

tetrahydropyridine, b.p. 176 to 177.5° at 738 mm., taken as a heart cut for a yield of 20%. Picrate 170–171°, (Lit. picrate 170 to 170.5°) (7).

Anal.—Calcd. for C₈H₁₆N: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.83; H, 12.01; N, 10.93.

A solution of 8 Gm. of 4-isopropyl-1,2,5,6-tetrahydropyridine in 30 ml. of glacial acetic acid was subject to hydrogenation at 45 lb./in.² in the presence of 2.5 Gm. of 10% palladium-on-charcoal until hydrogen was no longer taken up. After filtering off the catalyst, the solution was made alkaline to litmus with 10 *N* sodium hydroxide solution, and the alkaline solution steam distilled until the distillate was neutral to litmus. The distillate was saturated with potassium carbonate, and the amine separated and dried over potassium hydroxide pellets. Careful fractionation through a glass helices column resulted in 5.6 Gm. (69%) of 4-isopropylpiperidine, b.p. 171–172° at 738 mm., *n*_D²⁰ 1.4577, chloroplatinate 172–173°. (Lit. b.p. 168–171°, chloroplatinate 172°) (8).

Anal.—Calcd. for C₈H₁₇N: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.38; H, 13.42; N, 11.22.

1,1-(3-Isopropylpentamethylene)-3-(1-phenyl-2,3-

dimethyl-5-pyrazolon-4-yl)-2-thiourea.—A solution of 0.57 Gm. (0.05 mole) of 4-isopropylpiperidine and 1.0 Gm. (0.04 mole) of 1-phenyl-2,3-dimethyl-5-pyrazolon-4-isothiocyanate in 10 ml. of absolute alcohol was refluxed on a steam bath for 2 hours. After evaporation of the reaction mixture to one-third its original volume, crystals formed on cooling. Filtration and recrystallization from alcohol gave 1.35 Gm. (90%) of the thiourea, m.p. 188–189°.

Anal.—Calcd. for C₂₀H₂₈N₄OS: C, 64.48; H, 7.57; N, 15.02. Found: C, 64.67; H, 7.61; N, 14.80.

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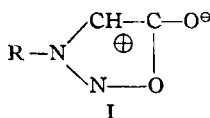
Prediction of Stability in Pharmaceutical Preparations XII

Solvolysis of Various Alkyl Sydnones

By EDWARD R. GARRETT

The kinetics of solvolysis of various alkyl sydnones—furfuryl, methyl, propyl, phenethyl, isopropyl, *s*-butyl, *t*-butyl, and 1,1,3,3 tetramethylbutyl, have been studied spectrophotometrically as a function of pH and temperature; rate-pH profiles have been determined. The order of reactivity on alkaline catalyzed solvolysis generally decreased in the order cited. Except for the furfuryl sydnone, the order of reactivity reversed on acid catalyzed solvolysis. The heats of activation for a specific type solvolysis were generally similar, and the greatest differences were in the entropies of activation. Only in the specific cases of 1,1,3,3-tetramethylbutyl, *t*-butyl, and furfuryl sydnones was a solvent or pH-independent solvolysis observed. In the alkaline pH range, the spectra shifts to that of the *N*-nitroso alkylamino acetic acid, whereas in acid solution absorbance is lost with time.

VARIOUS *meso*-IONIC 3-alkyl sydnones (1, 2) have been synthesized in these laboratories



by Kier and associates (3, 4) as potential thera-

peutic agents. They are pharmacologically active as central nervous system stimulants with a particularly stimulating effect on respiration. Several also possess antitumor activity (5).

It has been well known that the sydnones are hydrolyzed by hot aqueous alkali with regeneration of the original *N*-nitroso acid from which they are prepared and by hot acid to give a *R*-hydrazine, a carboxylic acid, and carbon dioxide (2, 6, 7).

It has also been stated that the stability of the sydnone ring, I, does not appear to depend to a significant extent on the nature of R (7). However, our preliminary kinetic studies had shown that this was not the case—that even

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among the alkyl sydnones alone, variations in R had a highly significant effect. The availability of the alkyl sydnones, R = methyl, propyl, phenethyl, isopropyl, *s*-butyl, furfuryl, *t*-butyl, and *t*-octyl (i.e., 1,1,3,3-tetramethylbutyl), synthesized by Dr. Kier and associates (3, 4), gave an excellent opportunity to define the effects of various alkyl substituents on the stability of the sydnone ring.

EXPERIMENTAL

General Procedure.—The isolation and characterization of the sydnones studied has been reported (4, 5). In general, the molar absorptivity of the sydnones was $\epsilon = 6000$ – 7000 in alkaline, acid, and neutral solutions as was expected (4), except for the phenethyl sydnone ($\epsilon = 3000$). The wavelength of maximum absorbance was shifted 2–4 $m\mu$ to the violet in the aqueous solution compared to those reported in ethyl alcohol (4). The absorbance of the sydnones' maxima was 284 and 286 $m\mu$. The absorbances and wavelengths of maximum absorbance did not significantly change with pH.

The general procedure for the kinetic studies was to dissolve a specific sydnone in nitrogen purged distilled water maintained at the temperature of the prospective kinetic study. The solution was subsequently diluted 1:1 with the appropriate nitrogen purged buffer solution, also thermally preequilibrated. In general, the final concentration was established at $10^{-4}M$ for optimum spectro-

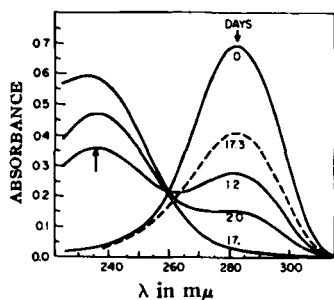


Fig. 1.—Typical spectrophotometric curves for the acid and alkaline degradation of alkyl sydnones. The absorbance of the 283 $m\mu$ band decreases with time in 0.5 M HCl (dashed line). A new 235 $m\mu$

band appears with time in 0.5 M NaOH. The sydnone is propyl sydnone ($10^{-4}M$) at 70° .

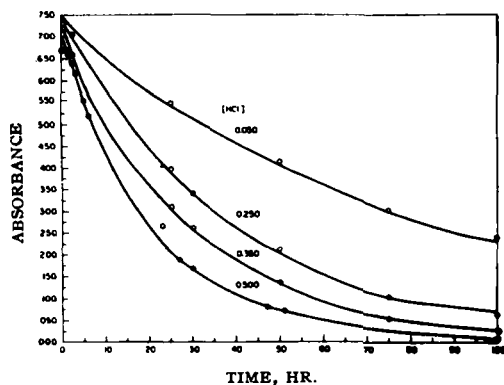


Fig. 2.—Typical curves for the loss of 284 $m\mu$ spectrophotometric absorbance of sydnones. The curves are obtained for the acid catalyzed solvolysis of *t*-butyl sydnone at 75° .

