

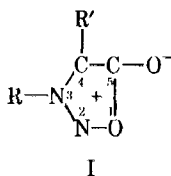
Solvolysis of 3,4-Dialkyl Sydnes

By EDWARD R. GARRETT and PARIMAL J. MEHTA

The kinetics of solvolysis of various dialkyl sydnones: 3-*tert*-butyl-4-methyl, 3-*n*-propyl-4-ethyl, 3-ethyl-4-methyl, 3-isopropyl-4-ethyl, 3-*n*-propyl-4-methyl, and 3-*n*-propyl-4-*n*-butyl sydnone, have been studied spectrophotometrically as a function of HCl and NaOH concentrations, pH, and temperature. The reactivity on acid-catalyzed solvolysis decreased in the order cited with only the first compound exhibiting pH-independent solvolysis and high reactivity, about 600 times that of the others. The reactivities of the remainder were only over a threefold range. The order of reactivity tended to reverse on alkaline solvolysis within a similar range, where 3-ethyl-4-methylsydnone was 1.7 times more reactive than the equally reactive 3-*n*-propyl-4-ethyl, 3-*n*-propyl-4-methyl, and 3-isopropyl-4-ethyl sydnones. The 3-*n*-propyl-4-*n*-butylsydnone was half as reactive as this group, whereas the 3-*tert*-butyl-4-methylsydnone was one quarter as reactive. The presence of α -hydrogens on the alkyl substituted sydnones tends to stabilize such structures against hydrogen ion and water attack. This can be explained by postulating extended equilibria among tautomeric structures which decrease the effective concentration of the reactive intermediate. The 3-benzylsydnone demonstrates a reactivity to hydroxyl ion attack equivalent to the more reactive furfuryl sydnone where the electron-attracting powers of the rings are not completely inhibited by the intervening methylene groups. The acid-catalyzed solvolysis of 3-benzylsydnone is of the order of magnitude of other 3-alkyl sydnones with α -hydrogens. The observed second-order dependency of reactivity on hydrogen ion concentration may be assigned to the delocalization of the charge of the singly protonated species, due to the probability of many mesomeric forms with the benzyl substituent.

THE MESOIONIC SYDNONES are of interest because of their unique structure and properties (1-3). In common with other mesoionic systems they may be potential medicinal agents (2-7). Some sydnones possess fungicidal (4) and ascaricidal (5) properties. Others have effects on the central nervous system (6) and show antitumor activity (7-9).

The sydnones have a small, planar, heterocyclic ring system and an aromatic character. They are highly polarized with relatively high dipole moments. Yet they are electrically neutral and have no apparent potentiometric or spectrophotometric pK_a values (1-3). The sydnones cannot be represented by a single covalent structure. Suitable symbolism is as a hybrid of a large number of mesomeric structures such as I (1).



They also possess a relatively high lipid solubility for such polar molecules (3). The sydnones are thus interesting model compounds to gain in-

sight into the solvolytic mechanisms of mesoionic compounds or the transport of dipolar molecules across biological membranes.

The sydnones are prepared by cyclodehydration of a properly substituted *N*-nitrosoglycine (1-3, 10, 11). Alkaline hydrolysis results in formation of the starting *N*-nitrosoglycine. Acid hydrolysis gives a substituted hydrazine, a carboxylic acid, and carbon dioxide (1-3, 10, 11). The solvolytic stability of the sydnone ring has been shown to depend significantly on the nature of the substituents in the 3-position in the ring (12) in contrast to previous statements (11). Electron donating 4-substituents are said to cause an instability in the sydnone ring, but the need for further work has been stated (2).

The present work was undertaken to obtain further evidence to improve understanding of the solvolytic processes in the sydnone series. In particular, the effects of alkyl 4-substituents which should have greater electron-donating properties than hydrogen are investigated to compare the results with those obtained for relevant 3-alkyl sydnones. The hydrolysis of 3-benzylsydnone was also studied to gain insight as to the possible reasons for the anomalous solvolytic behavior of 3-furfurylsydnone (12) which is similar in structure.

EXPERIMENTAL

Materials and Apparatus—The synthesis and characterization of the sydnones studied here have been reported previously by Kier and Dhawan (13), who also prepared the 3-benzylsydnone by methods in the literature (14). The compounds were stored

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in a vacuum desiccator in a refrigerator. All other chemicals used were of analytical reagent grade. Nitrogen-purged, glass-distilled water was used to make up all solutions. Spectrophotometric readings were taken on the Beckman model DU spectrophotometer. Spectra were recorded on the Cary model 15 recording spectrophotometer. Matched quartz cells (1.00 cm.) were used for all measurements and a slit width of 0.10 mm. employed. Acid and alkali solutions were standardized using the Sargent recording titrator model D. The pH values at the temperatures of study were calculated from activity coefficient data available in the literature (15) or extrapolated from those values. Ionic strengths of all other buffer solutions were adjusted to 0.10. The pH of these buffers was measured at the temperature of study by a Beckman model G pH meter. Constant-temperature baths were maintained to within $\pm 0.1^\circ$ of the temperature of study. The sydnones studied and the absorptivities at the wavelengths of their maximum spectrophotometric absorbances are listed in Table I.

