CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 19, No. 6 June 1971

Regular Articles

[Chem. Pharm. Bull. 19(6)1079—1088(1971)]

UDC 547.794.04 : 547.415.3.04

Chemical and Kinetic Study on Stabilities of 3-Morpholinosydnonimine and Its N-Ethoxycarbonyl Derivative[1]

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(Received November 24, 1969)

Stabilities of 3-morpholinosydnonimine (II), hydrochloride (I) and N-ethoxycarbonyl-3-morpholinosydnonimine (VIII) were examined by photometry, potentiometry, thin-layer chromatography and spectroscopy. In alkaline solution VIII goes to ethanol, carbon dioxide and II, which successively decomposes to N-morpholino-N-nitrosoaminoacetic acid (V) and N-cyanomethylenaminomorpholine (VI) *via* N-morpholino-N-nitrosoaminoacetonitrile (III). In the processes of $\text{I} \rightleftarrows \text{II} \rightarrow \text{III}$, the initial equilibrium is very rapid and the consecutive cleavage is a spontaneous first order reaction at pH 3—7 or a base catalyzed reaction at pH 8—10. The initial process of $\text{VIII} \rightarrow \text{II}$ is a base catalyzed first order hydrolysis of N-ethoxycarbonyl group. Hydrolyses of I and VII in hydrochloric acid form morpholine, nitrogen, chloroacetic acid and ammonium chloride. Photolyses of I and VII in acid solution at $\lambda < 320$ mμ give glycolic acid beside the products mentioned above. Formation of I from III and hydrolysis of VI to N-aminomorpholine are acid catalyzed pseudo-first-order reactions. Decomposition of III to VI seems to be a radical reaction.

Among many sydnonimines synthesized by Masuda, *et al.*[3] it was found that 3-dialkylaminosydnonimines and their N-acyl derivatives have potential pharmacological actions.[4] In connection with development of potent antianginal agents, the present paper deals with properties, chemical and kinetic study on the decomposition of 3-morpholinosydnonimine hydrochloride (I) and N-ethoxycarbonyl-3-morpholinosydnonimine (VIII) with alkali, acid and light. No paper has appeared on these particular compounds although stabilities of sydnones and sydnonimines have been studied by many researchers.[5-10] According to

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[1] Presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.

[2] Location: *Juso, Higashiyodogawa-ku, Osaka.*

[3] K. Masuda, Y. Imashiro, and T. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **18**, 128 (1970); K. Masuda, T. Kamiya, Y. Imashiro, and T. Kaneko, *ibid.*, **19**, 72 (1971).

[4] K. Kikuchi, M. Hirata, A. Nagaoka, and Y. Aramaki, *Japan. J. Pharmacol.*, **20**, 23, 102 (1970); F. Takenaka, N. Takeya, T. Ishihara, M. Sasai, M. Marumoto, S. Inoue, and K. Kikuchi, *Folia Pharmacol. Japan.*, **64**, 49 (1968).

[5] H.V. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2426 (1962); *idem, ibid.*, **47**, 3421 (1964).

[6] E.R. Garrett, *J. Pharm. Sci.*, **53**, 42 (1964); E.R. Garrett and P.J. Mehta, *ibid.*, **56**, 1468 (1967).

[7] G.S. Puranik and H. Suschitzky, *J. Chem. Soc. (C)*, **1967**, 1006.

[8] L.E. Kholodov and V.G. Yashunskii, *Z. Obshch. Khim.*, **37**, 670 (1967); *idem, ibid.*, **35**, 1551 (1965); *idem, ibid.*, **33**, 3409 (1953); S.A. Zotova and V.G. Yashunskii, *Z. Org. Khim.*, **3**, 942 (1967).

[9] D.A. Bochvar and A.A. Bagatur'yants, *Z. Fiz. Khim.*, **39**, 1631 (1965); *idem, ibid.*, **40**, 1366 (1966).

[10] L.B. Kier and E.B. Roche, *J. Pharm. Sci.*, **55**, 807 (1966); E.B. Roche, *Diss. Abst. B.*, **27**, 3045 (1967); L.B. Kier, *Tetrahedron Letters*, **1967**, 1233.

Daeniker,[5] sydnonimine salts and N-acylsydnonimines decompose to N-nitrosoaminacetonitriles, N-nitrosoaminoacetamides, and 1,2,3-triazoles in alkaline solutions. Masuda, *et al.*[3] have suggested the formation of N-morpholino-N-nitrosoaminoacetonitrile (III) and N-nitroso-N-morpholinoaminoacetic acid (V) on treating I with alkali and supported our proposal of cyanomethylenaminomorpholine (VI) as a product from I. The present authors have revealed that the decomposition of I to III and V is catalyzed by hydroxyl ion (OH^-) whereas the reaction from III to VI is not and that VIII decomposes to V, ammonia, monoethyl carbonate, ethanol and carbon dioxide in extreme alkaline solutions. 3-Morpholinosydnonimine (II), N-nitroso-N-morpholinoacetamide (IV) and 1-morpholino-4-hydroxy-1,2,3-triazole (IX) have been predicted as products from I and VIII.

Kholodov[8] has reported that 3-phenylsydnonimine decomposes to phenol, nitrogen, chloroacetic acid and ammonium chloride *via* phenyldiazonium salt and chloroacetamide in hydrochloric acid. Similar products were obtained in acid hydrolyses of I and VIII, in which morpholine (RH) took the place of phenol.

