Godwin O. Mbagwu [1] and R. Gerald Bass*

Department of Chemistry, Virginia Commonwealth University,
Richmond, Virginia 23284

Richard A. Glennon

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia,
Virginia Commonwealth University, Richmond, Virginia 23298

Received July 23, 1984

The ring-opening reactions of seven mesoionic thiazolo[3,2-*a*]pyrimidine-5,7-diones by a series of primary and secondary amines have been investigated. The rates of the ring fission of five *N*(8)-substituted mesoionic xanthines with benzylamine were measured and found to follow second order kinetics. The Hammett relationship is followed with ϱ value of +0.48 in *p*-dioxane as solvent. The dependence of rates on temperatures has been studied for the *N*(8)-ethyl derivative; the energy of activation (ΔE^*) is 25.3 kcals mol^{-1}, the enthalpy of activation (ΔH^*) is 24.7 kcals mol^{-1} and the entropy of activation (ΔS^*) is −4.9 e.u. A slight increase in rate of reaction was observed when the solvent was changed from *p*-dioxane to dimethyl sulfoxide. In *p*-dioxane at constant mesoionic xanthine concentration, the rate constant for ring opening decreased with increasing benzylamine concentration. These results are consistent with a bimolecular nucleophilic mechanism proceeding by the rate-determining formation of a charged tetrahedral transition state.

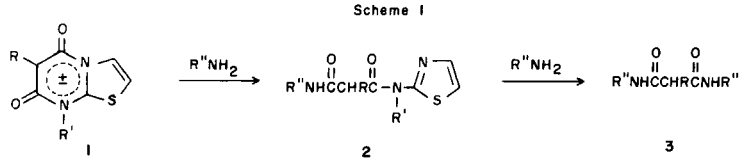
J. Heterocyclic Chem., **22**, 465 (1985).

During the past few years, a number of mesoionic xanthines and related compounds have been prepared and evaluated [2,3] for biological activity. Recently, two publications [4,5] from this laboratory have reported the preparation and evaluation of mesoionic 8-alkylthiazolo[3,2-*a*]-pyrimidine-5,7-diones, **1**, their 3-aza analogs and some related ring systems that exhibit theophylline-like activity as inhibitors of adenosine-3′,5′-monophosphate (cyclic AMP) phosphodiesterase (PDE).

The chemistry of mesoionic purinones has not been studied in detail. However, it is known that mesoionic purinones are unreactive to nucleophiles at room temperature [6] but that nucleophilic attack occurs selectively at the 5-carbonyl position, at elevated temperature, to give **2** in agreement with theoretical predictions [7]. It also has been reported that heating **1e** with benzylamine at elevated temperatures for a prolonged period of time leads to the ring opened symmetrical product, **3a** [8].

The work reported herein was undertaken to determine the rates and the activation parameters for the ring cleavage reaction, **1** to **2**, of a series of mesoionic thiazolo-[3,2-*a*]pyrimidine-5,7-diones with benzylamine and to correlate the results with a possible mechanism.

Scheme I



	R	R′
1a	H	CH_3
1b	H	C_6H_5
1c	H	p-$MeOC_6H_4$
1d	H	p-ClC_6H_4
1e	H	CH_3CH_2
1f	CH_3	CH_3CH_2
1g	CH_3CH_2	CH_3CH_2

	R″	R	R′
2a	C_6H_5	H	CH_3CH_2
2b	$C_6H_5CH_2$	H	CH_3CH_2
2c	$C_6H_5CH_2CH_2$	H	CH_3CH_2
2d	$CH_3CH_2CH_2$	H	CH_3CH_2
2e	$(CH_3)_2CH$	H	CH_3CH_2
2f	$(CH_3)_3C$	H	CH_3CH_2
2g	$C_6H_5CH_2$	H	CH_3
2h	$C_6H_5CH_2$	H	C_6H_5
2i	$C_6H_5CH_2$	H	p-$MeOC_6H_4$
2j	$C_6H_5CH_2$	H	p-ClC_6H_4
2k	$(CH_3CH_2)_2$	H	CH_3CH_2

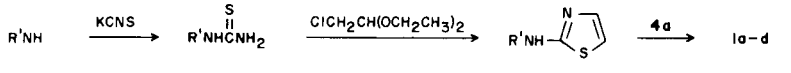
	R″	R
3a	$C_6H_5CH_2$	H
3b	$C_6H_5CH_2CH_2$	CH_3
3c	$C_6H_5CH_2$	CH_3CH_2

$R''NH_2$

$(RCH(COOC_6H_2Cl_3)_2$

4

	R
4a	H
4b	CH_3
4c	CH_3CH_2



Preparation of Mesoionic Purinones.

Compounds **1e-g** and their malonate ester precursors **4** were prepared as previously reported [6]. Four new mesoionic purinones **1a-d**, in which the *N*(8)-CH_2 function is absent were prepared from the appropriate thioureas as shown (Scheme I). The currently accepted nomenclature for mesoionic purinones of type **1a-e** is *anhydro*-(8-aryl or alkyl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium hydroxide). Reaction yields and some physical data for the new mesoionic purinones prepared are summarized in Table 1.