Kinetic Procedures—The general procedure was to dissolve a sydnone, 2.0×10^{-4} moles, in a few drops of ethanol and to make up the volume to 200 ml. with distilled water. This 10^{-3} M master solution was used for kinetic runs in acidic and alkaline media. In a typical case, 10 ml. of the master solution was pipetted into a 100-ml. volumetric flask containing 80 ml. of 1.0 M hydrochloric acid solution maintained at 80° . The volume was brought to mark with distilled water maintained at the same temperature to give a 10^{-4} M sydnone in 0.80 M hydrochloric acid at 80° .

In the acetate and phosphate buffers, a weighed amount of sydnone to obtain a 10^{-4} M solution was dissolved with the aid of a few drops of ethanol and the volume brought to 100 ml. with the appropriate buffer solution maintained at the temperature of study.

The wavelengths of maximum absorbance of these sydnones in aqueous solution were between 284 and 292 $m\mu$ (ϵ 6,000 to 8,000) in acidic, neutral, and alkaline solutions (Table I). The wavelengths of maximum absorbance and the magnitude of absorbance did not show any significant change with pH.

The absorbance at the wavelength of maximum absorbance decreased with time in each case. The decrease was followed by withdrawal of samples at intervals of time, cooling rapidly to room temperature, and reading against an appropriate blank until the residual absorbance, A_∞ , remained constant or asymptotically approached zero.

In all cases, except with the 3-*tert*-butyl-4-methylsydnone, a spectrophotometric absorbance assignable to the corresponding *N*-nitrosoglycine was found to increase concomitantly at a shorter wavelength (about 240 $m\mu$) and strongly indicated a 1:1 transformation.

No such band assignable to an alkyl substituted *N*-nitrosoglycine appeared during the hydrolysis of 3-*tert*-butyl-4-methylsydnone in sodium hydroxide, or for all the sydnones in hydrochloric acid, acetate, and phosphate buffers. Typical spectral curves are given in Fig. 1 for the alkali-catalyzed hydrolysis of 3-benzylsydnone.

Thin-Layer Chromatography—The degradation in 0.8 M HCl of 10^{-2} M solutions of 3-benzylsydnone

TABLE I—3R, 4R' DIALKYLSDYNONES USED IN THE PRESENT INVESTIGATION

R	R'	λ_{max} , $m\mu$	ϵ
<i>tert</i> -Butyl	Methyl	292	7,200
<i>n</i> -Propyl	Methyl	284	6,700
<i>n</i> -Propyl	Ethyl	284	6,700
<i>n</i> -Propyl	<i>n</i> -Butyl	291	6,800
<i>i</i> -Propyl	Ethyl	284	6,600
Ethyl	Methyl	284	6,400
Benzyl	H	292	7,000

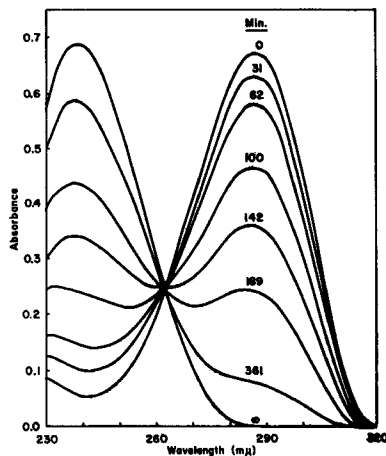


Fig. 1—Spectrophotometric absorbance curves for the solvolysis in 0.25 N NaOH of 3-benzylsydnone (10^{-4} M) at 70.0° .

at 80° was followed by thin-layer chromatography. A small volume of reaction mixture was brought to pH 6–7 and 20 mm.³ of the neutralized solution was applied on a thin-layer chromatography (TLC) plate. The TLC plates were prepared to obtain 0.4-mm. thick layers of Silica Gel GF₂₅₄ containing phosphor indicator (catalog No. 7730, Brinkmann Institute, Westbury, N. Y.). The chromatograms were developed in *n*-butanol–acetic acid–water (4:1:5) system until the solvent front reached a height of 10 cm. They were then dried and the resulting separation observed under a short wavelength ultraviolet lamp. The relative positions of the spots were noted. For control purposes, 10^{-2} M solutions of the benzylsydnone and benzyl hydrazine (Aldrich Chemical Co., Milwaukee, Wis.) were also spotted on the TLC plate.

RESULTS

Rate Constants—The apparent first-order rate constants, k , were calculated from the slopes of the plots of the logarithm of the difference in the absorbance A at time t and the final absorbance A_∞ against time according to:

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

where A_0 is the absorbance at zero time. Typical first-order fits obtained are shown for the acid-catalyzed hydrolysis of 3-*n*-propyl-4-methylsydnone in Fig. 2.