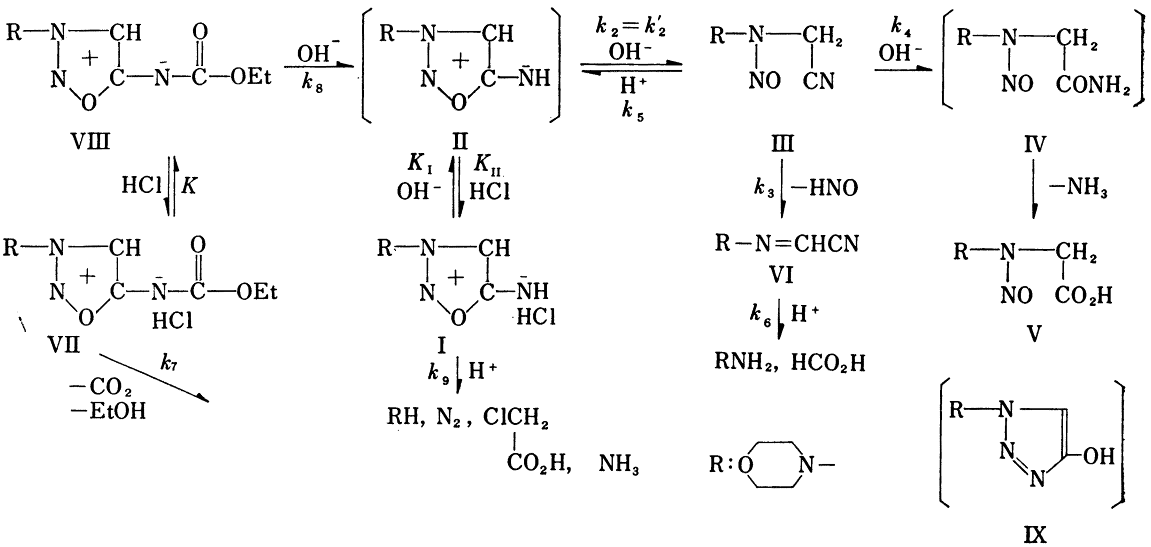

Chart 1

Experimental

Materials and Instruments——All samples were offered by Dr. K. Masuda, *et al.* Reagent chemicals were supplied from Wako Pure Chemicals, Ltd.

NMR spectra (Table I) were measured by Varian A-60A spectrometer, UV spectra with Perkin–Elmer 450, absorbance with Perkin–Elmer 139, mass spectra with Hitachi RMU6D, pH at 20—100° with Horiba F5 pH meter using electrodes (No. 1027-25A and 2530-25A) and titration curves with Radiometer's Titrigraph. Photolysis was performed by Tōshiba's SHL-UV-100 Hg lamp or by JASCO's CRM 50 concave-grating irradiater with 5 kW Xe lamp operated at 110 A, inlet slit width: 2 mm, resolution: 1.67 mμ/mm.

Identification of Decomposition Products

Alkaline Decomposition of 3-Morpholinosydnonimine Hydrochloride (I)——A solution containing 290 mg of I and 0.7 eq NaOH was heated at 100° for 1 hr and evaporated in vacuum. From ether extract of the residue, 270 mg of oily substance was obtained. This product was determined by NMR (Table I) to be a mixture (3:1) of N-morpholino-N-nitrosoaminoacetonitrile (III) and N-cyanomethylenaminomorpholine (VI).

A solution containing 300 mg of I, 0.9 eq NaOH and 40 ml of 0.01 M borax (pH 9.2) was heated at 50° for 30 min and extracted with 40 ml of EtOAc. Evaporating the extract, 280 mg of needles were obtained. This product was identified to be VI by the following properties. mp 71—72°. UV $\lambda_{\max}^{H_2O}$ mμ (ε): 278 (17000). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2220 (=CCN), 1540, 1267, 1177, 1110, 1015, 864, 810, comparing for C_6H_5 NHN=

Table I. NMR Parameters (τ) of 3-Morpholinosydnonimine (I) and Its Related Compounds

Subs.	Solv.	Morpholine	4-CH (CH_2)	Others
I	CF_3CO_2H	5.7 —6.3 m	2.24	2.64 (NH_2)
	$(CD_3)_2SO$		1.64	0.12 (NH_2)
	D_2O	5.83—6.25 m	2.10	
III	$CDCl_3$	6.06—6.56 m	(5.47)	
V	$CDCl_3$	6.08—6.58 m	(5.58)	1.3 (CO_2H)
VI	$CDCl_3$	6.15—6.73 m	3.78	
VIII	D_2O	5.94—6.35 m	D	8.71 t, 5.80 q (Et)
	1 N DCl	5.9 —6.1 m	1.28	8.61 t, 8.57 q
	$(CD_3)_2SO$	6.2 —6.4 m	1.87	8.83 t, 5.98 q
	CF_3CO_2H	5.7 —6.0 m	1.25	8.57 t, 5.48 q
	1 N NaOD	5.9 —6.7 m	D	8.69 t, 5.8 q
$EtCO_3Na$	1 N NaOD	—	—	8.73 t, 5.99 q
EtOH	1 N NaOD	—	—	8.78 t, 6.27 q
Et_2CO_3	1 N NaOD	—	—	8.77 t, 5.70 q

m: multiplet, t: triplet, q: quartet, D: deuterated

CHCN (2220 cm^{-1}), morpholino-N(NO)CH_2CN (2260 cm^{-1}). NMR is shown in Table I. Mass Spectrum *m/e*: 139 (M^+), 86 (morpholine $C_4H_8ON^+$), 81, 68, 56 ($C_3H_6N^+$), 54, 53, 42 ($C_2H_4N^+$), 30—26.

A solution of 0.01% I in 200 ml of 0.1 N NaOH was heated at 100° for 10 min, acidified with 1 N HCl and extracted twice with 200 ml of EtOAc. Evaporating the extract, N-morpholino-N-nitrosoaminoacetic acid (V) was obtained as oily residue in a yield of 89%. NMR is shown in Table I. IR $\nu_{max}^{liq.}$ cm^{-1}: 1730 (CO_2H). UV $\lambda_{max}^{H_2O}$ (ε): 230 (4600).