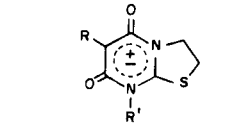
Ring-Opening Reactions.

Each of five mesoionic compounds **1a-e** and an equimolar amount of benzylamine was heated in refluxing tetrahydrofuran for periods of 20-24 hours to prepare and characterize the various ring-opened products and to establish suitable reaction parameters for kinetic experiments. In each case, the product **2b, 2g-2j** was isolated in yields ranging from 70-99% (Table 2).

When **2b** was heated with benzylamine in refluxing tetrahydrofuran at 66° over a period of 24 hours, no observable reaction occurred. However, when the reaction was repeated in refluxing dioxane, bond-cleavage occurred resulting in the displacement of 2-aminothiazole and quantitative formation of the diamide, **3a**.

Mesoionic compounds having an alkyl substituent at the C(6) position are found to exhibit reduced reactivity towards amines and do not react with benzylamine in refluxing tetrahydrofuran or dioxane. However, on heating **1f** in refluxing phenethylamine at 198° ring-cleavage occurred followed by transamination to give **3b**. Similarly, reacting **1g** with benzylamine in diphenyl ether (130°) affords **3c** in 90% yield. The inability of the C(6) alkylated derivatives to undergo ring-opening at low temperatures is thought to be due to steric inhibition of attack of the nucleophile. At elevated temperatures, however, this steric inhibition to ring-opening is overcome. The initial selective nucleophilic attack of the amines at the C-5 position rather than at the C-7 carbonyl of the mesoionic compound **1** is probably due to the steric interference by the *N*-alkyl substituent at the 8-position.

In contrast to the C(2)-C(3) unsaturated analogs, the mesoionic dihydrothiazolopyrimidines **5a,b**, regardless of whether the C-6 position is substituted or not, failed to react with benzylamine in refluxing tetrahydrofuran after 24 hours. This result may reflect the fact that the thiazoline may not be as good a leaving group as the fully-aromatic thiazole formed after ring-opening.



5a R = H, R' = CH_2–cyclopropyl

5b R = CH_3, R' = CH_3CH_2

The steric bulk of the amine nucleophiles seems to play no significant role in the observed selective attack at the C(5) position. For example, when the mesoionic xanthine analog **1e** was heated in refluxing tetrahydrofuran with aniline, benzylamine, propylamine, isopropylamine, *t*-but-

Table 1

Properties of Mesoionic Thiazolo[3,2-*a*]pyrimidine-5,7-diones **1a-g**

Compound	R	R'	Yield, [a] (%)	Mp, (°C)	Recrystallization Solvent [b]	formula		Analysis % Calcd.	Found
1a	H	CH_3	93	228-229	AE	$C_7H_6N_2O_2S$	C	46.15	46.00
							H	3.32	3.35
							N	15.38	15.28
1b	H	C_6H_5	88	218-219	TP	$C_{12}H_8N_2O_2S$	C	59.01	59.00
							H	3.30	3.32
							N	11.47	11.44
1c	H	*p*-$MeOC_6H_4$	95	212-213	A	$C_{13}H_{10}N_2O_3S$	C	56.93	56.79
							H	3.68	3.72
							N	10.21	10.15
1d	H	*p*-ClC_6H_4	90	225-227	A	$C_{12}H_7N_2O_2SCl$	C	51.71	51.82
							H	2.54	2.50
							N	10.05	9.99
1e	H	CH_3CH_2	98	207-208 [c]	AE	$C_8H_8N_2O_2S$			
1f	CH_3	CH_3CH_2	95	168-169 [d]	AE	$C_9H_{10}N_2O_2S$			
1g	CH_3CH_2	CH_3CH_2	79	182-183 [e]	EA	$C_{10}H_{12}N_2O_2S$			

[a] Yield refers to the final malonate condensation step. [b] Recrystallization solvents: absolute ethanol (AE), acetone (A), tetrahydrofuran-petroleum ether (TP), ethyl acetate (EA). [c] Lit [6] mp 206-208°. [d] Lit [6] mp 168-170°. [e] Lit [6] mp 182-183°.