The conditions and rate constants for the apparent

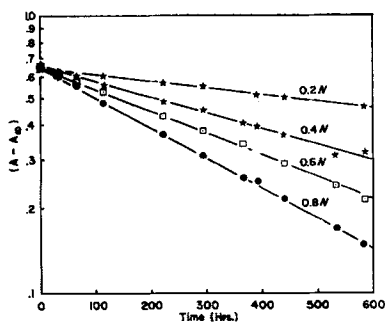


Fig. 2—Typical first-order plots at several $[HCl]$ for the loss of the 284 $m\mu$ absorbance (A) by acid-catalyzed solvolysis of 3-*n*-propyl-4-methylsydnone at 80.0°. The A_{∞} value is the residual absorbance at infinite time.

first-order acid- and alkali-catalyzed degradations of the sydnones studied are given in Tables II and III. The only compound showing pH-independent hydrolysis was 3-*tert*-butyl-4-methylsydnone (75°; pH 4.53, acetate buffer, $k_0 = 2.03 \times 10^{-5}$ sec.⁻¹; pH 5.83, phosphate buffer, $k_0 = 2.10 \times 10^{-5}$ sec.⁻¹; pH 7.82, phosphate buffer, $k_0 = 2.12 \times 10^{-5}$ sec.⁻¹). Catalysis by the buffer species was found to be absent (75°; pH 6.75, phosphate buffer in buffer strength 25% to 100% with a maintained ionic strength of 0.1, $k_0 = 1.95$ to 2.02×10^{-5} sec.⁻¹).

Dependence of Rate on the Catalytic Species—The dependence of the apparent first-order rate constants on the catalytic species is defined for specific alkali catalysis by:

$$k = k_{NaOH}[NaOH] + k_0 \quad (\text{Eq. 2})$$

where k is the apparent first-order rate constant, and k_0 is the apparent first-order rate constant for pH-independent hydrolysis. Plots of k against $[NaOH]$ should give straight lines with slopes k_{NaOH} , the bimolecular rate constant for the NaOH-catalyzed hydrolysis where the k_0 values are the intercepts of such plots. The k_{NaOH} and k_0 values are given in Table IV.

The dependence of k on hydrochloric acid is defined by:

$$k = k_{HCl}[HCl] + k_0 \quad (\text{Eq. 3})$$

where k_{HCl} , the bimolecular rate constant for the HCl catalyzed hydrolysis is obtained from the slopes of the plots of k against $[HCl]$ and k_0 , the pH-independent apparent first-order rate constant, is obtained from the intercepts. The k_{HCl} and k_0 values are given in Table V. Examples of these plots are given in Figs. 3 and 4 where nonzero intercepts of Fig. 3 demonstrate the presence of pH-independent hydrolysis in 3-*tert*-butyl-4-methylsydnone.

The log k -pH profiles for the hydrolysis of the 3-*tert*-butyl-4-methylsydnone at several temperatures exhibit a pH-independent hydrolysis (Fig. 5). The slopes of the log k -pH graphs related to acid- and alkali-catalyzed hydrolysis for all sydnones that do not exhibit pH-independent hydrolysis are -1 and $+1$, respectively, and are characteristic of specific

hydrogen and specific hydroxyl ion-catalyzed hydrolysis.

In the case of the 3-benzylsydnone, good first-order plots were obtained for the degradation in the

TABLE II—CONDITIONS AND RATE CONSTANTS (k sec.⁻¹) FOR THE APPARENT FIRST-ORDER ACID-CATALYZED DEGRADATION OF SYDNONES ($10^{-4} M$) AT 75°

Sydnone	$[HCl]$	$10^6 k$ (sec. ⁻¹)
3- <i>tert</i> -Butyl-methyl	0.395	142.8
	0.592	205.0
	0.790	294.4
3- <i>n</i> -Propyl-4-methyl	0.208	0.093
	0.413	0.167
	0.627	0.380
3- <i>n</i> -Propyl-4-ethyl	0.208	0.095
	0.413	0.199
	0.627	0.342
3- <i>n</i> -Propyl-4- <i>n</i> -butyl	0.848	0.494
	0.220	0.046
	0.425	0.081
3-Ethyl-4-methyl	0.637	0.122
	0.853	0.174
	0.198	0.034
3-Isopropyl-4-ethyl	0.395	0.192
	0.593	0.340
	0.790	0.505
3-Benzyl	0.220	0.162
	0.425	0.330
	0.637	0.475
	0.853	0.645
	0.208	0.070
	0.413	0.210
	0.627	0.370
	0.848	0.560

TABLE III—CONDITIONS AND RATE CONSTANTS (k sec.⁻¹) FOR THE APPARENT FIRST-ORDER ALKALI-CATALYZED DEGRADATION OF SYDNONES ($10^{-4} M$) AT 75°

Sydnone	$[NaOH]$	$10^6 k$ (sec. ⁻¹)
3- <i>tert</i> -Butyl-4-methyl	0.05	19.5
	0.10	20.5
	0.25	24.1
	0.50	30.6
3- <i>n</i> -Propyl-4-methyl	0.20	36.0
	0.40	86.7
	0.60	108.0
	0.80	154.0
3- <i>n</i> -Propyl-4-ethyl	0.20	32.1
	0.40	66.5
	0.60	112.0
	0.80	152.0
3- <i>n</i> -Propyl-4- <i>n</i> -butyl	0.20	21.6
	0.40	43.8
	0.60	68.1
	0.80	89.4
3-Ethyl-4-methyl	0.05	15.1
	0.10	29.2
	0.25	72.2
	0.50	156.6
3-Isopropyl-4-ethyl	0.20	4.87
	0.40	13.8
	0.60	25.6
	0.80	39.3
3-Benzyl	0.05	14.7
	0.10	28.4
	0.25	71.6
	0.50	154.3