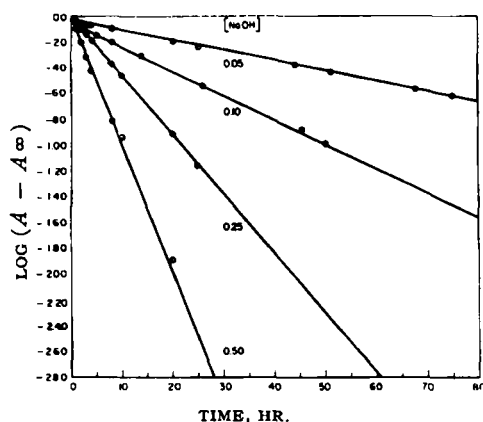


Fig. 3.—Typical first-order plots for the loss of 284 $m\mu$ absorbance (A) by alkaline catalyzed solvolysis for isopropyl sydnone at 75° . A_∞ is the asymptotic absorbance with time.

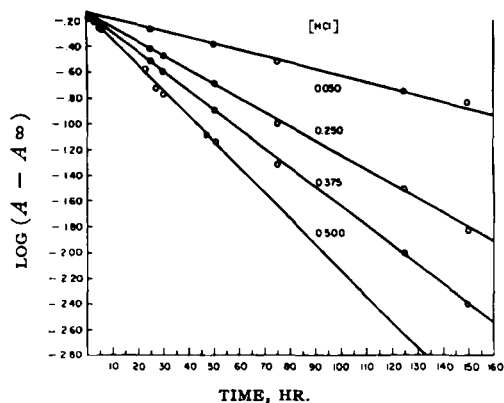


Fig. 4.—Typical first-order plots for the loss of 284 $m\mu$ absorbance, A , by acid catalyzed solvolysis, *t*-butyl sydnone at 75° . A_∞ is the asymptotic absorbance with time.

photometric absorbance reading, except for those specific cases where the effects of initial concentration on the apparent solvolytic rates were evaluated. In the phenethyl sydnone case the final concentration was adjusted to $2 \times 10^{-4}M$ to heighten the absorbances.

To abet solubilization, a few drops of ethanol were added to the sydnone prior to dissolution in the water. The alcohol percentage was negligible in a total final volume of 400 ml.

The aliquots to be assayed were rapidly cooled to room temperature before reading at the appropriate wavelengths on the Beckman model DU ultraviolet spectrophotometer.

Spectrophotometric Studies.—The absorbance, A , at the wavelength of the maximum for each sydnone (284 $m\mu$, except 286 $m\mu$ for phenethyl and furfuryl sydnone) was read as a function of time until a small residual spectrophotometric reading, A_∞ , remained constant or asymptotically approached zero.

In the cases of all sydnones but *t*-octyl a new band arose on alkaline catalyzed solvolysis but not on acid solvolysis. This new band had a maximum absorbance at wavelengths further toward the violet. Specifically, the maximum absorbance of the new absorption band was 232 $m\mu$ for propyl

TABLE I.—CONDITIONS AND RATE CONSTANTS (k IN SEC.⁻¹) FOR THE APPARENT FIRST-ORDER ACID CATALYZED DEGRADATION OF *t*-OCTYLSYDNONE^a ($10^{-4} M$)

Temp., °C.	[HCl]	pH ^b	10^3k	$10^3(k - k_0)^c$
50.0	0.050	1.39	0.390	0.13
50.0	0.125	1.02	0.518	0.25
50.0	0.250	0.73	0.781	0.42
50.0	0.375	0.56	1.07	0.71
50.0	0.500	0.44	1.43	1.08
54.7	0.050	1.39	0.710	0.07
54.7	0.125	1.02	1.03	0.39
54.7	0.250	0.73	1.50	0.86
54.7	0.375	0.56	1.95	1.31
54.7	0.500	0.44	2.47	1.83
61.0	0.050	1.39	1.82	0.18
61.0	0.125	1.02	2.61	0.97
61.0	0.250	0.74	3.37	1.73
61.0	0.375	0.57	4.36	2.72
61.0	0.500	0.44	6.59	4.95
64.9	0.125	1.02	4.21	1.86
65.2	0.250	0.74	5.58	3.23
64.9	0.375	0.57	7.71	5.36
64.9	0.500	0.44	9.96	7.61
69.0	0.0038	(2.31)	4.64	...
69.0	0.0063	(2.10)	4.54	...
69.0	0.0125	1.97	4.64	...
69.0	0.0188	1.78	5.60	1.00
69.0	0.025	1.60	5.63	1.03
69.0	0.050	1.39	6.23	1.63
68.3	0.100	1.11	7.93	3.33
68.3	0.200	0.83	9.49	4.9
69.6	0.250	0.74	11.4	6.8
68.3	0.300	0.66	12.8	8.2
68.3	0.500	0.45	18.2	13.6
75.0	0.050	1.39	11.6	1.1
74.9	0.125	1.02	14.7	4.2
75.0	0.250	0.74	24.0	13.5
75.0	0.375	0.58	29.6	19.1
75.0	0.500	0.45	38.3	27.8

^a 1,1,3,3-Tetramethylbutylsydnone. ^b The pH values listed were calculated from $\text{pH} = -\log f_{\text{HCl}}[\text{HCl}]$, where the mean activity coefficients, f_{HCl} , were obtained or extrapolated from data in the literature for the appropriate temperatures. The parenthetical values were observed pH values. ^c The k_0 values were obtained from the k values for runs in 0.25 M NaCl.

TABLE II.—CONDITIONS AND RATE CONSTANTS (k -SEC.⁻¹) FOR THE APPARENT FIRST-ORDER ACID CATALYZED DEGRADATION OF SYDNONES ($10^{-4} M$)^a

Sydnone	Temp., °C.	[HCl] ^b	10^3k	Sydnone	Temp., °C.	[HCl] ^b	10^3k
Furfuryl	75.0	0.50	363	Phenethyl	75.1	0.375	0.196
	75.1	0.375	326		75.1	0.25	0.118
	75.1	0.25	312		75.1	0.05	0.026
	75.1	0.05	266		70.1	0.50	0.205
	70.0	0.50	199		61.6	0.50	0.075
<i>t</i> -Butyl	61.5	0.50	71.8	Isopropyl	75.2	0.50	0.408
	75.1	0.50	12.00		75.1	0.375	0.244
	75.2	0.375	9.61		75.1	0.25	0.195
	75.2	0.25	7.07		75.1	0.05	0.046
	75.2	0.05	3.18		70.1	0.50	0.219
Propyl	70.0	0.50	6.40	<i>s</i> -Butyl	61.4	0.50	0.075
	61.6	0.50	1.88		75.0	0.50	0.227
	74.9	0.50	0.306		75.0	0.375	0.171
	75.1	0.375	0.259		75.0	0.25	0.136
	75.1	0.25	0.170		75.0	0.05	0.043
Methyl	75.1	0.05	0.038	70.1	0.50	0.166	
	70.1	0.50	0.197	61.6	0.50	0.077	
	61.6	0.50	0.061	
	74.9	0.50	0.376	
	75.1	0.375	0.286	
75.1	0.25	0.184		
75.1	0.05	0.048		
70.1	0.50	0.240		
61.6	0.50	0.072		

^a The phenethylsydnone kinetics were studied at $2.02 \times 10^{-4} M$. ^b The calculated pH at 75° for various [HCl] are 0.50 M 0.45; 0.375 M , 0.58; 0.25 M , 0.74; and 0.05 M , 1.39.

sydnone, isobestic at 259 $m\mu$; 256 $m\mu$ for furfuryl sydnone, isobestic at 268 $m\mu$, 235 $m\mu$ for isopropyl sydnone; and 235 $m\mu$ for methyl sydnone. The *t*-butyl and *s*-butyl sydnones also showed a new band with maximum absorbance at 232 $m\mu$ when subjected to 0.2–0.5 M NaOH. The *t*-octyl sydnone showed no such new band with time in NaOH, HCl, or acetate and phosphate buffer solutions. Solvolysis of furfuryl sydnone in the neutral pH region also did not demonstrate the appearance of a new absorption band.