Alkaline Decomposition of N-Ethoxycarbonyl-3-morpholinosydnonimine (VIII)——A solution of 242 mg of VIII in 2 ml of 1 N NaOH was heated at 100° for 30 min and diluted with 20 ml of H_2O. Dropping 5 ml of 1 N H_2SO_4 to the solution, formed CO_2 was absorbed with 50 ml of 0.1 N $Ba(OH)_2$ in a stream of N_2. The yield of CO_2 was estimated to be 74% by titration of the residual $Ba(OH)_2$ in the filtrate with 0.1 N HCl. The residual VIII in the acid solution was determined to be 12% by the absorbance at 285 mμ. A yield of ethanol, 77%, was determined by gas chromatography; t_R 3.2 min at 75° on a column of 20% PEG on "GC-Q" flowing H_2 at 1 kg cm^{-2}. Extracting the acid solution with ether, V was obtained in a yield of 60%. UV $\lambda_{max}^{H_2O}$: 230. NMR is shown in Table I.

Alkaline hydrolysis of the N-ethoxycarbonyl group in VIII to EtOH *via* $EtCO_3Na$ was observed by NMR of the ethyl groups (Table I). Ethyl carbonate, ethyl chlorocarbonate, and urethane hydrolyze in same manner.

Acid Decomposition of VIII——VIII in 0.1 N HCl (248 mg/23 ml) was heated at 92° for 24 hr. CO_2 in yield of 80% was determined by titration mentioned above. Residual solution gave $E_{1cm}^{1\%}$ 221 at 291 mμ corresponding to formation of 43% I. NMR spectrum of the product corresponds to a mixture of 7% of VIII, 45% of I, 50% of morpholine (RH), and trace of III and VI. A large amount of NH_4Cl and trace of primary amine were detected by amino acid analyser. By thin-layer chromatography (TLC), RH, I, VI, VIII, and some other products were detected.

For TLC, samples (0.5 M, 5 μl) were spotted on Merck's silica gel GF $_{254}$ of 0.25 mm in thick and developed by ascending method (Table II). I, V, VI, and VIII were detected by UV absorption. Spraying 0.5% sodium β-naphthoquinone-4-sulfonate in 0.1 N NaOH, morpholine (RH), N-amino-morpholine (RNH_2), I, V, and VIII gave orange spots whereas VI gave decolorized spot. III, V, RH, and RNH_2 were detected by ninhydrin.

Table II. *Rf* Values of Thin-Layer Chromatography on Silica Gel GF_{254} by Ascending Method

Solv.	I	V	VI	VIII	RH	RNH_2	VI′	X
A	0.35	0.59	0.90	0.60	0.25	0.3	0.6	0.2
MeOH	0.5			0.75	0.3			
EtOAc	0	0	0.87	0	0			
B	d	0.59	0.91	d	0.65	0.7	0.93	0.6

VI′: $RNHCH_2CN$ A: BuOH-AcOH-H_2O (5:1:4) B: EtOH-NH_3 (9:1) d: decomposition

Acid Decomposition of I——On heating I in 0.1 N HCl (306 mg/50 ml) at 100° for 11 hr, 38% of I decomposed to morpholine (RH), N_2, NH_4Cl and chloroacetic acid (X). Treating I in 0.1 M acetate buffer at pH 4—3 at 100° for 5 hr, 62% of I decomposed mainly to VI *via* III and partially to the acid hydrolysates (RH, NH_4Cl *etc.*).

Photolysis of I——Irradiating 4 ml of 1% I in 0.1 N HCl to high pressure mercury lamp for 13 hr, I decomposed completely with evolution of N_2. Morpholine was separated by ion exchange resin from the solution and identified as following: TLC *Rf* 0.65 (EtOH:NH_3=9:1), 0.25 (*n*-BuOH:AcOH:H_2O=5:1:4). IR ν_{max}^{KBr} cm^{-1}: 1100 (C-O), 870 (C-N), 1045, 1455, 1430, 1310. NMR τ' in D_2O: 6.6 (4H, multiplet), 5.9 (4H, multiplet). NH_4Cl was determined by amino acid analyser. Glycolic acid, 37% in yield, was determined by absorbance at 570 mμ after treatment with chromotropic acid–H_2SO_4 at 100° for 1 hr. Chloroacetic acid, 9% in yield, was identified by IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1090 (C-O), 1205, 1400, and determined by the chromotropic acid method after hydrolysis in 1 N NaOH at 100° for 1 hr.

Photolysis of VIII——Photolyzed products from VIII were analyzed by the same methods mentioned above to be glycolic acid (32%), chloroacetic acid (8%), morpholine, NH_4Cl, EtOH and CO_2.

Determination of Rates for Decomposition of I and VIII

Rate of Photolyses of VIII and I——A solution of VIII in 0.01 N HCl (0.62 mM, $1\times1\times1.4$ cm^3) was irradiated with monochromatic light from Xe lamp at 285±8 mμ with energy of 3900 erg cm^{-2} sec^{-1}. The absorbances at 285 mμ after dilution by 21 times decreased linearly from 0.48 to 0.16 within 1500 sec. Since $0.62\times1.4\times$ (0.48—0.16)/0.48 μmoles; 3.5×10^{17} molecules of VIII decomposed with absorption of $3900\times1.4\times1500=8.2\times10^6$ erg; 1.16×10^{18} photons, quantum yield was estimated to be 0.3.

Irradiating 0.97 mM I in 0.01 N HCl in the condition similar to above, absorbances at 291 mμ after dilution (×21) decreased linearly from 0.51 to 0.12 within 1500 sec. The quantum yield was estimated to be 0.5.

When aqueous solution of VIII (0.66 mM, $1\times1\times1.4$ cm^3) was irradiated with light at 310±8 mμ (4500 erg cm^{-2} sec^{-1}), absorbances of dilute solutions (×21) at 310 mμ decreased linearly from 0.48 to 0.16 within 600 sec, the quantum yield being 0.7.

