-1 and II-4 was heated without any solvent at 175°C for 1.5 hr under a slow stream of nitrogen. If the compounds II decomposed according to an ionic intermolecular mechanism involving the heterolytic cleavage of the (R, R′)N–C^1 bond and the Ar′N–C^2 bond, crossover products, such as 4-tolyl *N*,*N*-dimethylthionocarbamate (IIId) and phenyl *N*, *N*-diethylthionocarbamate (IIIb), should be detected in the crossover reaction mixture. The thin-layer chromatograms of that reaction mixture, however, showed no detectable amounts of IIIb or IIIb. This result suggests that the decomposition involves an intramolecular mechanism rather than an intermolecular mechanism.

Another possible mechanism for the decomposition of II is homolytic cleavages of the above-mentioned two bonds. In order to investigate this possibility, the decomposition reaction of the compound

II-1, mixed with a small amount (*ca.* 2 wt%) of a radical scavenger such as *p*-quinone or 1,1-diphenyl-2-picrylhydrazyl (DPPH), was studied at 175°C. As a result, the decomposition products were found to be the same as in the absence of the scavenger, while the rate was scarcely affected by the presence of the scavenger. In view of the above facts, one may presume that the decomposition did not involve a radical route.

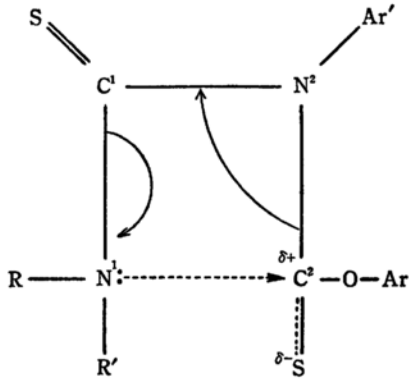


Fig. 2. Four-membered cyclic mechanism.

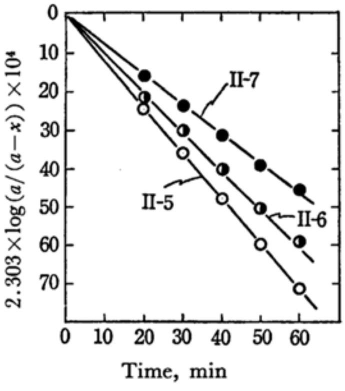


Fig. 3. First-order plots of kinetic data for II-5—II-7 at 175±0.5°C.

Taking the above results into consideration, it has been presumed that the decomposition of the compound II took place through an intramolecular mechanism involving a four-memberd cyclic intermediate structure, as in Fig. 2.

Since the decomposition reaction should be caused by a nucleophilic attack of the N^1 atom on the C^2 atom, it was expected that a stronger electron-donating inductive effect of the substituent (R, R′), which might promote the nucleophilic character of the N^1 atom, would result in a larger rate of decomposition. However, the results obtained concerning II-1—II-3 betrayed this expectation; the rate constants increased in the order of $R=CH_3>C_2H_5>n\text{-}C_3H_7$ (Table 2). This finding that the rate constants diminish regularly with an increase in the bulkiness of the alkyl groups indicates that the steric effect of R much outweighs the electronic effect. In an effort to determine the inductive effect of the substituent (R, R′) upon the decomposition, further kinetic studies were carried out on a series of N^1-(4-substituted-benzyl)-N^1-methyl- analogues (II-5—II-7). Since the steric effects in three compounds should be virtually the same, the substituent effect caused by the inductive effect upon the rate of the decomposition can be demonstrated clearly. The kinetic results obtained are shown in Fig. 3, while the rate constants are listed in Table 3.

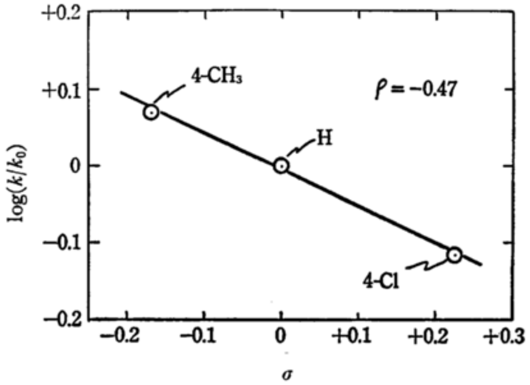


Fig. 4. Hammett plots for the thermal decompositions of II-5—II-7 at 175±0.5°C.