The rate of appearance of the new band on alkaline catalyzed solvolysis was the same as the rate of disappearance of the spectrophotometric absorption band of the sydnones. In general, the sum of the absorbances at the maxima of the disappearing and appearing bands was approximately constant.

Typical spectrophotometric curves as a function of time are given in Fig. 1 for propyl sydnone which demonstrate the appearance of a 235 $m\mu$ band on the disappearance of a 283 $m\mu$ band in alkaline solution. Typical curves for the disappearance of absorbance with time for the sydnones are given in Fig. 2 where the example given is for acid solvolysis.

CALCULATIONS AND RESULTS

Rate Constants.—The first-order rate constants, k , were calculated from the slopes of plots of the logarithm of the difference in absorbance, A_t at time t and the final absorbance, A_∞ , against time in accordance with:

$$\log(A - A_\infty) = -kt/2.303 + \log A_0 \quad (\text{Eq. 1})$$

Excellent first-order fits were obtained. Typical curves for alkaline and acid catalyzed solvolysis are given in Figs. 3 and 4.

The conditions and obtained rate constants for the acid catalyzed solvolysis of *t*-octyl sydnone which were studied in great detail are given in Table I. In addition, nine kinetic runs were studied in acetic acid-acetate buffers (0.05 M)

TABLE III.—CONDITIONS AND OBSERVED FIRST-ORDER CONSTANTS (k IN SEC.⁻¹) FOR THE APPARENT ALKALINE DEGRADATION OF SYDNONES ($10^{-4}M$)^a

Sydnone	Temp., °C.	[NaOH] ^b	10 ³ k	Sydnone	Temp., °C.	[NaOH] ^b	10 ³ k
Furfuryl	75.1	0.50	39.1	Phenethyl	75.0	0.50	10.37
	75.1	0.25	29.1		75.0	0.25	5.41
	75.0	0.10	22.1		75.0	0.10	2.02
	75.1	0.05	23.0		75.0	0.05	1.04
	69.8	0.50	24.9		69.8	0.50	5.50
	65.3	0.50	17.7		65.3	0.50	3.70
<i>t</i> -Butyl	40.1	0.50	8.57	Isopropyl	40.0	0.50	4.19
	75.1	0.50	4.34		75.1	0.50	5.92
	75.1	0.25	2.12		75.1	0.25	2.91
	75.1	0.10	0.908		75.2	0.10	1.12
	75.1	0.05	0.469		75.1	0.05	0.516
	70.0	0.50	2.67		69.7	0.50	3.87
Propyl	65.3	0.50	1.74	<i>s</i> -Butyl	65.3	0.50	2.50
	40.0	0.50	1.48		40.1	0.50	2.48
	75.0	0.50	8.57		75.2	0.50	6.89
	75.0	0.25	4.41		75.2	0.25	3.38
	75.3	0.10	1.45		75.1	0.10	1.25
	75.0	0.05	0.863		75.2	0.05	0.446
Methyl	70.0	0.50	5.45	<i>t</i> -Octyl	69.7	0.50	4.41
	65.3	0.50	3.45		65.3	0.50	2.66
	40.1	0.50	2.81		40.1	0.50	2.48
	75.0	0.50	10.45		79.6	0.05	15.9
	75.0	0.25	5.29		75.1	0.50	13.0
	75.0	0.10	1.78		75.1	0.25	11.6
	75.0	0.05	0.933		75.1	0.10	10.5
	70.0	0.50	6.26		75.1	0.05	9.63
	65.3	0.50	3.97		69.9	0.50	6.74
	40.0	0.50	3.77		69.9	0.25	5.80
		69.9	0.10	5.33
		69.9	0.05	4.85
...	69.9	0.005	5.18		
...	65.2	0.05	2.38		
...	61.1	0.50	2.07		
...	61.1	0.25	1.42		
...	61.0	0.05	1.41		
...	54.8	0.05	0.569		
...	50.0	0.05	0.313		

^a The phenethylsydnone kinetics were studied at $2.02 \times 10^{-4} M$. ^b Corresponding pH values can be calculated from $pOH = -\log f_{NaOH} [NaOH]$, $pH = pK_w - pOH$ where the activity coefficients, pOH , and the pK_w were given in or extrapolated from the data in the literature at 75°. Such calculated pH values are 12.24 for 0.50 *M* NaOH, 11.95 for 0.25 *M* NaOH, 11.61 for 0.10 *M* NaOH, and 11.34 for 0.05 *M* NaOH.

at 70.0° at pH values 2.98, 3.85, 4.29, 4.35, 4.51, 4.74, 4.92, 5.18, and 5.60; two runs were studied in phosphate buffers (0.10 *M*) at pH values 5.68 and 7.68; and four runs were studied in sodium chloride solutions at 0.01, 0.05, 0.10, and 0.30 *M*. The overall average 10^3k (sec.⁻¹) of these 15 runs was 4.82, standard deviation = 0.17. There was no significant effect of buffer, salt concentration, or pH on these rate values. Other studies on *t*-octyl sydnone hydrolysis in 0.25 *M* NaCl for various temperatures are: °C., 10^3k ; 50.0°, 0.307; 54.8°, 0.637; 61.0°, 1.64; 65.2°, 2.35; 75.1°, 10.5; 79.6°, 15.7.

Conditions and rate constants for the apparent first-order acid catalyzed degradation of the other sydnones studied are given in Table II. The only compounds in this table that demonstrated the pH-independent solvolysis, k_0 , characteristic of *t*-octyl sydnone were *t*-butyl sydnone (75°, pH 4.40, acetate buffer, $k = 2.5 \times 10^{-6}$ sec.⁻¹; pH 6.50, phosphate buffer, $k = 2.8 \times 10^{-6}$ sec.⁻¹) and furfuryl sydnone (75°, pH 4.40, acetate buffer, $k = 2.14 \times 10^{-4}$ sec.⁻¹; pH 6.50, phosphate buffer, $k = 2.27 \times 10^{-4}$ sec.⁻¹; 0.05 *M* NaCl, $k = 2.35 \times 10^{-4}$ sec.⁻¹; 0.25 *M* NaCl, 2.44×10^{-4} sec.⁻¹; 0.375 *M* NaCl, $k = 2.35 \times 10^{-4}$ sec.⁻¹; 0.50 *M* NaCl, $k = 2.66 \times 10^{-4}$ sec.⁻¹). The more general

TABLE IV.—CONDITIONS AND APPARENT FIRST-ORDER RATE CONSTANTS (10^3k IN SEC.⁻¹) FOR THE SOLVOLYSIS OF *t*-OCTYL SYDNONE IN VARIOUS ETHANOL-WATER MIXTURES

Vol. % Ethanol	Temp., °C.			
	61.3	65.0	70.0	75.0
0	1.65	2.36	4.70	10.1
10	1.13	1.98	2.66	6.65
20	0.589	1.22	2.05	4.12
30	0.409	0.531	1.06	1.96
40	0.162	0.267	0.528	1.04
50	0.164	0.168	0.287	0.56
60	...	0.089	0.205	...
70	0.124	...

evaluations of k_0 values are given below. All the other sydnones exhibited no significant change in spectrophotometric absorbance in the neutral pH regions, *viz.*, for 2 weeks at 75° in 0.5 *M* NaCl and also in acetate and phosphate buffers.