Table 2

Properties of *N'*-(2-thiazolyl)malonamide Ring-Opened Products **2a-k**

Compound	R''	R	R'	Yield, (%)	Mp (°C)	Recryst Solvent	Formula	Analysis (%)	Calcd.	Found
2a	C_6H_5	H	CH_3CH_2	73	118-120	TP [a]	$C_{14}H_{15}N_3O_2S$	C	58.11	58.35
								H	5.23	5.29
								N	14.52	14.22
2b	$C_6H_5CH_2$	H	CH_3CH_2	99	139-140° [b]	TP	$C_{15}H_{17}N_3O_2S$			
2c	$C_6H_5CH_2CH_2$	H	CH_3CH_2	90	106-107	TP	$C_{16}H_{19}N_3O_2S$	C	60.55	60.43
								H	6.03	6.07
								N	13.24	13.20
2d	$CH_3CH_2CH_2$	H	CH_3CH_2	70	85-86	TP	$C_{11}H_{17}N_3O_2S$	C	51.74	51.79
								H	6.71	6.70
								N	16.46	16.43
2e	$(CH_3)_2CH$	H	CH_3CH_2	92	123-125	TP	$C_{11}H_{17}N_3O_2S$	C	51.74	51.78
								H	6.71	6.72
								N	16.46	16.44
2f	$(CH_3)_3C$	H	CH_3CH_2	85	132-134	TP	$C_{12}H_{19}N_3O_2S$	C	53.51	53.53
								H	7.11	7.20
								N	15.60	15.56
2g	$C_6H_5CH_2$	H	CH_3	95	140-141	TP	$C_{14}H_{15}N_3O_2S$	C	58.11	58.01
								H	5.23	5.25
								N	14.52	14.49
2h	$C_6H_5CH_2$	H	C_6H_5	98	144-145	TP	$C_{19}H_{17}N_3O_2S$	C	64.94	65.17
								H	4.88	5.03
								N	11.96	11.75
2i	$C_6H_5CH_2$	H	*p*-$MeOC_6H_4$	99	160-163	TP	$C_{20}H_{19}N_3O_2S$	C	62.98	62.90
								H	5.02	5.01
								N	11.02	10.99
2j	$C_6H_5CH_2$	H	*p*-ClC_6H_4	90	190-192	TP	$C_{19}H_{16}N_3O_2SCl$	C	59.14	59.20
								H	4.18	4.17
								N	10.89	10.85
2k	$(CH_3CH_2)_2$	H	CH_3CH_2	99	[c]	TP	$C_{12}H_{19}N_3O_2S$	C	53.51	52.87
								H	7.11	7.51
								N	15.60	14.90

[a] TP refers to tetrahydrofuran-petroleum ether. [b] Lit [6] mp 139-140°. [c] Product was not crystalline and decomposed on standing therefore the elemental analysis was unsatisfactory. Spectral data supported the assigned structure.

Table 3

Properties of Symmetrical Malonamide Ring-Opened Products **3a-c**

Compound	R''	R	Yield (%)	Mp (°C)	Recrystallization Solvent [a]	Formula	Analysis (%)	Calcd.	Found
3a	$C_6H_5CH_2$	H	99 [b]	140-142	TH	$C_{17}H_{18}N_2O_2$	C	72.32	72.23
			98 [c]				H	6.43	6.47
			90 [d]				N	9.92	9.88
3b	$C_6H_5CH_2CH_2$	CH_3	18 [b]	184-185	TP	$C_{20}H_{24}N_2O_2$	C	74.05	73.97
			99 [c]				H	7.46	7.51
							N	8.64	8.61
3c	$C_6H_5CH_2$	CH_3CH_2	90 [b]	136-138	TH	$C_{19}H_{22}N_2O_2$	C	73.52	73.50
							H	7.14	7.15
							N	9.03	9.10

[a] Recrystallization solvents: tetrahydrofuran-hexanes (TH), tetrahydrofuran-petroleum ether (TP). [b] From ring-cleavage of mesoionic compound. [c] From malonate condensation. [d] From **2b** and benzylamine.

ylamine or diethylamine, which have differing steric requirements, high yields of **2a-f,2k** were obtained in every case.

Coburn and Glennon [2] confirmed the structure of the ring-opening product **2b** by an independent synthesis. In the present study, the structures of **3a-c** were confirmed by condensing the unsubstituted, methyl or ethyl bis(2,4,6-trichlorophenyl)malonate ester **4** with benzylamine or phenethylamine at 160°. The products obtained were identical to the ring-fission products **3a-c** (Table 3).

Analytical data of the ring-opened products obtained in the present study are listed in Tables 2 and 3. The ring-cleavage reactions are summarized in Scheme I.

Treatment of Kinetic Data.

In the present investigation, the kinetic measurements were made in deuteriodimethyl sulfoxide using ^{1}H nmr spectroscopy and in *p*-dioxane employing uv spectroscopy.

In the ^{1}H nmr studies, the kinetics of the ring-opening reaction of an equimolar (0.24 *M*) solution of mesoionic 8-ethylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1e**) and benzylamine were studied over a temperature range of 60-75°. Under these conditions, the ring-opened compound **2b** was the only product isolated. The rate of reaction was determined by measuring the integration curves for the disappearance of one of the AA' BB' doublet signals at δ 8.04 due to the thiazole protons of the mesoionic compound. The methyl triplet, centered at δ 1.2, due to the *N*(8)-ethyl substituent of **1e** and its ring-opened product **2b** was used as an internal standard for integration. The concentration ratio (H_s/H_m) of the thiazole proton (H_s) to the internal standard (H_m) was obtained for each sample. The value of this ratio at time zero was used to relate the thiazole/standard ratio at later times to the concentration of the mesoionic compound **1e**.

The ^{1}H nmr kinetic data were fitted to the integrated second-order rate equation [9,10] where $[M]_0$ and $[M]_t$ are the

$$kt = [M]_t^{-1} - [M]_0^{-1} \qquad (1)$$

molar concentration of **1e** at time equal to zero and at t, respectively, and k is the second-order rate constant.