TABLE 3. FIRST-ORDER RATE CONSTANTS (k_1) OF THE DECOMPOSITION REACTION AT 175±0.5°C FOR II-5—II-7

Compd. No.	$k_1\times10^4$ (min^{-1})	Relative rate
II-5	12.0	1.18
II-6	10.2	(1)
II-7	7.8	0.77

Hammett plots of $\log(k/k_0)$ *vs.* σ gave a straight line, with $\rho=-0.47$ (Fig. 4). This fact indicates that the decomposition should be essentially accelerated by a stronger electron-donating inductive effect of the substituent on the N^1 atom.

The results of the carbon-14 labeling experiment, the crossover experiment, the scavenger experiment, and the Hammett correlation lend some support to the presumption of an internal four-membered cyclic mechanism such as that expressed in Fig. 2.

Experimental[*2]

Materials. *p*-Chlorophenyl Isothiocyanate (IVa). This was obtained by the usual method. Mp 44—45°C.[2)]

1,1-Disubstituted-3-(4-chlorophenyl)-2-thioureas. These were prepared by the reaction of *p*-chlorophenyl

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[*2] All boiling and melting points are uncorrected.

2) G. M. Dyson, "Org. Synth.," Coll. Vol. I, p. 165 (1948).

isothiocyanate with a proper secondary amine: 1,1-dimethyl- mp 168—169°C,3) 1,1-diethyl- mp 89—90°C. Found: C, 54.22; H, 5.87%. Calcd for $C_{11}H_{15}ClN_2S$: C, 54.43; H, 6.19%. 1,1-Di-*n*-propyl- mp 108—109°C. Found: C, 57.40; H, 6.80%. Calcd for $C_{13}H_{19}ClN_2S$: C, 57.67; H, 7.02%. 1-Benzyl-1-methyl- mp 157—158°C. Found: C, 61.78; H, 4.88%. Calcd for $C_{15}H_{15}ClN_2S$: C, 61.96; H, 5.16%. 1-(4-Chlorobenzyl)-1-methyl- mp 136—137°C. Found: C, 55.20; H, 4.15%. Calcd for $C_{15}H_{14}Cl_2N_2S$: C, 55.38; H, 4.31%. 1-(4-Methylbenzyl)-1-methyl- mp 126—127°C. Found: C, 62.80; H, 5.61%. Calcd for $C_{16}H_{17}ClN_2S$: C, 63.05; H, 5.58%.

Aryl Chlorothionoformates. These were prepared by the reaction of a corresponding phenol with thiophosgene according to a procedure described earier;1) phenyl- bp 101—103°C/18 mmHg, 4-tolyl- bp 102—103°C/8 mmHg.

1,1-Disubstituted-3-(4-chlorophenyl)-3-(aryloxythiocarbonyl)-2-thioureas (II-1—II-7). *These* compounds were pepared from an appropriate 1,1-disubstituted-3-(4-chlorophenyl)-2-thiourea and a proper aryl chlorothionoformate, as has been reported previously.1) The data are shown in Table 1.