Conditions and rate constants for the apparent first-order alkaline degradation of the studied sydnones are given in Table III.

Effect of Sydnone Concentration on Rates.—There was no significant effect of sydnone concentration on the apparent first-order rate constant. In the following instances kinetic runs at 70° were

effected in 0.5 M HCl at $1.008 \times 10^{-4}M$ and $2.016 \times 10^{-4}M$ in sydnone (except for phenethylsydnone which was at twice these values). Aliquots of the higher concentration were diluted 1:1 with 0.5 M HCl so that it could be read at relatively the same absorbance as the lower concentration. The sydnones and the rate constants as 10^6k obtained at these two kinetic concentrations were: furfuryl, 199, 198; isopropyl, 0.219, 0.203; *s*-butyl, 0.166, 0.189; phenethyl, 0.205, 0.192; *t*-butyl, 6.40, 6.75; propyl, 0.197, 0.200; methyl, 0.240, 0.246.

The rate constants for the solvolysis of *t*-octyl sydnone in various ethanol-water mixtures and at several temperatures are given in Table IV.

Rate Dependency on Catalytic Species.—The log *k*-pH profiles for the solvolysis of sydnones that possess pH-independent regions of solvolysis (*t*-octyl, *t*-butyl, and furfuryl) are given in Fig. 5. The pH for the acidic region is calculated from

$$\text{pH} = -\log f_{\text{HCl}}[\text{HCl}] \quad (\text{Eq. 2})$$

where the mean activity coefficient f_{HCl} was obtained or extrapolated from data in the literature (8). The pertinent values are given in Tables I and II.

The pH for the alkaline region is calculated from

$$\text{pH} = \text{p}K_w - \text{pOH} = \text{p}K_w + \log f_{\text{NaOH}}[\text{NaOH}] \quad (\text{Eq. 3})$$

where the mean activity coefficient f_{NaOH} and the $\text{p}K_w$ was obtained or extrapolated from data in the literature (8).

There are several ways (9) of quantifying kinetic expressions to define explicitly dependence of apparent first-order rate constants on the catalytic variables. Specific acid catalysis can be considered in the expression

$$k = k_{\text{HCl}}[\text{HCl}] + k_o \quad (\text{Eq. 4})$$

where k is the apparent first-order rate constant for solvolysis in the acid region and k_o is the pH-independent apparent first-order rate constant. It follows that k plotted against $[\text{HCl}]$ should permit estimation of the slope k_{HCl} , the bimolecular rate constant for the HCl catalyzed solvolysis, and the intercept k_o . Such plots are given in Figs. 6 and 7 for the various sydnones at several temperatures and the derived k_{HCl} and k_o values are given in Table V.

Figure 6 is such a plot with nonzero intercepts for the sydnones that exhibited pH-independent solvolysis, whereas Fig. 7 is for those where pH-independent solvolysis was not significant.

An alternate method of rate constant determination is valid for the postulated rate dependence

$$k - k_o = k_{\text{H}^+}a_{\text{H}^+} \quad (\text{Eq. 5})$$

where k_{H^+} is the specific hydrogen ion catalytic rate constant and a_{H^+} is the activity of the hydrogen ion so that

$$\log(k - k_o) = \log k_{\text{H}^+} - \text{pH} \quad (\text{Eq. 6})$$

where pH can be calculated as in Eq. 2.

Such plots are given in Fig. 8 for *t*-octyl sydnone and *t*-butyl sydnone where the intercepts of the plots of the expected theoretical slope (*i.e.*, -1) are the $\log k_{\text{H}^+}$ values given on the semilog plot as k_{H^+} . An example of such a plot for a sydnone,

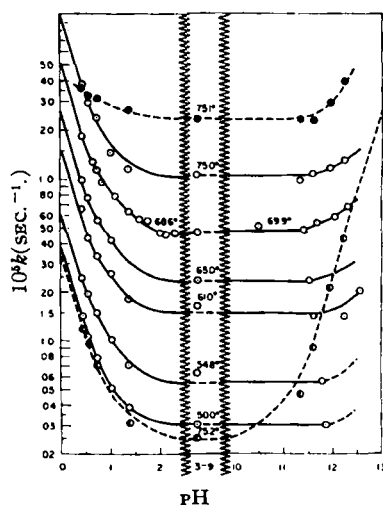


Fig. 5.—Profiles of the dependence of rate constants on pH for the solvolysis of sydnones that show a pH-independent region of solvolysis. Key: \circ *t*-octyl sydnone, \bullet furfuryl sydnone, \ominus *t*-butyl sydnone.

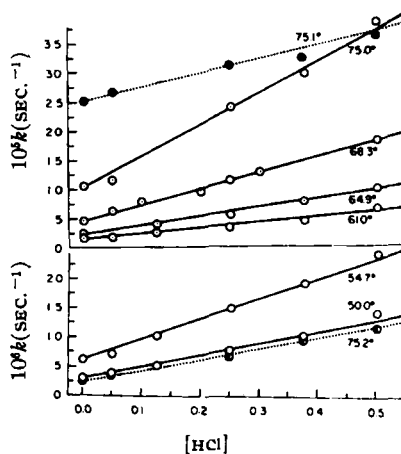


Fig. 6.—Apparent first-order rate constant, k , dependence on $[\text{HCl}]$ at various temperatures for sydnones that exhibit pH-independent solvolysis. Key: \circ *t*-octyl sydnone, \bullet furfuryl sydnone, \ominus *t*-butyl sydnone.

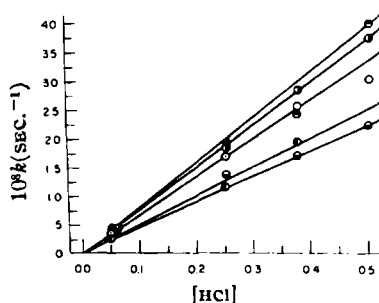


Fig. 7.—Apparent first-order rate constant, k , dependence on $[\text{HCl}]$ at 75° for sydnones that do not exhibit pH-independent solvolysis. Key: \circ propyl, \bullet methyl, \ominus phenethyl, \bullet isopropyl, \bullet *s*-butyl.