A common characteristic of the mesoionic thiazolopyrimidines is the occurrence of two absorption maxima at 245 nm and 275 nm in their uv spectra. In contrast, the ring-opened products **2**, in the presence of benzylamine and the mesoionic thiazolopyrimidines, exhibit absorbances at 255 nm and 275 nm. The rates of reaction of a series of mesoionic thiazolo[3,2-*a*]pyrimidines **1a-e** and benzylamine in *p*-dioxane at 70° were determined by measuring the decrease in absorbance at 245 nm accompanying formation of the ring-opened product (Table 4). It was convenient [9,11] to treat all the reactions for spectrophotometric measurement as occurring under pseudo first-order conditions, since the ratio of amine to mesoionic compound was always very large. Under this condition, the expression employed to fit the experimental data was the integrated pseudo first-order equation [9] where A_0, A_∞ and

$$kt = 2.303 \log \frac{A_0 - A_\infty}{A_t - A_\infty} \qquad (2)$$

A_t are the absorbances at time equal to zero, infinity, and t, respectively; t is the time of reaction and k is the observed pseudo first-order rate constant.

Table 4

Rates of Reaction [a] of Mesoionic 8-Ethylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1e**) and Benzylamine in *p*-Dioxane at 70°

(**1a**) Mole/ℓ	(Benzylamine) Mole/ℓ	k_{obs}(hr^{-1})	k(M^{-1}hr^{-1})	1/k
0.005	0.60	0.12 (±0.02) [b]	0.20	5.0
0.005	0.45	0.16 (±0.01)	0.36	2.8
0.005	0.30	0.40 (±0.02)	1.33	0.75
0.005	0.15	0.53 (±0.03)	3.5	0.29

[a] Reaction rate determined by uv method. [b] Standard error.

Order of Reaction.

From the ^{1}H nmr data, a linear plot of $[1/M_t\text{-}1/M_0]$ *versus* time indicated the ring-opening reaction of **1e** with benzylamine was second-order overall at the specified temperatures (Figure 1). The plots of log $(A_t - A_\infty)$ *versus* time from the uv spectrophotometric data for the five *N*(8)-substituted xanthine analogs with excess benzylamine indicated that first-order kinetics were obeyed in each case. A typical

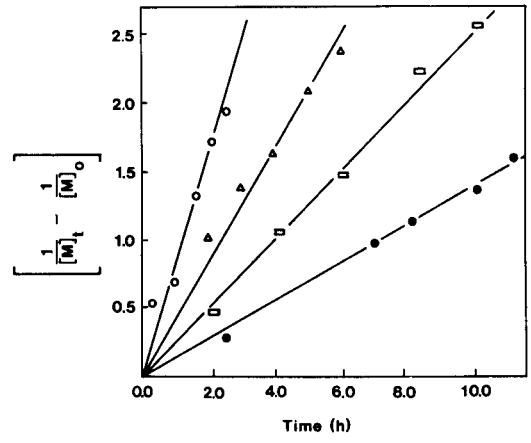


Figure 1. Second-order Plots for the Ring-Opening Reaction of Mesoionic 8-Ethylthiazo[3,2-*a*]pyrimidine-5,7-dione (**1e**) and Benzylamine in DMSO-d_6 at 60° (●); 65° (□); 70° (Δ) 75° (○).

plot for **1d** is shown in Figure 2. In addition, by varying the concentration of the benzylamine (0.15-0.60 *M*) while maintaining **1e** at constant concentration (0.005 *M*), the pseudo first-order dependence of rate on the amine concentration was also demonstrated (Table 4). The rate data obtained from both the uv and ^1H nmr methods, therefore, clearly show that the ring-opening reactions studied exhibit a first-order dependence on substrate and a first-order dependence on amine.

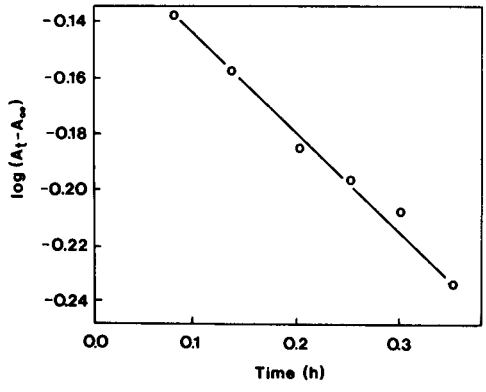


Figure 2. Typical Pseudo First-Order Plot for the Benzylamine Induced Ring Fission of Mesoionic 8-*p*-Chlorophenylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1d**) in *p*-Dioxane at 70°.

Dependence of the Rate on Amine Concentration.

In order to determine the kinetic dependence of the rate on benzylamine concentration, the concentration of 8-ethylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1e**) was maintained at 0.005 *M* and the concentration of the amine was varied from 0.15 to 0.6 *M* [11]. The results of the uv spectrophotometric kinetic runs for **1e** at 70° in *p*-dioxane are given in Table 4. The second-order rate constant, k, was obtained by dividing the first-order constant, k_{obs}, by the total initial benzylamine concentration [9]: $k_{obs} = k\,[AMINE]$. A plot of the reciprocal of the second-order rate constant, 1/k, as a function of initial benzylamine concentration is shown in Figure 3. A reasonably good correlation ($r = 0.98$) was obtained from a least-squares fit.