TABLE IV—CATALYTIC CONSTANTS FOR THE ALKALI AND NEUTRAL SOLVOLYSIS OF SYDNONES

Sydnone	Temp., °C.	$10^5 k_{\text{NaOH}}^a$ (L. mole ⁻¹ sec. ⁻¹)	$10^5 k_1^a$ (sec. ⁻¹)
3- <i>tert</i> -Butyl-4-methyl	80.0	7.45	2.90
	75.0	3.05	1.75
	70.0	1.77	1.03
	60.0	1.02	0.32
3- <i>n</i> -Propyl-4-methyl	80.0	25.8	
	75.0	18.6	
	70.0	12.0	
	60.0	4.5	
3- <i>n</i> -Propyl-4-ethyl	80.0	25.9	
	75.0	17.1	
	70.0	12.0	
	60.0	4.7	
3- <i>n</i> -Propyl-4- <i>n</i> -butyl	80.0	13.9	
	75.0	10.2	
	70.0	7.62	
	60.0	3.65	
3-Ethyl-4-methyl	80.0	43.5	
	75.0	29.5	
	70.0	18.8	
	60.0	7.65	
3-Isopropyl-4-ethyl	80.0	27.8	
	75.0	16.5	
	70.0	10.1	
	60.0	3.75	
3-Benzyl	80.0	43.0	
	75.0	29.2	
	70.0	19.1	
	60.0	8.60	

^a Determined as slopes and intercepts of plots of the apparent first-order rate constants (k sec.⁻¹) against $[\text{NaOH}]$ according to the expression $k = k_{\text{NaOH}}[\text{NaOH}] + k_0$.

TABLE V—CATALYTIC CONSTANTS FOR THE ACID AND NEUTRAL SOLVOLYSIS OF SYDNONES

Sydnone	Temp., °C.	$10^5 k^a_{\text{HCl}}$ (L. mole ⁻¹ sec. ⁻¹)	$10^5 k_0^a$ (sec. ⁻¹)
3- <i>tert</i> -Butyl-4-methyl	80.0	622.0	30.0
	75.0	322.0	20.0
	70.0	142.0	15.0
	60.0	34.0	5.0
3- <i>n</i> -Propyl-4-methyl	80.0	0.915	0.00
	75.0	0.475	
	70.0	0.295	
	60.0	0.120	
3- <i>n</i> -Propyl-4-ethyl	80.0	1.53	0.00
	75.0	0.670	
	70.0	0.340	
	60.0	0.120	
3- <i>n</i> -Propyl-4- <i>n</i> -butyl	80.0	0.470	0.00
	75.0	0.220	
	70.0	0.150	
	60.0	0.040	
3-Ethyl-4-methyl	80.0	1.10	0.00
	75.0	0.575	
	70.0	0.305	
	60.0	0.101	
3-Isopropyl-4-ethyl	80.0	1.01	0.00
	75.0	0.752	
	70.0	0.403	
	60.0	0.145	
3-Benzyl		$10^5 k_1^b$	$10^5 k_2^b$
	80.0	0.500	1.75
	75.0	0.280	0.830
	70.0	0.161	0.337
	60.0	0.050	0.069

^a Determined as slopes and intercepts of the plots of the apparent first-order rate constants (k sec.⁻¹) against $[\text{HCl}]$ according to the expression $k = k_{\text{HCl}}[\text{HCl}] + k_0$. ^b Determined as intercepts, k_1 , and slopes, k_2 , of the plot of $k/[\text{HCl}]$ against $[\text{HCl}]$ according to the expression $k/[\text{HCl}] = k_1 + k_2[\text{HCl}]$.

acid medium. Plots of the apparent first-order rate constants, k against $[\text{HCl}]$, however, did not yield the expected straight lines but showed an apparent exponential increase in such constants with $[\text{HCl}]$. This was most readily observed at the higher temperatures. The plots were reasonably linear when k was plotted against $[\text{HCl}]$. In solutions of the

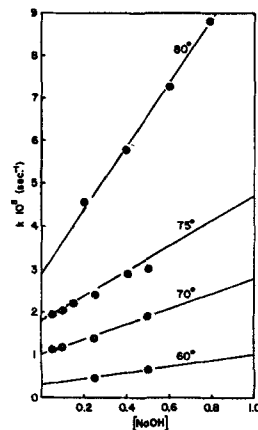


Fig. 3—Dependence of the apparent first-order rate constant, k , on $[\text{NaOH}]$ for the base-catalyzed solvolysis of 3-*tert*-4-methylsydnone at several temperatures.

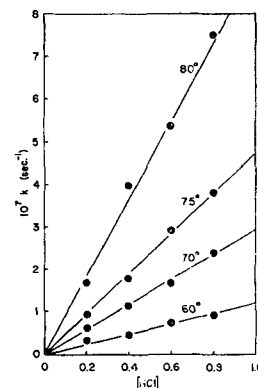


Fig. 4—Dependence of the apparent first-order rate constant, k , on $[\text{HCl}]$ for the acid-catalyzed solvolysis of 3-*n*-propyl-4-methylsydnone.

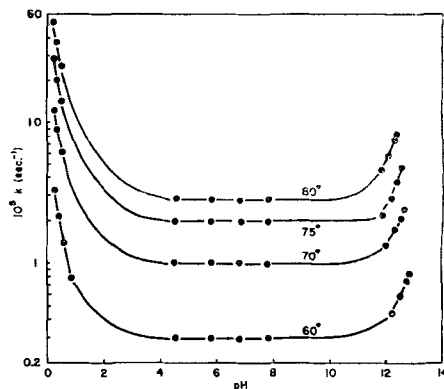


Fig. 5—Log k -pH profile of the dependence of the rate constant, k , on pH for the solvolysis of 3-*tert*-butyl-4-methylsydnone at several temperatures with a demonstrated region of pH-independent solvolysis.