TABLE V.—CATALYTIC CONSTANTS FOR THE ACID AND NEUTRAL SOLVOLYSIS OF THE ALKYL SYDNONES (k_i IN SEC.⁻¹)

Sydnone	Temp., °C.	$10^6 k_{\text{HCl}}^a$	$10^6 k_o^a$	$10^6 k_{\text{H}^+}^b$
<i>t</i> -Octyl	50.0	20.2	3.1	27.2
	54.7	35.2	6.3	49.3
	61.0	90.0	16.0	120
	64.9	148	25	203
	68.3	222	46	420
	75.0	530	105	725
<i>t</i> -Butyl	75.2	19.0	2.5	27
Furfuryl	75.1	232	250	350
Methyl	75.1	0.676	0.00	1.08
Propyl	75.1	0.760	0.00	0.96
Phenethyl	75.1	0.508	0.00	0.68
Isopropyl	75.1	0.800	0.00	1.08
<i>s</i> -Butyl	75.0	0.450	0.00	0.70

^a Determined from the slopes and intercepts of plots of the apparent first-order rate constants k (sec.⁻¹) against $[\text{HCl}]$ according to the expression $k = k_{\text{HCl}}[\text{HCl}] + k_o$. ^b Determined from the intercept of plots of $\log(k - k_o)$ against pH according to the expression $\log(k - k_o) = \log k_{\text{H}^+} - \text{pH}$ where $\text{pH} = -\log f_{\text{HCl}}[\text{HCl}]$, where f_{HCl} is the mean activity coefficient obtained from the literature (8).

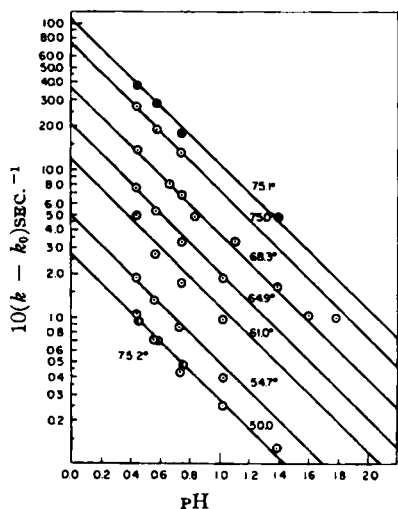


Fig. 8.—Semilogarithmic plots of the apparent first-order rate constants due to specific acid catalyzed solvolysis of sydnones, $k - k_o$, as a function of calculated pH. Key: ○, *t*-octyl, ○, *t*-butyl. ● methyl.

methyl sydnone, whose degradation is nonsolvent catalyzed (*i.e.*, $k_o = 0$) is also given in Fig. 8. The k_{H^+} values so determined are also given in Table V. Either catalytic rate constant, k_{H^+} or k_{HCl} , is valid for the prediction of the apparent first-order rate constant, k , provided that it is used in the appropriate equation for the acidity function appropriately defined.

Similarly, the specific hydroxyl ion catalytic rate constants can be determined from the slopes of plots of the apparent first-order rate constants, k , against $[\text{NaOH}]$ according to the expression

$$k = k_o + k_{\text{NaOH}}[\text{NaOH}] \quad (\text{Eq. 7})$$

Typical examples are given in Fig. 9, the pertinent data are given in Table VI.

Rate Dependency on Temperature.—The logarithmic version of the Arrhenius expression is

$$\log k = -\Delta H_a/RT + \log P \quad (\text{Eq. 8})$$

Such Arrhenius plots of the logarithms of various catalytic rate constants for the solvolysis of *t*-octyl sydnone are given in Fig. 10 for k_{H^+} , the specific acid catalytic rate constant where acidity is defined in terms of activity (Eqs. 5 and 6); k_{HCl} , where the acid is defined in terms of molar concentrations of hydrochloric acid (Eq. 4); k_o , the first-order rate constant for pH-independent solvolysis; and $k_{(0.5 M \text{ NaOH})}$, the apparent first-order rate constant for the solvolysis; in 0.5 *M* NaOH. The slopes of such plots for the variously derived k_i values are not significantly different, indicative of the fact that the heats of activation, $\Delta H_a = 30$ Kcal./mole, for acid, neutral or alkaline solvolysis of *t*-octyl sydnone are the same. Also in Fig. 10 are Arrhenius plots for $k_{(0.5 M \text{ HCl})}$ (apparent first-order rate constants for solvolysis in 0.5 *M* HCl) for *t*-butylsydnone, furfuryl sydnone, and isopropyl sydnone. The latter was typical of the other sydnones.

Arrhenius plots for solvolysis of other alkyl sydnones in 0.5 *M* NaOH are given in Fig. 11. The pertinent ΔH_a and $\log P$ values are listed in Table VII.

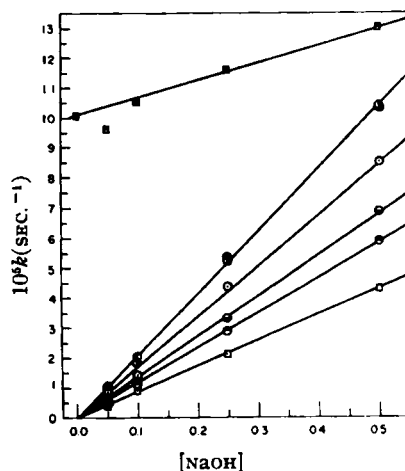


Fig. 9.—Apparent first-order rate constant, k , dependence on $[\text{NaOH}]$ at 75° for *t*-octyl sydnone, □, methyl sydnone, ○; phenethyl sydnone, ○; propyl sydnone, ○; *s*-butyl sydnone, ○; isopropyl sydnone, ○; and *t*-butyl sydnone, □.

 TABLE VI.—CATALYTIC CONSTANTS FOR THE ALKALINE AND NEUTRAL SOLVOLYSIS OF THE ALKYL SYDNONES (k_i IN SEC.⁻¹)

Sydnone	Temp., °C.	$10^6 k_{\text{NaOH}}$	$10^6 k_o$
<i>t</i> -Octyl	75.1	5.90	10.05
	69.9	3.46	4.95
Furfuryl	75.1	37.2	20.4
<i>t</i> -Butyl	75.1	8.70	0.25
Propyl	75.0	17.0	0.00
Methyl	75.0	20.8	0.00
Phenethyl	75.0	20.8	0.00
Isopropyl	75.1	11.8	0.00
<i>s</i> -Butyl	75.2	13.6	0.00

Rate Dependency on Ethanol Content.—The limiting case for a dipolar molecule-dipolar molecule reaction is usually independent of ionic strength but dependent on dielectric constants, D (10, 11).

$$\log k = \log k_{(D=\infty)} - K(1/D) \quad (\text{Eq. 9})$$

Plots of logarithms of the first-order rate con-

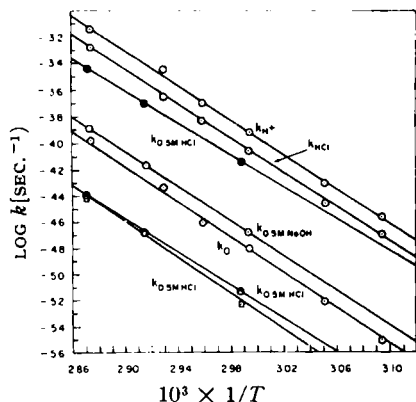


Fig. 10.—Arrhenius plots for the solvolysis of *t*-octyl sydnone, \odot ; *t*-butyl sydnone, \square ; isopropyl sydnone, \ominus ; and furfuryl sydnone, \bullet ; The k_i are: the specific hydrogen ion catalyzed solvolysis derived from hydrogen ion activity, k_{H^+} , and derived from hydrochloric acid molarity, k_{HCl} ; and the apparent first-order rate constants in $0.5 M NaOH$, $k_{0.5 M NaOH}$ and in $0.5 M HCl$, $k_{0.5 M HCl}$.

stants (Table IV) for *t*-octyl sydnone solvolysis in ethanol-water mixtures against the reciprocal of the dielectric constants for such mixtures are given in Fig. 12. The values of K , $\log k_{(D=\infty)}$ and $k_{(D=\infty)}$ for several temperatures are listed in Table VIII. The dielectric constant, D , was obtained from the values of such ethanol-water mixtures at 25° (8) after conversion of the per cent by volume data to per cent by weight values (12).