A linear relation between log (absorbance) and irradiated time with a slope of 2.4×10^{-3} sec^{-1} was observed in lower absorbance (0.33) of VIII in 0.01 N HCl solution (0.02 mM, 1 cm or 0.2 mM, 0.1 cm). The rates of photolyses of I (0.024 mM, 1 cm or 0.24 mM, 0.1 cm) in 0.01 N HCl at 291 mμ were close to that of VIII.

Dilute solutions of 0.034 mM VIII or 0.048 mM I in 0.01 N HCl (l=1 cm) were irradiated with light at different wave length in a constant energy of 5×10^5 erg. Percentage decompositions measured photometrically were 11, 13, 15, 13, 9, and 2% for VIII, and 10, 14, 18, 20, 17, and 3% for I at 250, 270, 280, 290, 300, and 320 mμ, respectively.

Kinetic Procedure——Aliquot 2 ml of 0.01% I or VIII in a buffer solution was heated in an ampoule under N_2 atmosphere. Aliquot 1 ml of the solution was mixed with 9 ml of 0.1 N HCl to stop the reaction and subjected to the photometric determination. For rapid reaction, aqueous solution of I (0.5 ml) in a small beaker was turned over under N_2 in a buffer (10 ml) dipped in thermostat to start the reaction, which was stopped by pouring 1 ml of 2 N HCl.

Buffer Solutions——HCl (pH 0—2), 0.01 M NaOAc-HCl (pH 3—7, μ=0.01), 0.01 M Na_2HPO_4-KH_2PO_4-NaOH (pH 6—10), 0.01 M $Na_2B_2O_7$-HCl-NaOH (pH 6—10) and NaOH (pOH 0—2) were used. The pH values at 20—100° were measured with glass electrode for high temperature in oil thermostat after calibration with standard buffers.[11a] Accuracy of pH at 100° is expected to be ±0.1. Temperature dependence of pH observed was close to that in reference.[11a] Differences of pH at 100°—pH at 20° were +0.02 (0.1 N HCl), +0.1 (acetate), +0.02 (phosphate, pH 7), −0.25 (borate, pH 8), −0.4 (borax, pH 9.2), and −0.6 (borate, pH 10.2 at 20°). Values of pKw at 2, 25, 40, and 60° were taken for 14.86, 13.997, 13.535, and 13.017, respectively[11b] and pKw at 80 and 100° were calculated to be 12.6 and 12.3±0.05, respectively using empirical equation.[11b] pOH of 0.1 N NaOH is 1.11—1.12 at 0—70°.[11c]

Measurement of p*K* of VIII—VII——Titrating 0.02 M VIII in H_2O with 1 N HCl at 25°, pK of VIII—VII was estimated to be 3.34 from pH at 0.5 eq neutralization. The pK at 88° was measured to be 3.03 from pH of 0.02 M VIII with 0.01 N HCl by the method mentioned above. The pK 3.0±0.1 at 100° was assumed from these values.

pH Stat Method to Observe Dissociation and Decomposition of I——Rates of consumption of 0.1 N NaOH with 10 ml of 4 mM I were automatically recorded on the pH stat, setting the end point at pH 8—10, the proportional band at 0.1, the injecting rate at 0.6 ml/min, the chart speed at 4 cm/min, and the temperature of jacket cell at 2° or 25°. The pK_I values of I were estimated to be 9.6 at 2° and 9.1 at 25° by the equation, $pK_I=pH-\log[v_e/(v_\infty-v_e)]$, where v_e was volume of NaOH to reach initially the given pH and v_∞ was that (1 eq) in final. The same pK_I values were also obtained by rapid potentiometric titration within 20 sec,

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11) *a*) R.G. Bates, "Meaning and Standardization of pH Measurements," ASTM Special Technical Publication No. 190, 1957, p. 5; *b*) M.S. Harned and B.B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, 1958, pp. 634—649; *c*) G. Åkerlöf and G. Kegeles, *J. Am. Chem. Soc.*, **62**, 620 (1940).

whereas false pK_I 6—8.9 were obtained by slow titrations (0.001—1.5 eq/min) at 25° because of the decomposition of I to III and HCl. The rate of decomposition was also automatically measured with the pH stat. Linear plots for log $[(v_\infty - v)/(v_\infty - v_e)]$ *vs.* t were obtained in every run (Fig. 1).

Ultraviolet Spectra of 3-Morpholinosydnonimine (II)——UV spectra of II could not be measured by ordinary method because II decomposed immediately in alkaline solution. Then the steady states at 8 sec after mixing 2 mM I with buffer solutions of pH 1—10.3 (1:1) were observed by flowing the mixtures in a cell of 1 mm in light path at 25°. The spectra at pH 1—7 were that of I as same as that observed by ordinary method: λ_{max} 291 mμ. The spectra at pH 9—10.3 were ascribed to mixtures of I and II, λ_{max} 325 mμ. Correct absorbance of II could not be observed even by the flow method because of the unstability.

Photometric Determination of I——Extracting 10 ml of test solution in 0.1 N HCl with twice 10 ml of EtOAc, 99% of I remained in the aqueous layer, whereas 99% of the decomposed products (III—VI) were taken off from the acid layer. Absorbance of the clear acid solution at 291 mμ was measured to determine I.

Photometric Determination of VIII——VIII was determined by the same procedure as I. The hydrochloride (VII), $\lambda_{max}^{0.1N\ HCl}$: 285 mμ. Extracting aqueous solution of VIII and I at pH 5—7 with $CHCl_3$, only VIII was transferred to the $CHCl_3$ layer. VIII, $\lambda_{max}^{CHCl_3}$: 326 mμ. Decomposed products of VIII, apart from I and VI, have no absorption which might interfere the determination.