TABLE VI—APPARENT FIRST-ORDER RATE CONSTANTS FOR THE ACID-CATALYZED SOLVOLYSIS (0.80 *M* HCl) AS A FUNCTION OF IONIC STRENGTH^a AT 80°

Ionic Strength	10 ³ <i>k</i> sec. ⁻¹	
	3-Benzyl-sydnone	3-Isopropyl-sydnone
0.80	12.07	10.10
1.00	14.10	11.10
1.20	17.00	12.50

^a Ionic strength adjusted with KCl.

TABLE VII—APPARENT THERMODYNAMIC QUANTITIES^a FOR THE SOLVOLYSIS OF SYDNONES

Sydnone	HCl		NaOH	
	ΔH_a Kcal./mole	log <i>P</i>	ΔH_a Kcal./mole	log <i>P</i>
3- <i>tert</i> -Butyl-4-methyl	32.8	16.9	33.1	17.0
3- <i>n</i> -Propyl-4-methyl	23.6	8.5	23.1	10.8
3- <i>n</i> -Propyl-4-ethyl	23.6	8.6	19.2	9.3
3- <i>n</i> -Propyl-4- <i>n</i> -butyl	30.0	12.2	24.2	10.2
3-Ethyl-4-methyl	31.8	13.2	20.0	9.0
3-Isopropyl-4-ethyl	24.1	8.9	23.6	8.3
3-Benzyl	27.5 ^b 3.20 ^c	10.8 ^b 14.1 ^c	18.6	8.1

^a These quantities are obtained from the logarithmic form of the Arrhenius equation: $\log k = \log P - \Delta H_a/2.303RT$, where *k* is in sec.⁻¹ for the hydrolysis in 1.0 *M* HCl and 1.0 *M* NaOH, the ΔH_a is the experimental activation energy in Kcal./mole, *R* is the gas constant in cal. deg.⁻¹ mole⁻¹, *T* is the absolute temperature, and log *P* is a constant associated with the entropy of activation. ^b Determined from intercepts, *k*₁, of the plot of $k/[HCl]$ against $[HCl]$ according to the expression $k/[HCl] = k_1 + k_2[HCl]$. ^c Determined from the slope, *k*₂, of such plots.

same hydrochloric acid concentration but differing ionic strengths, the apparent *k* increased as would be expected for a reaction between two like-charged species (16), according to the following equation:

$$\log k = \log k' + z_A z_B \sqrt{\mu} \quad (\text{Eq. 4})$$

where *z*_A and *z*_B are the respective signed charges on the reacting species.

The hydrolysis of 3-isopropylsydnone was also studied under similar conditions as a model compound for the other 3-alkyl sydnones. A smaller salt effect was observed in this case. The apparent first-order rate constants for these two sydnones as a function of the ionic strength are given in Table VI.

Plot of log *k* against pH for the acid-catalyzed hydrolysis of the 3-benzylsydnone gave slopes ranging from -1.4 at 60° to -1.8 at 80°, rather than the normally expected slopes of -1 for the single proton catalyzed hydrolysis.

Dependence of Rate on Temperature—The Arrhenius expression $k = Pe^{-\Delta H_a/RT}$ can be written in the logarithmic form:

$$\log k = \log P - \frac{\Delta H_a}{2.303 RT} \quad (\text{Eq. 5})$$

Plots of the logarithms of the various catalytic rate constants against the reciprocal of the absolute temperature permit calculation of the ΔH_a and log *P* values of Eq. 5. These values are listed in Table VII.

Thin-Layer Chromatography—The acid hydrolysis of 3-benzylsydnone was monitored by thin-layer chromatography (*n*-butanol-acetic acid-water, 4:1:5) and observed under ultraviolet light. The spot, *R*_f = 0.65, due to the benzylsydnone became smaller and fainter with time and finally disappeared completely. The only other spot was due to appearance of benzyl hydrazine, *R*_f = 0.48, which increased in size and intensity with time. This showed that benzyl hydrazine was the major product of acid hydrolysis.

DISCUSSION

Comparative Reactivities of Sydnones—The reactivities of the 3,4-dialkyl sydnones can be readily compared with respect to their solvolytic rate constants (Tables II-V) when one substituent is kept constant and the other is varied. This is shown in Table VIII for alkali- and acid-catalyzed hydrolysis at 75°. The comparison for 4-H sydnones was based on data given previously (12).

The sequences (Table VIII) when the 4-substituent is methyl and the 3-substituent is varied, and when the 3-substituent is *n*-propyl and the 4-substituent is varied in the acid-catalyzed region, are in accordance with the expected induction effects of the alkyl groups. It is expected that the greater the electron-releasing capacity of a substituent, the less positive the sydnone ring, the less the reactivity to hydroxyl ion attack, and the greater the reactivity to hydrogen ion attack. However, the sequence is not rigorous in those cases (Table VIII) when the 4-substituent is ethyl, the 3-substituent is *n*-propyl, and the other substituent is varied. In fact, substitution of an ethyl or a methyl for a hydrogen in the 4-position does not significantly change the reactivity of 3-*n*-propyl sydnones to alkaline solvolysis. It does have an effect on acid solvolysis, however.