DISCUSSION

Prediction of Stability.—The stability of the sydnones in aqueous solutions can be calculated from the apparent first-order rate constants, k in sec.^{-1} , where the half-life in days (9),

$$t_{1/2} = 8.03 \times 10^{-6} / k \quad (\text{Eq. 10})$$

The apparent first-order rate constants, k_{HCl} [HCl] and k_{NaOH} [$NaOH$], for the solvolysis of alkyl sydnones that do not exhibit pH-independent solvolysis can be estimated from the $k_{0.5 M}$ values derived from the Arrhenius parameters listed in Table VII.

$$k_{0.5 M} = P e^{-\Delta H_a / RT} \quad (\text{Eq. 11})$$

where $k_{HCl} = 2 k_{0.5 M HCl}$ and $k_{NaOH} = 2 k_{0.5 M NaOH}$ since a bimolecular rate constant can be estimated from the quotient of the apparent first-order rate constant and the molar concentration of the catalytic species. Estimates of a k_o' at an absolute temperature T' for those sydnones that do exhibit pH-independent solvolysis can be based on the same heat of activation as obtained in $0.5 M HCl$ (Table VII) and one k_o value for a particular temperature, T (Table V)

$$k_o' = k_o e^{-\Delta H_a / R(1/T' - 1/T)} \quad (\text{Eq. 12})$$

Thus the first-order rate constants for the solvolysis of these sydnones can be calculated from

$$k = k_{HCl} [HCl] + k_{NaOH} [NaOH] + k_o \quad (\text{Eq. 13})$$

or

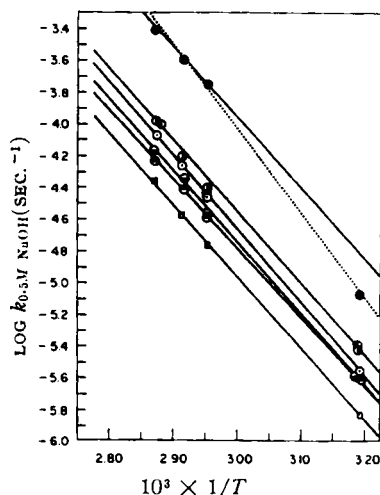


Fig. 11.—Arrhenius plots for the apparent first-order rate constants of solvolysis of alkyl sydnones in $0.5 M NaOH$. Key: \square , *t*-butyl sydnone; \ominus , isopropyl sydnone; \ominus , *s*-butyl sydnone; \odot , propyl sydnone; and \bullet , furfuryl sydnone. Two possible alternative relations are given for furfuryl sydnone.

$$k = k_{H^+} [H^+] + k_{OH^-} [OH^-] + k_o \quad (\text{Eq. 14})$$

dependent on the definition of the catalytic rate constants with respect to the catalytic species (9).

Application of these relations shows that the majority of the alkyl sydnones are quite stable at 30° . For example, the half-lives of the methyl, propyl, etc., sydnones are *ca.* 10 years in $0.1 M HCl$ and *ca.* 2 years in $0.5 M HCl$; but the furfuryl sydnone has a half-life of 6 days in $0.5 M HCl$.

The half-lives of the *t*-octyl and furfuryl sydnone in water alone at 30° can be predicted as measurable in days—13 days for furfuryl and 100 days for *t*-octyl (7 years for *t*-butyl). Such solutions would be unstable for pharmaceutical use.

Fortunately, the pH-independent solvolysis is highly restricted by dielectric constant. The plots

TABLE VII.—APPARENT THERMODYNAMIC QUANTITIES^a FOR THE SOLVOLYTIC DEGRADATION OF THE ALKYL SYDNONES

Sydnone	0.5 M [HCl]		0.5 M [NaOH]	
	ΔH_a	$\log P$	ΔH_a	$\log P$
<i>t</i> -Octyl ^b	30.1	15.5	30.2	15.1
<i>t</i> -Butyl	31.0	14.6	20.5	8.52
<i>s</i> -Butyl	29.0	11.8	20.5	8.73
Propyl	29.0	11.8	21.2	9.23
Isopropyl	29.0	12.0	19.9	8.30
Methyl	29.0	12.0	21.7 ^c	9.70 ^c
Phenethyl	29.0	12.0	21.7 ^c	9.70 ^c
Furfuryl	27.6	13.9	20.4 ^d	9.42 ^d

^a The quantities are derived from the logarithmic form of the Arrhenius relation: $\log k = -(\Delta H_a / 2.303 R) (1/T) + \log P$, where the k is in sec.^{-1} for solvolysis in $0.5 M HCl$ and $0.5 M NaOH$, the ΔH_a is the heat of activation in Kcal./mole, R is the gas constant in cal./degree/mole, T is the absolute temperature, and $\log P$ is a constant associated with entropy.

^b For k_o , pH-independent solvolysis of *t*-octylsydnone, $\Delta H_a = 30.6$ and $\log P = 14.9$. For k_{HCl} defined by $k_{HCl} = (k - k_o) / [HCl]$, where k is the apparent first-order rate constant in a given molarity of $[HCl]$, $\Delta H_a = 29.7$ and $\log P = 15.7$. For k_{H^+} defined by $k_{H^+} = (k - k_o) / [H^+]$, where $[H^+] = 10^{-pH}$ where $pH = \log [HCl] / [H^+]$ where $[HCl]$ is the mean activity coefficient as given by or extrapolated from literature values, $\Delta H_a = 29.8$ and $\log P = 15.8$. ^c Alternative values omitting the 40° study are $\Delta H_a = 23.7$ and $\log P = 10.9$. ^d Alternative values weighting the apparent deviate study at 40° are $\Delta H_a = 24.4$ and $\log P = 11.96$.

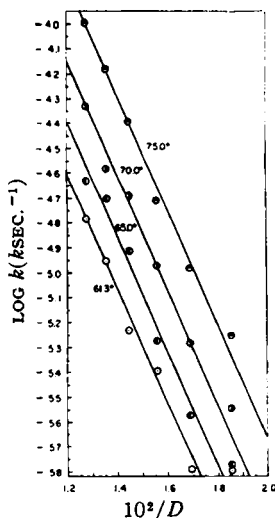


Fig. 12.—Plots of logarithms of first-order rate constants for the pH-independent solvolysis of *t*-octyl syndnone in ethanol-water mixtures against the reciprocal of the dielectric constant for such solvents.

or Fig. 12 and the values of Tables IV and VII show more than a tenfold decrease in rate from water to 50% ethanol-water. The magnitude of the slope, K , is equivalent to that observed for the great effect of dielectric constant on the rate of aspirin anhydride solvolysis in various dioxane-water mixtures (13).

The fact that Eq. 9 is applicable to the solvolysis of the *t*-octylsyndnone that exhibits pH-independent solvolysis in the intermediate pH region is consistent with the model of a dipolar molecule attack on the dipolar molecule. It excludes the cases of like charged ions reacting and the attack of a positive ion on a dipolar molecule (9).