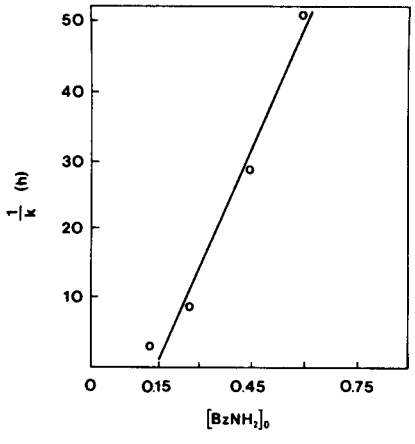


Figure 3. Plot of 1/k for the Reaction of Mesoionic 8-Ethylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1e**) *vs.* the Initial Benzylamine Concentration $[BzNH_2]_0$ in *p*-Dioxane at 70°.

The results in Table 4 and Figure 3 indicate that the bimolecular rate constant, k, decreases with increasing benzylamine concentration. Hence in going from 0.15 *M* to 0.60 *M* benzylamine, the rate constant, k, changes from 0.53 hr^{-1} to 0.12 hr^{-1}. This result is interesting and surprising. Rheinlander [12], Singh and Peacock [13] and Ross and Kuntz [14] have reported similar unusual behavior in the bimolecular substitution nucleophilic reaction of anilines with 2,4-dinitrochlorobenzene in 50% ethanol-ethyl acetate. Ross and Kuntz [14] attributed the rate decrease with increasing amine concentration to charge-transfer complex formation between substrate and nucleophile. Since benzylamine is a donor molecule and mesoionic thiazolopyrimidines are acceptor molecules [6], molecular complex (charge-transfer complex) formation is possible when both reactants are mixed together in solution [15,16]. However, we do not have any experimental evidence in support of this hypothesis because no spectrophotometric band assignable to a charge transfer-complex was observed [15] nor was any color formation of the charge-transfer type observed when the reactants were mixed in solution [14,16].

The observed rate phenomenon may be explained, in part, in terms of medium effects resulting from intermolecular hydrogen bonding between the amine molecules [17, 18]. An increase in the concentration of the benzylamine could result in an increase in the degree of intermolecular interactions due to the closer average proximity of the amine molecules [16]. The equilibrium, $n\,RNH_2 \rightleftharpoons (R\,NH_2)_n$, will tend to be shifted to the right at higher amine concentration leading to the formation of aggregates of amine [16].

This situation should reduce the nucleophilic ability of the amine resulting in the observed apparent decrease in second-order rate constant. However, when the ^1H nmr shifts of benzylamine were measured over a concentration range of 5-50% in *p*-dioxane as solvent, there was no observable shift in the solvent peak (δ 3.5) or in the amino proton resonance (δ 1.4). This result implies that the solvent is not forming hydrogen bonds with the amine [18]. This result presumably rules out the aggregation of benzylamine in concentrated *p*-dioxane solutions [17] as a cause for the decrease in rate.

Another possible explanation is that the amine interacts with the mesoionic compounds through the exocyclic oxygen atoms to form hydrogen bonded complexes. Some energy expenditure would probably be required to disrupt

these hydrogen bonds and this may influence the transition-state and the rate of reaction [18]. Because of their relatively low solubility in *p*-dioxane, it was not possible to vary the concentration of the mesoionic compounds sufficiently to establish the possible role of hydrogen bonding by ^{1}H nmr studies.

Effect of Temperature on the Reaction Rate.

The dependence of the rate of reaction on temperature was investigated by the ^{1}H nmr technique. The reaction conditions were kept constant while the temperature was varied from 60° to 75° in five degree increments. As is expected, the rate of the ring-opening reaction increases with increasing temperature (Figure 1). The corresponding rates of ring fission reaction of **1e** and benzyl amine in DMSO-d_6 at four different temperatures are given in Table 5. These second-order rate constants were employed in an Arrhenius plot and an Eyring plot to determine ΔE^*, the activation energy, (25.3 kcals mol^{-1}), ΔH^*, the enthalpy of activation, (24.7 kcals mol^{-1}) and ΔS^*_{348}, the entropy of activation, (−4.9 e.u.) [9,10].

Table 5

The Effect of Temperature on the Rates of Reaction [a] of Equimolar Solution of 8-Ethylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1e**) and Benzylamine in Dimethyl Sulfoxide

T (°C)	1/T × 10^3 (°K)	k (M^{-1} hr^{-1})	log k	$\frac{k}{\log T\ (°K)}$
60	3.00	0.14 (±0.02) [b]	−0.860	−3.383
65	2.96	0.27 (±0.02)	−0.572	−3.102
70	2.92	0.34 (±0.02)	−0.469	−3.004
75	2.87	0.78 (±0.09)	−0.106	−2.647

[a] Reaction rates determined by ^{1}H nmr method. [b] Standard error.

Effect of Substituents on the Reaction Rate.