Kier and Roche (3) have cited unpublished data to support their contention that the 2-nitrogen is predicted to be energetically the least likely point of attack of hydroxide ion as based on molecular orbital calculations of anion localization energies. They preferred hydroxyl ion attack on the 5-carbon in I, the atom adjacent to the oxygen assigned a high formal and localized negative charge (3). Since the presence of a formal charge in all known molecules inhibits the attack of a like charged species (16), it is difficult to expect that a highly polar anion such as hydroxyl would attack an atom

TABLE VIII—RELATIVE REACTIVITIES OF THE 3*R*, 4*R'*-DIALKYL SYDNONES AS COMPARED AT 75°

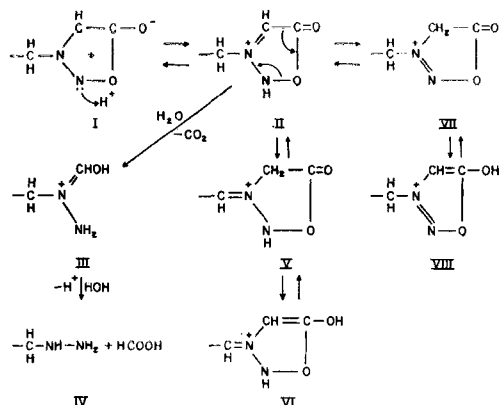
	<i>k</i> _{NaOH}	<i>k</i> _{HCl} (L./mole/sec.)
<i>R</i> = <i>n</i> -Propyl	<i>R'</i> : H ~ Me ~ Et > <i>n</i> -Bu	<i>R'</i> : H > Et > Me > <i>n</i> -Bu
<i>R'</i> = Ethyl	<i>R</i> : <i>n</i> - Pr ~ <i>i</i> - Pr	<i>R</i> : <i>n</i> - Pr ~ <i>i</i> - Pr
<i>R'</i> = Methyl	<i>R</i> : Et > <i>n</i> - Pr > <i>t</i> - Bu	<i>R</i> : <i>t</i> - Bu >> <i>n</i> -Pr ~ Et

adjacent to one with a highly localized negative charge. It was predicted (12) that if this were so, 3,4-dialkylated sydrones should demonstrate significantly less susceptibility to hydroxyl ion attack than solely 3-alkylated sydrones. It is apparent (Table VIII) that the more electron-donating methyl and ethyl substitution for hydrogen in the 4-position, which is adjacent to the postulated attack on the 5-carbon site, had no effect on diminishing reactivity to hydroxyl ion attack. Substitution of a methyl for a hydrogen in the 4-position did decrease the rate of hydroxyl ion attack on the 3-*n*-propyl and 3-*tert*-butylsydrones by 40–60%, but substitution of an ethyl had no significant effect on 3-*n*-propylsydnone reactivity and actually increased the reactivity of 3-*i*-propylsydnone to hydroxyl ion attack by 40%.

It is just as probable that hydroxyl ion attack occurs elsewhere in the sydnone ring than on the 5-position adjacent to the strong anionic charge. Electronic redistributions can be readily induced on the approach of the hydroxyl ion through the bonded *p*-orbital of the atoms of the aromatic sydnone ring, and this sensitizes other sites for reaction. Orbital calculations are based on approximations for the ground state of a molecule, and the results reflect these approximations and exclude the perturbations induced by attacking species. A definitive experiment is needed to resolve the question of site and mechanism of hydroxyl ion attack on sydrones in aqueous solutions.

Still unresolved are the reasons for the enhancement of comparative acid-catalyzed solvolytic rates when the 3-substituent in 3-alkyl sydrones is highly branched, tertiary, and possesses no α -hydrogens, e.g., 1,1,3,3-tetramethylbutyl, 3-*tert*-butyl (12), and 3-*tert*-butyl-4-methyl sydrones (Table V). In addition, these are the only alkyl sydrones that show significant water attack.

We may accept as likely the mechanism of acid hydrolysis based on that of Baker and Ollis (3, 17), i.e., the sequence I–IV to the hydrazine in Scheme I. The net mechanism is similar whether we add water to II and then form III (12) or have the decomposition products of II react with the components of water (3). It is possible that the availability of hydrogens on the α -carbon of the 3-alkyl substituent permits the equilibria to V and VI *via*



Scheme I

acid-catalyzed enolization-like mechanisms. This distribution among other species diminishes the concentration of a reactive intermediate, such as II, necessary for the production of the hydrazine product in acid solution. The conjugations of VI and VIII should be stabilizing influences. When no α -hydrogens on a 3-alkyl are available, such as in the *tert*-alkyl sydnone cases cited, the equilibria with VI and VII are not possible. Thus, the increased concentration of the reactive intermediate (II) could lead to a higher over-all rate of acid catalyzed solvolysis.