Aryl *N,N*-Disubstituted-thionocarbamates (III). These compounds were prepared from a corresponding secondary amine and an aryl chlorothionoformate following the general procedure given in the literature:4) phenyl *N,N*-dimethyl- (IIIa) bp 118—120°C/3 mmHg mp 29.5—30°C,5) phenyl *N,N*-diethyl- (IIIb) bp 125—126°C/3 mmHg mp 34—35°C. Found: C, 62.88; H, 7.05; N, 6.70%. Calcd for $C_{11}H_{15}NOS$: C, 63.16; H, 7.18; N, 6.70%. Phenyl *N,N*-di-*n*-propyl- (IIIc) bp 131—132°C/0.6 mmHg. Found: C, 66.10; H, 7.68; N, 5.70%. Calcd for $C_{13}H_{19}NOS$: C, 65.83; H, 7.68; N, 5.71%. 4-Tolyl *N,N*-dimethyl- (IIId) mp 96—97°C.6) 4-Tolyl *N,N*-diethyl- (IIIe) mp 67.5—68.5°C. Found: C, 64.70; H, 7.35; N, 6.22%. Calcd for $C_{13}H_{17}NOS$: C, 64.57; H, 7.62; N, 6.28%. Phenyl *N*-benzyl-*N*-methyl- (IIIf) colorless oil*3 n_D^{23}: 1.6137. Found: C, 69.90; H, 5.88; N, 5.21%. Calcd for $C_{15}H_{15}NOS$: C, 70.04; H, 5.84; N, 5.45%. Phenyl *N*-(4-chlorobenzyl)-*N*-methyl- (IIIg) colorless oil*3 n_D^{23}: 1.6173. Found: C, 61.70; H, 4.88; N, 4.98%. Calcd for $C_{15}H_{14}ClNOS$: C, 61.75; H, 4.80; N, 4.80%. Phenyl *N*-(4-methylbenzyl)-*N*-methyl- (IIIh) colorless needles (from methanol) mp 57—58°C. Found: C. 70.70; H, 6.27; N, 5.15%. Calcd for $C_{16}H_{17}NOS$: C, 70.85; H, 6.28; N, 5.17%.

Carbon-14 Labeling Experiments. The sodium formate-^{14}C (specific activity: 10.8 mCi/mmol) was obtained from the Radiochemical Centre in England; it was dissolved into nonradioactive formic acid in order to obtain a moderate radioactive formic acid-^{14}C.

Labeled 4-Chloroformanilide. This was prepared in a 96% yield from 4-chloroaniline and the above formic acid-^{14}C.

Labeled (4-Chlorophenyl)imidocarbonyl Chloride. This was prepared in a 77% yield using the above labeled anilide and according to a procedure described in the literature.7) Bp 132—135°C/29 mmHg.

Labeled Phenyl *N*-(4-Chlorophenyl)chloroformimidate. This was prepared in a 57% yield from the above labeled chloride and phenol, as has been described earlier.1) Bp 157—159°C/4 mmHg.

Lableld *O*-Phenyl-*S*-(*N,N*-dimethylthiocarbamoyl) *N*-(4-Chlorophenyl)thiolimidocarbonate ((^{14}C)I-1). This was prepared from sodium *N,N*-dimethyldithiocarbamate and the above labeled chloroformimidate by a method reported previously.1) The crude reaction product was recrystallized several times from ethanol-acetone to give colorless prisms in a 58% yield. Specific activity: 1.40 μCi/mol.

Labeled 1,1-Dimethyl-3-(4-chlorophenyl)-3-(phenoxythiocarbonyl)-2-thiourea ((^{14}C)II-1). This was prepared by the thermal rearrangement of (^{14}C)I-1, as has been reported previously.1) In order to obtain the pure product, the crude product was chromatographed on silica gel twice and then recrystallized several times from ethanol - acetone to give colorless prisms in a 28% yield. A thin-layer chromatographic analysis of that refined product showed that it contained no impurities. Specific activity: 1.51 μCi/mol.

Thermal Decomposition of II. The apparatus used for the decomposition consisted of a 5-m*l*, pear-shaped flask fitted with an air condenser. Thin-layer chromatography was conducted by the use of silica gel (WAKO GEL B5-F); the prepared plate was activated at 110°C for 1hr and then stored in a deciccator. Silica-gel - column chromatography was carried out by the use of silica gel (WAKO GEL C-200) activated at 110°C for 1hr before use.