The negative ΔS^* implies that the transition state is restricted in orientation and is probably charged in nature [9]. One useful method to probe the presence of a charged transition state is to investigate the effect of substituents on the rate of reaction. A polar transition state would be expected to display some sensitivity to substituent electronic effects [15,19]. The reaction of benzylamine and five *N*(8)-substituted mesoionic thiazolo pyrimidines (**1a**, R′ = CH_3; **1b**, R = C_6H_5; **1c**, R′ = *p*-$MeOC_6H_4$; **1d**, R′ = *p*-ClC_6H_4; **1e**, R′ = CH_3CH_2), was studied spectrophotometrically in *p*-dioxane at 70°, under pseudo first-order conditions, to determine the dependence of the rate on substituents. From the half-lives and the relative rates, the observed sequence of decreasing ease of ring-opening in *p*-dioxane is *p*-chlorophenyl > phenyl > *p*-methoxyphenyl > methyl > ethyl (Table 6).

Table 6

Dependence of Pseudo First-order Rate Constants [a] and Half-lives on *N*(8)-Substituents for Ring Openings of Mesoionic Xanthines by Benzylamine in *p*-Dioxane at 70°

Compound [b]	k(hr^{-1})	Relative Rate	$t_{1/2}$ (hr)
1a	0.23 (±0.03) [c]	1.9	3.0
1b	0.64 (±0.02)	5.3	1.1
1c	0.46 (±0.01)	3.8	1.5
1d	0.79 (±0.06)	6.6	0.9
1e	0.12 (±0.02)	1.0	5.8

[a] Reaction rate determined by uv method. [b] Concentrations of mesoionic compounds and benzylamine are 0.005 *M* and 0.60 *M*, respectively. [c] Standard error.

It seems that the observed differences in rate of reaction result from changes in charge redistribution associated with the transmission of electronic influences of the substituents *via* the π-electron system of the aromatic mesoionic compounds [15,19-21]. Compared to the *N*(8)-alkyl analogs, the *N*(8)-aryl derivatives have generally higher relative rates. This is probably due, in part, to the electron withdrawing influence of the aryl ring [22,23], which, in contrast to the alkyl substituents, can participate in interannular or π-electron delocalization with the aromatic ring of the mesoionic compound. Within the aryl series, the *p*-chlorophenyl and the *p*-methoxyphenyl derivatives exhibit the highest and lowest relative rates respectively. This observation lends further support to the proposition that the more electron withdrawing substituents would be expected to enhance the relative ease of nucleophilic attack at the electron deficient 5-carbonyl position.

A Hammett linear free energy treatment of the data, (Table 6 and Figure 4) using the σ_p-constants for the substituents in the phenyl ring, gives an excellent correlation ($r = 0.995$) for the aryl substituents. The ρ value derived from these data is +0.48. The use of σ_+ gave a poor correlation. The points for the alkyl (methyl and ethyl) substituents show significant deviation from the best straight line through the remaining points. This deviation from a simple correlation can probably be expected for the alkyl substituents which have no π-electrons and, therefore, are expected to exhibit reduced resonance interaction with the mesoionic ring. From the magnitude and sign of ρ and the observed relative rates it can be concluded that the ring-opening reaction exhibits a moderately low sensitivity to electron attracting substituents. This implies that there is little redistribution of charge involved in forming the transition state [23].

Garrett [25] has shown that the stability of several alkyl sydnones in aqueous solutions can be expressed in terms of the half-lives derived from the experimental pseudo first-order rate constants. In the present work, the stability of a series of *N*(8)-substituted mesoionic purinones in diox-

ane-benzylamine solution was estimated from the half-lives (Table 6). The data show that the compounds investigated are quite reactive at 70° and have half-lives of one to six hours. The aryl derivatives are generally more reactive than the alkyl analogs.

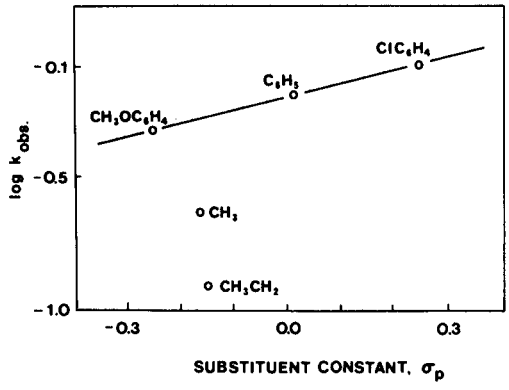


Figure 4. Plot of log k_{obs} agains σ_p, for the Reaction of Benzylamine with a series of *N*(8)-Substituted Mesoionic Thiazolo[3,2-*a*]pyrimidine-5,7-diones **1a-e** in *p*-Dioxane at 70°.

Effect of Solvent on the Reaction Rate.