There is a great enhancement of hydrogen ion-catalyzed solvolysis when a methyl is substituted for a hydrogen in the 4-position in the case of *tert*-butylsydnone. The second-order rate constant for the acid catalyzed solvolysis of 3-*tert*-butyl-4-methylsydnone at 75° (Table V) is 16 times greater than that of 3-*tert*-butylsydnone (12). Admittedly, it could be argued that the electron-releasing properties of the 4-methyl substituent promoted the hydrogen ion attack on a more negative site in the sydnone ring. Its magnitude is difficult to accept on this premise, however, since the introduction of a 4-alkyl for the hydrogen has only minor enhancing effects on acid-catalyzed solvolysis of 3-alkyl sydrones with α -hydrogens. (Compare Table V and the data in Reference 12.) A possible explanation may be based on consideration of the equilibria in Scheme I of II \leftrightarrow VII \leftrightarrow VIII remaining available to *tert*-butylsydnone. Substitution of a methyl for a hydrogen in the 4-position should lower the electron density on the 4-carbon and not favor the net transfer of hydrogen from the 2-nitrogen in this equilibria. This could lead to a net increase in the concentration of the reactive species II.

The fact that of all the 3-alkyl sydrones only these tertiary alkyl sydrones demonstrate pH-independent solvolysis is significant. This pH-independent solvolysis implicates water attack since it drastically decreases in alcohol-water mixtures of lessened water content (12). An activated state similar to one or several of the postulated hybrids of the numerous dipolar and tetrapolar forms (3, 17) may undergo attack by water in a mechanism similar to that of Scheme I with an activated state similar to II (12). It can be argued that the concentration of this reactive intermediate is reduced by the formation of equilibrating structures similar to V and VI when α -hydrogens on the 3-alkyl are present. Only in the cases of 3-*tert*-alkyl sydrones may there be a sufficient concentration of the reactive intermediate for a pH-independent water attack to be observed. An argument similar to that made previously for increased concentration of the reactive species may be made for the enhancement of water attack on 3-*tert*-butyl-4-methylsydnone over 3-*tert*-butylsydnone, about 10 times more reactive at 75°. (Compare Table V and the data in Reference 12.)

Reactivity of 3-Benzylsydnone—The results obtained for the alkali-catalyzed hydrolysis of 3-benzylsydnone agree with expectations for an apparent first-order dependence on hydroxide ion concentration (Table III). However, the apparent first-order rate constant, *k*, is not strictly linear with the HCl concentration (Table II). It is a function of some power of the HCl concentration and this dependence is more pronounced at higher

temperatures. The log k -pH plots in their acid branch vary from -1.4 at 60° to -1.8 at 80° . The ionic strength effect is of the type expected for a reaction between two like-charged species (Table VI), and the main product of the acid hydrolysis is benzyl hydrazine. These results suggest that acid-catalyzed hydrolysis of 3-benzylsydnone contains a contribution proportional to $[\text{HCl}]^2$. At constant acid concentrations the rate dependence of benzylsydnone solvolysis can be formulated (18) as:

$$-d[\text{benzylsydnone}]/dt = k_1[\text{HCl}] [\text{benzylsydnone}] + k_2[\text{HCl}]^2[\text{benzylsydnone}] \quad (\text{Eq. 6})$$

where the apparent first-order rate constant is:

$$k = k_1[\text{HCl}] + k_2[\text{HCl}]^2 \quad (\text{Eq. 7})$$

and

$$k/[\text{HCl}] = k_1 + k_2[\text{HCl}] \quad (\text{Eq. 8})$$

A plot of $k/[\text{HCl}]$ against $[\text{HCl}]$ should give a straight line with a slope k_2 , the apparent termolecular rate constant, where the intercept, k_1 , should estimate the bimolecular rate constant for the HCl-catalyzed hydrolysis. The values of k_1 and k_2 obtained from such a plot (Fig. 6) show that, for 1.0 M HCl, the relative contribution of k_2 to the over-all rate constant, k , with respect to k_1 , *i.e.*, the ratio k_2/k_1 , increases from 60° to 80° (Table V). Plots of $\log k_1$ and $\log k_2$ against $1/T$ give activation energies of 27.5 and 32.0 Kcal./mole, respectively, and show that k_2 is favored over k_1 at the higher temperatures. Similar plots of the data in Table II for other dialkyl sydnones also show that there may be present, although to a much lesser extent, a concurrent first and second-order dependence on hydrogen ion of the type expressed by Eq. 8. The $k/[\text{HCl}]$ values showed a tendency to increase with $[\text{HCl}]$, but the slopes of such plots were small and the major contribution to solvolysis was the first power of the HCl concentration. The compound other than benzylsydnone that showed the greatest such dependency on the $[\text{HCl}]^2$ was 3-ethyl-4-methylsydnone. However, Eq. 3 was reasonably adequate for quantitative characterization since the k_2 value was relatively small.

These kinetic observations can be interpreted in terms of two concurrent pathways, one discussed previously in Scheme I and the other involving a second protonation.

Second protonation is likely in cases similar to 3-benzylsydnones because of the possibility of mesomeric structures and delocalization of the positive charge through the many possible mesomeric structures mediated by the benzyl substituent and its labile α -hydrogens. A few typical examples are given in Scheme II before and after single protonation, *i.e.*, structures like IX, X, and XI can be represented where one positive charge can be delocalized.

It can be argued that the labile hydrogens of the benzylsydnone permit contributions of structures which may be similar to the V, VI, VII, and VIII of Scheme I. These may dilute out the effective concentration of an activated state as represented by II. Thus, an effective concentration of single protonated hybrids such as XI may occur which react further to products after a second protonation.