Reactions of N-Morpholino-N-nitrosoaminoacetonitrile (III) and N-Cyanomethylenaminomorpholine (VI)

Formation of I from III——III converted to I in 1 N HCl and EtOH (9:1). The rate constant ($k'_5 = 3 \times 10^{-4}$ sec^{-1}) for the formation of I at 24° was estimated from the slope of linear plot of log $(A_\infty - A_t)$ *vs.* time, where A_∞ and A_t were absorbance at 291 mμ in final (at 4 hr) and at t sec, respectively (Fig. 1, No. 5). The reaction completed within 2 min at 100°. The yields of I from III in 1, 0.1 and 0.01 N HCl were 90, 16 and 5%, respectively, where the residual portions of III decomposed to VI.

Decomposition of III——III decomposed to VI with the evolution of NO, which was detected on Mass Spectrum (*m/e*:30). In 0.01 M buffer solutions at pH 2, 4, 7, 9, and 12, absorbance at λ_{max} 278 and 200 mμ for VI rapidly increased in the cost of absorbance at λ_{max} 232 mμ for III. The rate constants (k_3) for the formation of VI from III were estimated from slopes of linear plots of log $(A_\infty - A_t)$ *vs.* time, where A_∞ and A_t were absorbance at 278 mμ in final and at t sec, respectively (Fig. 1, No. 3). The k_3 values were close to 2×10^{-4} sec^{-1} at 22±1° in pH 2—12.

The nitrile (III) was hydrolyzed to the carboxylic acid (V) and NH_3 *via* IV on heating in 0.1—1 N NaOH at 100°.

Hydrolysis of VI——Treating VI (15 mg) in 1 N DCl at 100° for 5 min, N-aminomorpholine (RNH_2) and HCO_2H were detected as following. NMR (in DCl) τ': 6.07, 6.74 (8H, multiplet, RNH_2), 1.74 (1H, HCO_2H). IR ν_{max}^{KBr} cm^{-1}: 1575, 1530, (NH_3^+), 1175, 1075, 910, 860 (morpholine ring). UV: no peak at $\lambda > 210$ mμ. Mass Spectrum *m/e*: 102 (RNH_2^+), 86 (R^+), 44, 28.

Rate constants (k_6) of the hydrolysis of VI were estimated from slopes of linear plots of log (absorbance at 278 mμ) *vs.* time (Fig. 1, No. 6). The $10^3 k_6$ values (sec^{-1}) in 0.1 N HCl, 0.01 N HCl, 0.1 N NaOH at 100° and in 0.1 N HCl at 21° were 1.65, 0.16, 1.3, and 0.0024, respectively. No decrease of VI was observed on heating the neutral solution at 100° for 5 hr.

Result and Discussion

Decomposition of 3-Morpholinosydnonimine Hydrochloride (I)

I is a salt of strong base, 3-morpholinosydnonimine (II), with acid dissociation constant pK_I 9.1 at 25° or 9.6 at 2°. The site of protonation is assumed to be 5-N from the NH_2^+ peak in nuclear magnetic resonance (NMR) and from the highest electron density.[8] In aqueous solution at pH above 2, I decomposes easily to N-morpholino-N-nitrosoaminoacetonitrile (III) releasing hydrochloric acid. The rate of reaction of I to III was measured by consumption of alkali with pH stat. The initial rapid consumption is ascribed to the immediate equilibrium of $I \rightleftharpoons II$ since the volume (v_e)-pH curve resembles the titration curve of I. The successive slow consumption of alkali is due to the neutralization of hydrochloric acid released in the decomposition of I to III, which seems to be a first order reaction (Fig. 1, No. 1). The residual ratio $(I)/(I_0)$ in consecutive reversible reaction, $I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} II \underset{k_5}{\overset{k_2}{\rightleftharpoons}} III$ after the initial equilibrium, is generally given by Eq. 1,[12] where $k_1 + k_{-1} \gg k_2 \gg k_5$.

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[12] S. Funahashi and M. Tanaka, *Bunseki Kagaku*, 18, 913 (1969); A.A. Frost and R.G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, 1961, p. 173, 195, 216.

$$(\mathrm{I})/(\mathrm{I}_0)=[k_1/(k_1+k_{-1})]\exp[-k_1k_2t/(k_1+k_{-1})] \qquad \text{Eq. 1}$$

Using the relations: $k_1/k_{-1}=(\mathrm{II_e})/(\mathrm{I_e})=K_\mathrm{I}/(\mathrm{H^+})=(\mathrm{OH^-})/K_\mathrm{II}=v_\mathrm{e}/(v_\infty-v_\mathrm{e})$ and $(\mathrm{I_e})+(\mathrm{II_e})=(\mathrm{I_0})$, the rate constant ($k_2$) is given by Eq. 2, where subscripts o, e, ∞ and none mean initial, equilibrium, final and at t sec after the equilibrium, and K_II is base dissociation constant of II.

$$\begin{aligned} k_2 &= \left[1+\frac{(\mathrm{H^+})}{K_\mathrm{I}}\right]\frac{2.3}{t}\log\frac{(\mathrm{I_0})}{(\mathrm{I})}\cdot\frac{1}{1+K_\mathrm{I}/(\mathrm{H^+})} \\ &= [(\mathrm{I_0})/(\mathrm{II_e})](2.3/t)\log[(\mathrm{I_e})/(\mathrm{I})] \\ &= (v_\infty/v_\mathrm{e})(2.3/t)\log[(v_\infty-v_\mathrm{e})/(v_\infty-v)] \qquad \text{Eq. 2} \end{aligned}$$

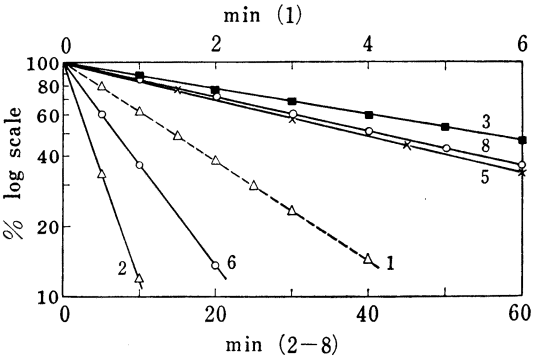

Fig. 1. Typical First-order Plots for Residual Percentage in Logarithmic Scale *vs.* Time