Although a detailed study of solvent effects was not undertaken, the difference in reactivity of **1e** in *p*-dioxane and in DMSO-d_6 was determined. From the ^{1}H nmr method, the second-order rate constant obtained in DMSO-d_6 at 70° for compound **1e** was 0.34 M^{-1} hr^{-1}. The corresponding second-order rate constant in *p*-dioxane (70°) using the uv method was 0.20 M^{-1} hr^{-1}. The relative rate ($k_{DMSO}/k_{dioxane}$) is 1.7. This result implies that DMSO-d_6, which has a larger dielectric constant than dioxane, causes a slight increase in rate, and is indicative of a small increase in charge density on going from the reactants to the transition state [21]. Most bimolecular nucleophilic substitution reactions in which neutral reactants generate polar activated complexes are solvent dependent [21], implying that the transition state is stabilized by an increase in the dielectric constant of the solvent. This stabilization results in decreased energy of activation accompanied by an increase in the rate of reaction [21]. It is interesting to note that the small values of ΔS^*_{348} (−4.9), the Hammet ϱ constant value of +0.48 and the relative rate $k_{DMSO}/k_{dioxane}$ (1.7) are indicative of a small redistribution of charge density in forming the transition state [15,23].

Mechanism of Ring-Opening Reaction.

The observation of a second-order rate for the reaction of benzylamine and mesoionic 8-ethylthiazolo[3,2-*a*]pyrimidine-5,7-dione (**1e**) is consistent with a bimolecular reaction in which the attacking species and the substrate are intimately involved in the rate determining step [9,21]. The observed negative entropy of activation, ΔS^*, is expected for a bimolecular process in which two species come together to form a single complex [20,21].

On the basis of the data available from the present kinetic studies, it is proposed that the ring-opening reaction of benzylamine and the mesoionic thiazolopyrimidines involves the formation of a polar tetrahedral transition state in which the attacking amine becomes partially bonded to the electron deficient carbonyl carbon, C(5), in the rate-determining step. Formation of the tetrahedral transition state is followed by the fast decomposition to a trigonal product accompanied by ring-cleavage of the C(5)-N(4) bond. Part of the energy required to cause the breaking of the C(5)-N(4) bond of the mesoionic compound is furnished by the formation of the C(5)-NHR bond between the amine and the substrate [20].

As in bimolecular nucleophilic substitution reactions involving nucleophilic acyl substitution, the rate determining step is expected to be slowed or blocked completely by substituents which become crowded together in the transition-state [21,26]. This expected steric crowding probably explains the observation that alkyl substituents at the C(6) position tend to retard nucleophilic ring-cleavage in the mesoionic analogs **1f** and **1g**. In addition, in the C(6) unsubstituted mesoionic compounds **1a-e**, the C(5) carbonyl carbon selectively undergoes nucleophilic attack by amines in preference to the sterically more hindered C(7) carbonyl carbon. However, it is not clear why bulky substituents in the amine nucleophiles do not appear to significantly affect the ease of ring-opening of the mesoionic compounds. Finally, the postulated mechanism provides a reasonable rationale for the expected stabilization of the negative charge on the oxygen of the 5-carbonyl position in the proposed transition state.

EXPERIMENTAL

General.

Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. All compounds were prepared using starting materials obtained from either commercially available sources or made by standard literature procedures. Reagent grade solvents were used in all reactions and column chromatographic separations. The solvents were freshly distilled before use. Thin-layer chromatography (tlc) was performed on tlc plates precoated with aluminum oxide (Analtech, Newark, Delaware). The visualization of products in thin-layer chromatograms was accomplished by uv absorbance or iodine.

Infrared spectra (ir) were recorded as potassium bromide disks on a Perkin-Elmer 283 spectrophotometer. Proton magnetic resonance spectra (^{1}H nmr) were obtained with either a Varian T-60 or a JEOL FX90QII spectrometer. The concentration of the samples was approximately 35 mg/0.5 ml of dimethyl-d_6 sulfoxide (DMSO-d_6) or deuteriochloroform as specified. All ^{1}H nmr spectra were obtained using 5 mm spinning tubes and signals were referenced to internal tetramethylsilane (TMS). The ^{1}H nmr signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad singlet. Ultraviolet spectra (uv) were re-

corded on a Beckman Acta MVII spectrophotometer using either spectrograde or purified solvents. Results are expressed as λ max in nanometers (nm).

Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia and unless stated otherwise were within ±0.4% of the theoretical value. If a compound was prepared by more than one method, mixture melting points and comparisons of spectral data were performed.

Anhydro-(8-methyl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium Hydroxide) (**1a**).

An intimate mixture of 2-(methylamino)thiazole [29] (350 mg, 3.1 mmoles) and *bis*(2,4,6-trichlorophenyl)malonate (1.55 g, 3.1 mmoles) was heated neat at 160°, under a slow stream of nitrogen, until a clear melt resulted (3 minutes). When cool, the resultant gum was triturated with anhydrous diethyl ether and the solid product was collected by filtration. Recrystallization from absolute ethanol gave 530 mg (94%) of **1a** as small yellow crystals, mp 228-229°; ir: 1640, broad (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.4 (s, 3H, N-CH_3), δ 4.6 (s, 1H, C(6)-H), δ 7.5 (d, 1H, J = 4 Hz) and δ 8.1 (d, 1H, J = 4 Hz thiazole protons); uv (*p*-dioxane): λ max 245 nm (log ε 4.2), 275 (3.5).