Confirmation of the existence of these additional

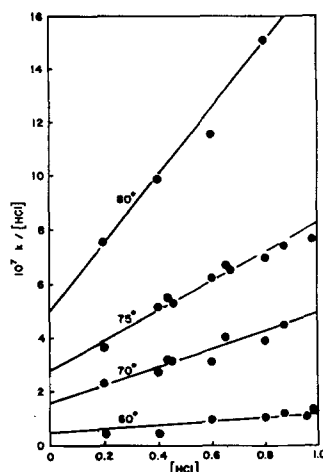
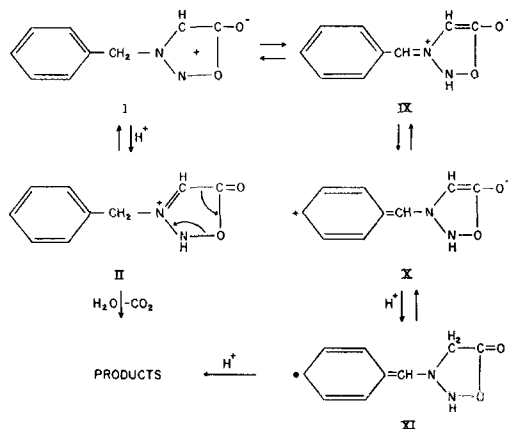


Fig. 6.—Dependence of $k/[\text{HCl}]$ on $[\text{HCl}]$ at different temperatures, according to $k/[\text{HCl}] = k_1 + k_2[\text{HCl}]$, for the apparent first-order rate constant values, k , of benzylsydnone.

mesomeric structures with 3-benzylsydnone is obtained from its ultraviolet spectrum (Fig. 1). The 3-benzylsydnone, with one methylene group intervening between the benzene and sydnone rings, shows a single absorbance maximum at $292 \text{ m}\mu$ ($\epsilon = 7,000$). However, 3-phenylethylsydnone, with two intervening methylene groups between the rings, exhibits two distinct absorbance maxima at 254 and $286 \text{ m}\mu$ ($\epsilon_{286} = 3,000$) (12). This indicates that the benzene ring and the sydnone ring maintain their separate chromophores in 3-phenylethylsydnone and that there is little or no conjugation between the π -electron systems of these rings. In the case of the 3-benzylsydnone, however, the solitary methylene group does not appear to prevent such conjugation. The ultraviolet absorption spectrum indicates that conjugation of the π -electron systems of the two rings exists, together with a bathochromic shift in the wavelength of maximum absorbance, as has been predicted for such cases (19). The partial positive charge, instead of remaining on the sydnone



Scheme II

ring only, may now be smeared over two rings. This results in the sydnone ring in 3-benzylsydnone having less partial positive charge than in the case of the other 3-alkyl sydnones. The results obtained in the study of the ionic strength effects (Table VI) also support this explanation of a smaller positive charge on the neutral sydnone ring in the 3-benzylsydnone, since the greater positive ionic strength effect on acid-catalyzed solvolysis implies a greater significant hydrogen ion attack on a positively charged species.

On the basis of energetic factors, hydrogen ion attack on the nonprotonated sydnones is the favored pathway at lower temperatures because of the smaller activation energy (Table VII). At higher temperatures, however, hydrogen ion attack on the protonated sydnone will be the major route (Scheme II).

It was previously anticipated (12) that the benzyl radical would behave similarly to the furfuryl radical, in that the intervening single methylene group does not insulate the rings and both these radicals may act as electron sinks with greater electron attracting properties on hydroxyl ion attack. In the general sense this anticipation was confirmed and the rates of alkaline solvolysis were equivalent. The hydroxyl-ion-catalyzed solvolyses of benzyl (Table III) and furfuryl sydnones (12) are more than twice the rates of other 3-alkyl sydnones at comparable temperatures (12).

However, the acid-catalyzed solvolysis of 3-benzylsydnone (Table II) is similar in magnitude to those values for the simpler 3-alkyl sydnones, whereas the 3-furfurylsydnone acid- and water-catalyzed solvolyses are anomalously high (12). Thus, the previously given prediction (12) that benzylsydnone would not be as readily solvolyzed in acid and neutral solutions as furfurylsydnone appears valid. This prediction was based on the feasible stabilization of the activated complex of furfurylsydnone by the oxygen of the furfuryl ring which is sterically positioned adjacent to the 2-nitrogen.

Extrathermodynamic Free Energy Relationships—Simple linear free energy relationships can also usually provide information as to whether any substituent effects are present. The best known of these is the Hammett $\sigma\rho$ equation. Use of the σ values obtained from the literature (20) did not provide any meaningful correlation in the Hammett plot (20). Since the sydnones were considered to be of an aromatic nature, these substituent values

for phenyl systems were preferred over the Taft parameters.

It is interesting to note that when, according to Leffler and Grunwald (21), the derived ΔH^* values for the sydnones were plotted against the derived ΔS^* values (22) a reasonably linear relationship was obtained with a slope of 380°. This should represent the isokinetic temperature when all reactions of this series of compounds have the same free energy of activation. At this temperature, effects due to alkyl substituent should completely disappear (21). However, in our case the criticism of Petersen (23, 24) of this approach is valid since plots of $\log k/T$ versus $1/T$ had no common point of intersection, and the observation of an apparent isokinetic temperature was an artifact of the data in the Leffler and Grunwald method (21) of determining extrathermodynamic parameters.

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