Order of Reactivities of Alkyl Syndnones.—The sequence of reactivities (Table VI) for alkaline catalyzed solvolysis of the syndnones at 75° is: furfuryl > methyl ~ phenethyl > propyl > *s*-butyl ≥ isopropyl > *t*-butyl > *t*-octyl. This is a reasonable sequence for expected inductive effects; *i.e.*, the more electron donating the substituent, the less reactivity to hydroxyl ion attack. However, this sequence is not capable of being assigned to significant variations in the heats of activation determined for hydrolysis in 0.5 *M* NaOH (Table VII) where inductive effects might conceivably be demonstrated (14). The heats of activation as determined in 0.5 *M* NaOH were 21 Kcal./mole for all within the error of estimate, except for *t*-octyl syndnone (30 Kcal./mole). In this case it must be realized that in 0.5 *M* NaOH the pH-independent solvolysis rather than the hydroxyl ion catalyzed solvolysis provides the major route of degradation. The lack of appearance of a spectrophotometric band capable of being assigned to the *N*-nitroso *t*-octylamino acid anion made this apparent, whereas

TABLE VIII.—DEPENDENCE OF RATE CONSTANT (k IN SEC.⁻¹) FOR *t*-OCTYL SYDNONE SOLVOLYSIS ON THE RECIPROCAL OF THE DIELECTRIC CONSTANT, D , OF ETHANOL-WATER SOLUTIONS AS PER THE EXPRESSION $\text{LOG } k = -K(1/D) + \text{LOG } k(D = \infty)$

Temp., °C.	K	$\text{log } k(D = \infty)$	$10^2 k(D = \infty)$
61.3	230	-1.85	1.41
65.0	230	-1.65	2.24
70.0	231	-1.38	4.18
75.0	230	-1.07	8.51

a comparable band appeared in the cases of the 0.5 *M* NaOH solvolysis of the other syndnones.

The sequence of alkaline catalyzed reactivities at 75° (Table VI) is almost the same as that for decreasing $\text{log } P$ values (or decreasing entropies of activation) as listed in the second column of Table VII for solvolysis in 0.5 *M* NaOH. The values for the *t*-octyl and furfuryl syndnones must be excluded because the degradation by pH-independent solvolysis contributes greatly under the stated experimental conditions (0.5 *M* NaOH) for $\text{log } P$. In this instance methyl ~ phenethyl > propyl > *s*-butyl > *t*-butyl > isopropyl. The only radical slightly displaced is isopropyl. The reactivity and $\text{log } P$ sequence is also consistent with expectation on the basis of branching of the substituent where the greater the branching the greater the decrease in entropy (*i.e.*, the lower the $\text{log } P$) on passing from reactants to the transition state (15, 16a). Also, the greater the positivity of the reacting syndnone ring, the less the decrease in entropy (or $\text{log } P$) on reaction with a negative ion (16b). In this manner the correlation of rate magnitude and $\text{log } P$ on electron withdrawing substituents (primary > secondary > tertiary alkyls) could be rationalized.

The reactivity sequence, except for the fascinating case of the furfuryl syndnone, virtually reverses itself for the acid catalyzed solvolysis (Table V) of the syndnones at 75°—*t*-octyl > furfuryl >> *t*-butyl >> isopropyl ≥ propyl ≥ methyl > phenethyl ≥ *s*-butyl. This sequence is reasonably in accordance with the expected relation for electron donating groups (tertiary > secondary > primary alkyls), except for the furfuryl syndnone and the slight displacement of *s*-butyl in the series. There are no great differences among the heats of activation (29–30 Kcal./mole), except for the furfuryl syndnone which shows a decreased value. The tertiary alkyls have slightly higher values than the secondary and primary (Table VII).

The reactivity sequence (Table V) is almost the same as that for decreasing $\text{log } P$ values (Table VII) obtained from solvolysis of the syndnones in 0.5 *M* HCl—*t*-octyl > *t*-butyl > furfuryl > methyl ~ isopropyl ~ phenethyl > *s*-butyl ~ propyl. However, the concept of branching decreasing the entropy of activation and $\text{log } P$ values is not applicable here (15, 16a). When ions attack like-charged species, relatively large decreases in entropy are expected in the formation of the activated state (16b). The sequence of reactivities (tertiary > secondary or primary) can be rationalized as entropy effects since enhancement of the positive charge on the syndnone ring could be affected by electron withdrawing groups.

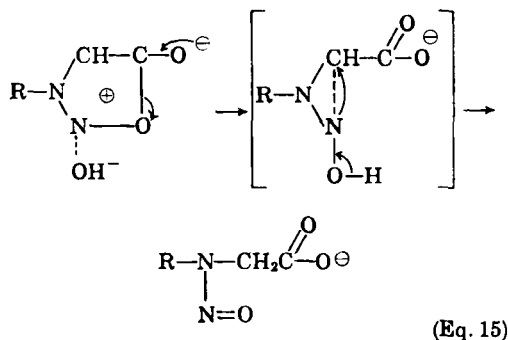
In the three cases of pH-independent solvolysis of the alkyl syndnones, the reactivity at 75° is in the sequence furfuryl > *t*-octyl >> *t*-butyl. The accentuated solvolytic attack by acid and the presence of highly significant pH-independent solvolysis with the highly branched *t*-octyl syndnone possibly implicates a degree of desolvation to the activated state. Such an explanation implies that solvation is greatest in the simple alkyl syndnones where the activated state for pH-independent and acid catalyzed solvolysis is relatively less solvated. It is reasonable to expect hydrogen ion attack to involve induction of the polarized *meso*-ionic syndnone to one

less so. Thus a relatively lower log P (or a greater decrease in entropy) would occur with the more solvated simpler alkyl sydnone. It is indicative that *t*-butyl, *t*-octyl, and furfuryl sydnone have higher melting points (4) and thus tend to become ordered more readily than the other sydnone.

Since the proton attacks the positively charged sydnone ring on acid catalyzed solvolysis, it is expected that the heat of activation would be greater than for hydroxyl ion attack (Table VII).

The higher log P values for acid catalyzed solvolysis of the sydnone over alkaline catalyzed solvolysis may be accounted for by a difference in mechanism. If the products of one reaction are greater in number than those of another, the entropy of the reaction usually increases (16a). However, a more explicit explanation can be related to the reaction mechanism.

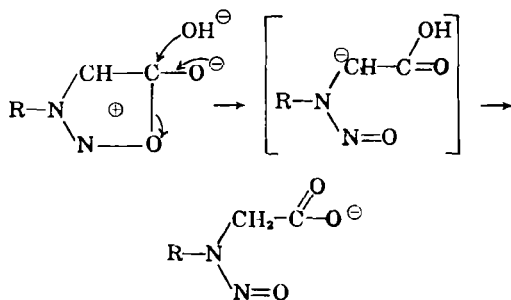
Reaction Mechanisms.—The alkaline catalyzed solvolysis of sydnone produces the respective *N*-nitroso acids (2) as was substantiated by the appearance of a spectral band capable of being assigned to these compounds. A plausible mechanism for this degradation¹ would be



The incipient 2,4 bond or quasidiazomethane is reasonable in light of literature observations of such additions (17, 18).