1) I to III at pH 8.8, 25° by pH stat, 2) I to III at pH 8.6, 25° by loss of absorbance at 291 mμ (A_{291}), 3) III to VI at pH 7.2, 22° by increase of A_{278}, 5) III to I in 1 N HCl at 24° by increase of A_{291}, 6) VI to RNH_2 in 0.1 N HCl at 100° by loss of A_{278}, 8) VIII to V in 0.01 N NaOH at 100° by loss of A_{285}

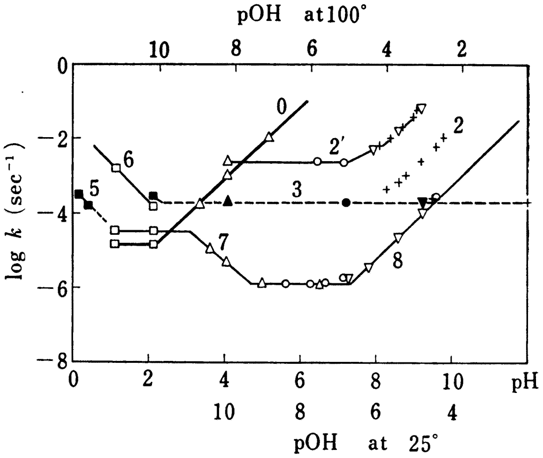

Fig. 2. pH Profiles of Rate Constants (k in $\mathrm{sec^{-1}}$) for First-order Reactions

0) k_obs for I to III at 100°, 2) k_2 for II to III at 2°, 2') k_2 or k_2' for II to III at 25°, 3) k_3 for III to VI at 22°, 5) k_5' for III to I at 24°, 6) k_6 for VI to RNH_2 at 100°, 7) k_7 for VII to RH at 100°, 8) k_8 for VIII to II at 100°, buffers: □ HCl, △ acetate, ○ phosphate, ▽ borate, + NaOH

At pH 8—10, linear relationships between log k_2 and pOH were obtained as shown in Fig. 2, No. 2 and 2': $k_2=4\times10^3\,(\mathrm{OH^-})$ at 25° and $k_2=1.4\times10^3\,(\mathrm{OH^-})$ at 2°. The cleavage of II to III revealed to be $\mathrm{OH^-}$ catalyzed reaction. The activation enthalpy ΔH^{*} 7 kcal $\mathrm{mole^{-1}}$ and the activation entropy ΔS^{*} —18 cal $\mathrm{mole^{-1}}$ $\mathrm{deg^{-1}}$ were estimated from the temperature dependence of log k_2.

The residual concentration of I plus II was also determined by absorbance(A) at 291 mμ in the acid solution of I and II converted to I after the decomposed products (III—VI) were eliminated by extraction. The apparent first-order rate constant (k_obs) is calculated by Eq. 3.

$$k_\mathrm{obs} = (2.3/t)\log(A_0/A) \qquad \text{Eq. 3}$$

The rate constant (k_2') for the cleavage of II to III is given by Eq. 4.

$$\begin{aligned} k_2' &= \frac{k_1+k_{-1}}{k_1}\cdot\frac{2.3}{t}\log\frac{(\mathrm{I_0})}{(\mathrm{I})+(\mathrm{II})} \\ &= \left[1+\frac{K_\mathrm{II}}{(\mathrm{OH^-})}\right]k_\mathrm{obs} \qquad \text{Eq. 4} \end{aligned}$$

The k_2' values measured at 25° in 0.01 M borate buffers at pH 8—10 or aqueous solution adjusted with pH stat coincide with the k_2 to suggest the negligible effect of borate on the rate.

In the condition of $(OH^-) \ll K_{II}$, Eq. 4 is reduced to $k_2' = k_{obs}\ K_{II}/(OH^-)$. The k_{obs} at pH 4—7 was proportional to (OH^-), whereas k_2' 2.5×10^{-3} (sec^{-1}) at 25° was independent of (OH^-). Considering the consecutive process, $I \rightleftharpoons II \rightarrow III$, the small amount of II in equilibrium with I cleaves spontaneously to III in the pH region. Another less preferable process is base catalyzed reaction of I→III with the rate of k_{obs} (I) (OH^-). The k_{obs} in pH 3.3—5.2 at 100° was also proportional to (OH^-): $k_{obs} = 1.6 \times 10^5\ (OH^-)$. The base dissociation constant (K_{II}) at 40—100° is assumed to be 10^{-5} order from the pK_{II} 4.9—5.2 at 25-2° since it could not be measured as the unstability of II. The k_2' at 100° was estimated at about 1.6.

Dependence of the k_{obs} on the concentration of acetate buffer (Ac) at pH 4 (ionic strength $\mu = 0.04$) at 100° was very small as shown in Table III and $k_{obs} = 1.6 \times 10^5\ (OH^-) + 3 \times 10^{-3}$ (Ac). Acetate will behave as a weak catalyzer for the decomposition of II and may modify the K_{II}.