In a run, a weighed amount (*ca.* 100 mg) of II was placed in the reaction flask. The flask was flushed with nitrogen for 10 min at room temperature and then heated to 175±0.5°C in a constant-temperature bath for the desired length of time, nitrogen being passed into the flask at a slow rate throughout the decomposition. The reaction mixture, which showed two main spots besides the unchanged II upon thin-layer chromatography with a solvent mixture of *n*-hexane and chloroform (2/1), was chromatographed on a silica-gel column (15×250 mm) with the same solvent as was used above. After about 200 m*l* of the solution had been eluted, fractions (5 m*l* each) were tested by thin-layer chromatography in order to separate the newly-formed products. The two main products thus separated were identified by means of IR and melting-point comparisons with authentic samples.

Decomposition of (^{14}C)II-1. (^{14}C)II-1 (200 mg) was decomposed for 1.5hr in the same manner as above. IIIa and IVa, which had been carefully separated by cloumn chromatography, were each recrystallized several times from ligroin. Thus 15 mg of IIIa (specific activity: 1.44 μCi/mol) and 18 mg of IVa (specific activity: 0) were obtained.

Crossover Experiment. An equimolar mixture of II-1 and II-4 was heated at 175°C for 1.5 hr under a slow stream of nitrogen. The reaction mixture was then submitted to thin-layer chromatography on silica gel, using a solvent mixture of *n*-hexane - chloroform - acetic acid

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3) R. H. Hunter and E. S. Styles, *J. Chem. Soc.*, **1927**, 1211.

4) R. P. Mull, *J. Am. Chem. Soc.*, **77**, 581 (1955).

5) H. Rivier, *Bull. Soc. Chim. France*, (3) **35**, 837 (1906).

6) A. Kaji, This Bulletin **34**, 254 (1961).

*3 These compounds were obtained as a viscous oil and were purified by chromatography.

7) German Pat. 1094737; *Chem. Abstr.*, **55**, 25860 (1961).

TABLE 4. DECOMPOSITION RATES OF II-1 WITH A SCAVENGER

	t(min)	10	20	30	40
$\ln(a/(a-x))$	(quinone)	0.128	0.267	0.368	0.490
	(DPPH)	0.125	0.261	0.372	0.480
	(neat)	0.130	0.270	0.370	0.493

(30 : 1 : 1) as the developer. After repeated attempts at chromatography, five major products: (R_f=0.31 (unchanged II-1), 0.45 (unchanged II-4), 0.47 (IIIa), 0.66 (IIIe) and 0.93 (IVa)) were obtained. However, neither IIIb (R_f: 0.61) nor IIId (R_f: 0.51) was detected.

Decomposition with a Scavenger. II-1, mixed with a small amount (*ca.* 2 wt% of II-1) of a scavenger, was heated at 175±0.5°C under a slow stream of nitrogen. The decomposition rates at each interval were as follows:

Decomposition Rate Measurement. In the above-described decomposition procedure, five or six runs for Compound II were started at the same time. Each one of these was taken out from a bath at every appropriate interval and cooled to room temterature by immersion in cold water. Each run thus obtained was then submitted to column chromatography in order to separate the IVa. The absorbance of the elute containing IVa was then measured at 275 mμ, which is the characteristic absorption for IVa. Since the change in the absorbance with the concentration of IVa in the solvent followed Beer's law well, the amount of IVa could be determined from the calibration line, which was decided in advance. Good first-order straight lines were obtained in this way (Figs. 1 and 3). From these data, the rate constants were calculated (Tables 2 and 3). The absorbance was measured on a Shimadzu MPS-50L spectrophotometer.

Radioactivity Counting. The radioactivity was measured by a liquid scintillation spectrometer (Nuclear Chicago Corp., Model 6801) using the following scintillator: naphthalene, 120 g; PPO, 7g; POPOP, 0.05 g; dioxane, 1000 m*l*.

The author wishes to express his deep gratitude to Professor Ryōzō Gotō of Kyoto Universiy for his kind direction, to Professor Aritsune Kaji of same University for his valuable suggestions and continuous encouragement, and to Dr. Jun-ichi Hayami of the same University for his helpful advice. Thanks are also due to Dr. Teruhisa Noguchi of the Biological Research Laboratory of Nippon Soda Co., Ltd., for his eager interest throughout the course of this investigation.