The point of attack of the hydroxyl ion could be at the nitrogen in the 2-position of the sydnone, the atom to which is assigned the greatest formal negative charge of the sydnone ring (2). It is apparent that an electronic redistribution must be induced on approach of the hydroxyl ion through the bonded p -orbitals of the atoms of the aromatic sydnone ring for this attack to be effective. How-

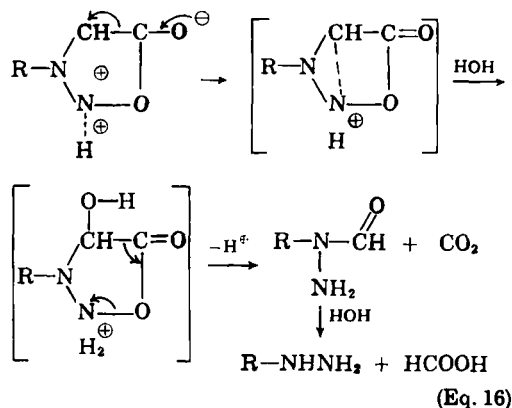
¹ An alternative mechanism could be postulated by an hydroxyl ion attack on the 5 position, the oxygen bonded carbon.



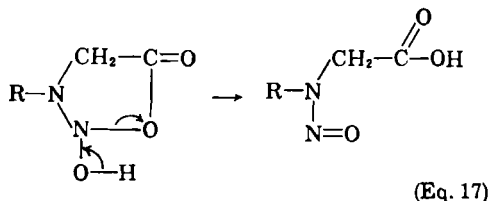
This position has an excess of positive formal charge (2). If this is a preferred mechanism, 5-alkylated sydnone should demonstrate significantly less susceptibility to hydroxyl ion attack than the sydnone studied herein.

ever, proton attack on the 2-position should cause less "ordering" to form the activated state; thus a more positive entropy of activation is (Table VII) and should be present on proton catalyzed solvolysis than with hydroxyl ion catalyzed solvolysis. The reactions of oppositely charged species have more positive entropies of activation than the reactions of similarly charged species (16).

Since it has been reported that acid hydrolysis of sydnone gives an alkyl hydrazine, a carboxylic acid, and carbon dioxide (2, 6, 7), a possible detailed mechanism based on that given in the literature (2) would be

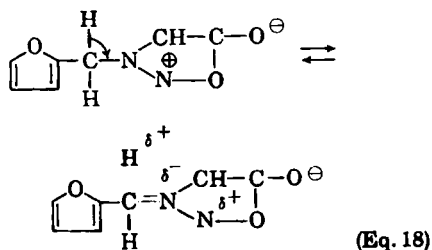


Of course, water attack could occur similarly without prior protonation. An alternative mechanism could be visualized where water is added inversely across the incipient diazomethane



However, the lack of appearance of a spectral band for the *N*-nitroso alkylamino acetic acid on acidic and neutral solvolysis diminishes this possibility and implies similar mechanisms in acid and nonhighly alkaline solutions. The *N*-nitroso compound does show significant acid degradation but no significant change in ultraviolet absorbance in alkaline solution. Studies on the kinetics of hydrolysis of the corresponding *N*-nitroso alkylamino acetic acids are in process to clarify this point.

The most anomalous of the sydnone was the furfuryl which showed high reactivity in acid, alkaline, and intermediate solutions. If the furan ring is considered as an electron sink it may provide electron attracting properties to the furfuryl radical on hydroxyl ion attack. This implies that the intervening methylene group does not insulate the furan ring from polarizing the sydnone and suggests that the benzyl radical may act similarly. Also, the relatively unfilled p -orbital of the 3-position of the sydnone ring (2) may accept electrons readily from the furfuryl carbon and promote a mesomeric or quasi conjugated system—thus readily polarize the sydnone ring for hydrogen ion attack.



A molecular model of furfuryl syndnone indicates the possibility of stabilization of the activated complex by the oxygen of the furfuryl ring which is sterically positioned adjacent to the 2-nitrogen.

Furthermore, this conformation allows the maximum hyperconjugation between the methylene and 4-nitrogen position. The probability of hyperconjugation is further enhanced by the resulting extended conjugation since the two rings are coplanar in this conformation. If this explanation is valid, benzyl syndnone would not be so readily solvolyzed as furfuryl syndnone. However *o*-amino-benzyl or *o*-hydroxybenzyl or a pyrrole analog of furfuryl syndnone would have greatly accelerated solvolysis.

It is also possible to define the reaction sequence in alkali by hyperconjugative stabilization of the transition state by α -hydrogens since methyl syndnone has three—propyl, furfuryl, and phenethyl have two—isopropyl and *s*-butyl have one—and *t*-butyl and *t*-octyl have no α -hydrogens.

SUMMARY

1. The kinetics of solvolysis of a series of *meso*-ionic compounds, the 3-alkyl syndnones, have been studied spectrophotometrically in aqueous solutions by the measurement of absorbance at *ca.* 284 m μ .

2. There was no significant effect of buffer kind or buffer and syndnone concentration on the apparent first-order rate constants.

3. The reactivity on alkaline catalyzed solvolysis generally decreased in the order furfuryl, methyl, propyl, phenethyl, isopropyl, *s*-butyl, *t*-butyl, and 1,1,3,3-tetramethylbutyl syndnone. Except for the furfuryl syndnone, the order of reactivity generally reversed on acid catalyzed solvolysis. These sequences are in accordance with what would be expected from electron inductive effects.

4. The heats and entropies of activation were determined from rate studies and various temperatures. The variation in reactivities on alkaline catalyzed solvolysis is largely assigned to the entropy factor and can be explained by the branching of the alkyls, the variation in positivity of the syndnone ring due to the substituents which affects the attack of a negative ion, and/or the hyperconjugative stabilization of the transition state by α -hydrogens on acid catalyzed solvolysis. The

variation in positivity of the syndnone ring due to the substituents which affects the attack of a positive ion could affect the entropy factor.

5. The highly branched alkylsyndnones, *t*-butyl and 1,1,3,3, tetramethylbutyl, demonstrate a pH-independent solvolysis in the order implying a similar mechanism of attack as by acid catalyzed solvolysis. No spectrophotometric band assignable to a *N*-nitroso alkylaminoacetic acid was observed in acid and pH-independent solvolysis. Alternate points of possible attack of hydroxyl ion are at the 2 or 5 positions with the end product being the spectrophotometrically observed *N*-nitroso alkylaminoacetic acid.

6. The only truly anomalous compound in the sequence of reactivities is the furfuryl syndnone which is highly reactive on both acid and base catalyzed solvolysis and also exhibits a pH-independent solvolysis. Possible explanations are by intramolecular assistance of solvolysis by the furfuryl oxygen or by extension of conjugation because of a labile methylene hydrogen.

7. The solvolysis of 1,1,3,3-tetramethylbutyl syndnone in aqueous solvents of increasing ethanolic content is dramatically inhibited and can be related to the decrease in dielectric constant which implies a dipolar molecule attack on a dipolar molecule rather than a reaction of like charged ions or of a positive ion on a dipolar molecule in the rate-determining step.

8. On the basis of the heats of activation and entropy factors derived from the rate studies, stability of the various syndnones are predicted for various pH, acidic, and basic conditions.

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