Table III. Effect of Acetate Buffer (pH 4.0) on the Rate Constant (k_{obs}) at 100°

HOAc	NaOAc	KCl	$k_{obs} \times 10^3$ sec^{-1}
0.16 M	0.04 M	0 M	1.42
0.08	0.02	0.02	1.11
0.04	0.01	0.03	0.96

The k_{obs} at pH 4 depends on ionic strength ($\mu = 0.02$—1) as shown in Fig. 3. Activity coefficient (γ) of ion such as I correlates with ionic strength: $\log\gamma = -0.5\ \mu^{1/2}$, whereas activity coefficients of molecules such as II and water are independent of ionic strength.[13] Therefore the k_{obs} is predicted to correlate with ionic strength whereas the k_2' does not. The experimental results agreed well with the prediction as shown in Eq. 5, where a was activity and $1 + K_{II}/(OH^-)$ in Eq. 4 was reduced to $(I_e)/(II_e)$ at pH 4.

$$\begin{aligned} \log k_{obs} &= \log k_2' + \log [(II_e)/(I_e)] \\ &= \log k_2' + \log (a_{II}/a_I) + \log \gamma_I \\ &= \bar{3}.00 - 0.46\mu^{1/2} \end{aligned} \qquad \text{Eq. 5}$$

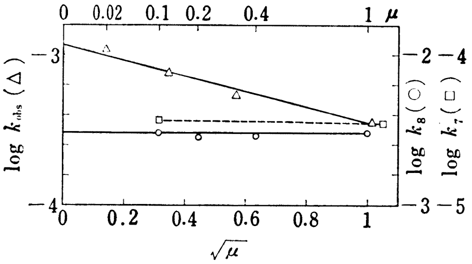

Fig. 3. Effects of Ionic Strength (μ) on the Rate Constants (k in sec^{-1}) at 100°

k_{obs} for I to III at pH 4 (△), k_7 for VII to RH in 0.1 N HCl (□), k_8 for VIII to II in 0.1 N NaOH (○)

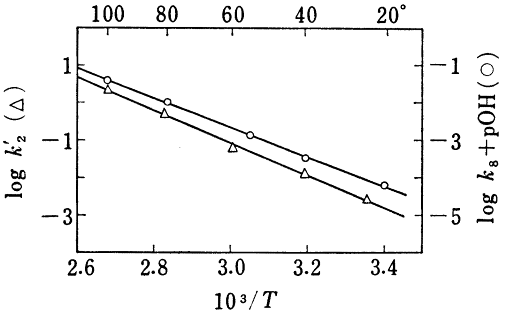

Fig. 4. Arrhenius Plots of Rate Constants

△: k_2' for II to III in acetate buffer of pH 4.05 at 25—100°, pOH 9.95—8.25
○: k_8 for VIII to II in 0.1 N NaOH, pOH 1.12 at 20—100°

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[13] E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, 1960, pp. 159—198.

The temperature dependence of k_{obs} was measured in the acetate buffer solution (pH 4) at 25—100°. A linear Arrhenius plot (Fig. 4) was obtained for k_2' which was calculated with $\log k_2' = \log k_{\mathrm{obs}} + \mathrm{pOH} - \mathrm{p}K_{\mathrm{II}}$, where $\mathrm{p}K_{\mathrm{II}}$ was postulated to be about 5 at 25—100°. The thermodynamic parameters, ΔH^{*} 20 kcal mole^{-1} and ΔS^{*} —4 cal mole^{-1} deg^{-1}, are different from those in alkaline solution probably because of the different reaction processes. It is difficult to discuss the ΔS^{*} since temperature dependence of $\mathrm{p}K_{\mathrm{II}}$ has been neglected.

Stability of N-Morpholino-N-nitrosoaminoacetonitrile (III)

III goes in 3 ways: (1) to N-cyanomethylenaminomorpholine (VI) and HNO in aqueous solutions (pH 2—12) or in solid state, (2) to N-morpholino-N-nitrosoaminoacetic acid (V) and ammonia in extreme alkaline solution, and (3) to I in hydrochloric acid. 3-Dialkylaminosydnonimines give fragments eliminated NO$^{\cdot}$ and HNO from the molecule in mass spectra[14] probably because of the stable quarternary ammonium structures($>N^{+}=NCH_2CN$), whereas 3-alkylsydnonimines do not give such fragments. The rate of reaction from III to VI is independent of pH (Fig. 2, No. 3). The reaction is not ionic but radical process.

Reverse reaction from III to I takes place in strong acid solution. The equilibrium tends to I in hydrochloric acid stronger than 1 N, whereas the decomposition of III to VI exceeds the formation of I at pH above 1. The cyclization of III to I is first-order reaction for III (Fig. 1, No. 5) and accelerates with acid (Fig. 2, No. 5). I has been synthetized from III in methanolic hydrochloric acid at room temperature.[3]

In extreme alkaline solution, hydrolysis of III to V overcomes the decomposition of III to VI since the hydrolysis accelerates with alkali.

The azomethine in VI hydrolyzes successively to N-aminomorpholine (RNH_2) and formic acid probably *via* cyanoformaldehyde.[15] The reaction is first order for VI (Fig. 1, No. 6) and the rate constant (k_6) depends on (H^+) or (OH^-) as shown in Fig. 2, No. 6.

Decomposition of N-Ethoxycarbonyl-3-morpholinosydnonimine (VIII)

VIII is stable in acid or neutral solutions. In extreme alkaline solutions, VIII decomposes to the carboxylate (V), ammonia, monoethyl carbonate, which further decomposes to ethanol and carbon dioxide.

Decomposition of VIII and its salt (VII) measured by photometry can be treated as a pseudo-first-order reaction. The rate constants (k_7 and k_8) are calculated by Eq. 3. No detectable difference was observed in the rates measured in different buffer solutions at same concentration and pH. The pH profile of log k at 100° is shown in Fig. 2. The rate is constant at pH 4.5—7.5 and relates linearly to the activity of hydroxyl ion (OH^-) at pH 7.5—10 as given in Eq. 6.

$$k_8 = 1.26\times10^{-6} + 0.126(\mathrm{OH}^-) \quad \text{at pH 4.5—10} \qquad \text{Eq. 6}$$

The rate at pH 1—4.5 is given by Eq. 7, where K is dissociation constant of VII to VIII ($\mathrm{p}K=3.0$ at 100°).

$$k_7 = 3.2\times10^{-5}/[1+K/(\mathrm{H}^+)] \quad \text{at pH 1—4.5} \qquad \text{Eq. 7}$$

The protonation of the base (VIII) to the salt (VII) is so fast as to be excluded from the rate-determining step of the decomposition. The rate of decomposition of VII is independent to the activity of hydrogen ion(H^+) in $(H^+) \gg K$ and proportional to the concentration of VII in

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[14] T. Shima, A. Ouchida, and Y. Asahi, *Mass Spectroscopy*, **17**, 661 (1969).

[15] C. Grundmann, *Chem. Ber.*, **97**, 566 (1964).

equilibrium with VIII in $(H^+) \leq K$. The hydrolysis of VIII in pH 4.5—7.5 seems to proceed in a constant rate with attack of water on VIII.

The rate (k_8) of base-catalyzed hydrolysis of VIII is hardly affected by ionic strength (Fig. 3). This suggests[13] formation of anionic activated complex with the same charge as the reactants, hydroxyl anion and the dipolar molecule (VIII). The rate (k_7) of hydrolysis of VII is also independent of ionic strength (Fig. 3). This fact predicts again to form the cationic complex from the cation (VII) and dipolar water.

The rate of decomposition of VIII at pOH 1.12 was measured at 20—100°. From a linear plot of log k_8+pOH *vs.* $1/T$ (Fig. 4), $\Delta H^{\neq}$ 18 kcal mole^{-1} and $\Delta S^{\neq}$ —18 cal mole^{-1} deg^{-1} were estimated for the reaction. The ratio of rate constants, $k_{100°}/k_{20°}$, was 1000 at the constant pOH. VIII is more stable for alkali than I by 3×10^5 times. The large negative activation entropy suggests[13] activated complex with restricted motion such as hydroxyl attached on the carbonyl of VIII.

Considering the kinetic and chemical study of hydrolysis of VIII, the mechanism is postulated as following (Chart 2). The initial process is hydrolysis of the N-acyl. Electron density distribution in the N-acyl was calculated[8] to be +0.185 (N), +0.214 (C) and —0.316 (O). The acyl carbon with positive partial charge will be attacked by OH$^-$ ion to form a transition state with negative charge. The successive hydrolysis of monoethyl carbonate is explained by the same process. The fragment of sydnonimine decomposes rapidly as same as I.

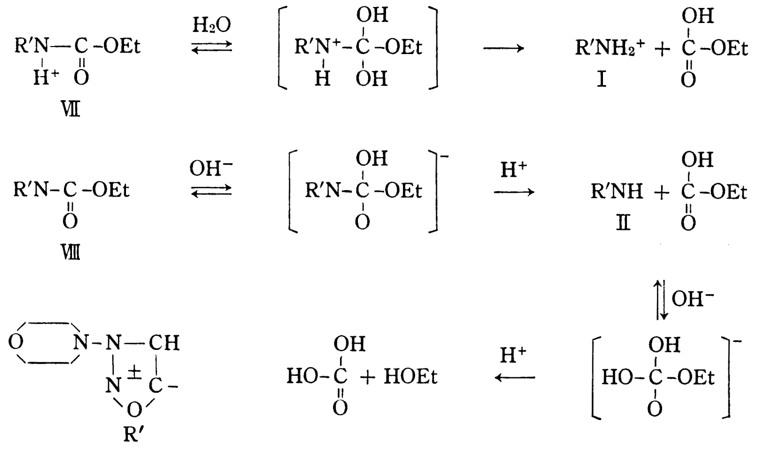

Chart 2

Photolysis of Sydnonimines

Irradiating I and VII in acid solution with ultraviolet (UV) light, nitrogen, morpholine, ammonium chloride, chloroacetic acid, and glycolic acid are obtained. Although these products resemble those of acid decomposition, this is not thermolysis but photolysis since the reaction proceeds even at 0° with monochromatic light.

The photolyses of I and VIII in low absorbance proceed in first order with regard to the residual concentrations. The light quantity effective to the photolyses will decrease exponentially in the course of reactions, in which the excited molecules decompose in first order to the products with no absorbance. The photolyses in high absorbance, however, are zeroth order reactions since the irradiated light is completely absorbed by the reactants until almost end of the photolyses. The quantum yields, numbers of molecule decomposed by a photon, were fairly high (0.3—0.7). Dependences of the rates of photolyses on wave length of irradiation in low absorbance resemble the absorption curves of reactants. This fact suggests that absorption of the effective light initiates the photolyses and that the efficiency of light depends on absorbance of the solution at certain wave length.

Conclusion

Practically useful informations on the stabilities of I and VIII are obtained from this study. Periods to reach 10% of loss at particular temperatures and pH are estimated as shown in Table IV. It is difficult to produce aqueous preparation of I with enough stability although I is very stable in extreme acid solution. Whereas VIII is very stable in aqueous solution at pH 5—7. The both are sensitive to light ($\lambda < 320$ mμ), which can be easily protected by appropriate vessels.

Table IV. Periods for 10% Loss of Sydnonimines (I, VIII)

	I			VIII	
pH	$t_{20°}$	$t_{100°}$	pH	$t_{20°}$	$t_{100°}$
9	2.6 sec		11	40 day	1.6 min
8	53 sec		10	400 day	16 min
6	15 hr		5—7	950 day	25 hr
4	67 day	92 sec	4	250 day	5.9 hr
1—2	13 year	2 hr	1—2	38 day	1.0 hr

Pharmaceutical activities of I, VIII, and their related compounds have been reported.[4] It is noteworthy that the decomposed product (III) hold the activity of I but VI does not. Other products such as ethanol, carbon dioxide, ammonia and morpholine, are predicted to be harmless.

Acknowledgement The authors express their sincere thanks to Dr. S. Tatsuoka and Dr. Y. Abe for permission to carry out this work. Thanks are due to Dr. K. Masuda and his colleagues for their offering materials and suggestion.