The mesoionic compounds **1a-g** and **5a-g** were all prepared in the same manner as **1a** using the appropriate amine and malonate ester.

Anhydro-(8-phenyl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium Hydroxide) (**1b**).

From 290 mg (0.57 mmole) of *bis*(2,4,6-trichlorophenyl)malonate and 100 mg (0.57 mmole) of 2-(phenylamino)thiazole [29] there was obtained 120 mg (88%) of **1b**, mp 218-219°, (tetrahydrofuran-petroleum ether); ir: 1700 and 1670 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.6 (s, 1H, C(6)-H), δ 7.4 (d, 1H, J = 4 Hz, thiazole proton), δ 7.6 (s, 5H, phenyl protons), δ 8.1 (d, 1H, J = 4 Hz, thiazole proton); uv (*p*-dioxane): λ max 245 nm (log ε 4.3), 275 (3.6).

Anhydro-(8-*p*-methoxyphenyl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium Hydroxide) (**1c**).

From 660 mg (1.3 mmoles) of *bis*(2,4,6-trichlorophenyl)malonate and 270 mg (1.3 mmoles) of 2-(*p*-methoxyphenylamino)thiazole [30] there was obtained 340 mg (95%) of **1c**, mp 212-213° (absolute ethanol); ir: 1650, broad (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.8 (s, 3H, -OCH_3), δ 4.7 (s, 1H, C(6)-H), δ 7.2 (d, 1H, J = 4.5 Hz, thiazole proton), δ 7.4-7.5 (q, 4H, ArH), δ 8.0 (d, 1H, J = 4.5 Hz, thiazole proton); uv (*p*-dioxane): λ max 245 nm (log ε 4.5), 275 (3.8).

Anhydro-(8-*p*-chlorophenyl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium Hydroxide) (**1d**).

From 240 mg (0.48 mmole) of *bis*(2,4,6-trichlorophenyl)malonate and 100 mg (0.48 mmole) of 2-(*p*-chlorophenylamino)thiazole [28] there was obtained 120 mg (90%) of **1d**, mp 225-227° (absolute ethanol); ir: 1700 and 1650 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.7 (s, 1H, C(6)-H), δ 7.4 (d, 1H, J = 4 Hz, thiazole proton), δ 7.6 (d of d, 4H, J = 3 Hz, ArH), δ 8.1 (d, 1H, J = 4 Hz, thiazole proton); uv (*p*-dioxane); λ max 245 nm (log ε 4.4), 275 (2.7).

Anhydro-(6-methyl-8-ethyl-5-hydroxy-7-oxothiazolino[3,2-*a*]pyrimidinium Hydroxide) (**5b**).

From 360 mg (0.77 mmole) of *bis*(2,4,6-trichlorophenyl)methylmalonate and 100 mg (0.77 mmole) of 2-ethylamino-2-thiazoline there was obtained 140 mg (92%) of **5b**, mp 214-215° (absolute ethanol-diethyl ether) (lit [5] mp 214-215°); ir: 1650, broad (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.2 (t, 3H, ethyl-CH_3, J = 4 Hz), δ 1.7 (s, 3H, C(6)-CH_3), δ 3.6 (q, 2H, N(8)-CH_2-, J = 4 Hz), δ 3.8 (t, 2H, J = 4.5 Hz) and δ 4.4 (t, 2H, J = 4.5 Hz, thiazoline protons).

N-Phenyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**2a**).

A solution of **1e** (500 mg, 2.6 mmoles) and aniline (240 mg, 2.6 mmoles) in tetrahydrofuran (60 ml) was heated at reflux until tlc (95% ethanol) analysis indicated the disappearence of starting material (112 hours). The solvent was removed *in vacuo*. Recrystallization of the product from tetrahydrofuran-petroleum ether afforded 540 mg (73%) of **2a** as white crystals, mp 118-120°; ir: 3360 (N-H), 1700, 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3, J = 6 Hz), δ 3.7 (s, 2H, -$COCH_2CO$-), δ 4.2 (q, 2H, N(8)-CH_2, J = 6 Hz), δ 6.8-7.4 (m, 7H, phenyl and thiazole protons), δ 8.1 (br, 1H, NH, exchanged with deuterium oxide).

Compounds **2b-k** were prepared in a manner similar to that employed for **2a**.

N-Benzyl-*N'*-(2-thiazolyl)-*n'*-ethylmalonamide (**2b**).

From **1e** (200 mg, 1 mmole) and benzylamine (100 mg, 1 mmole) in tetrahydrofuran (50 ml) there was obtained after 24 hours 299 mg (99%) of **2b**, mp 139-140° (lit [6] mp 139-140°).

N-Phenethyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**2c**).

From **1e** (500 mg, 2.6 mmoles) and phenethylamine (310 mg, 2.6 mmoles) in tetrahydrofuran (60 ml) there was obtained after 24 hours 720 mg (90%) of **2c** as white crystals, mp 106-107° (tetrahydrofuran-petroleum ether); ir: 3300 (N-H), 1660 (C=O), 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, CH_3), δ 2.7 (t, 2H, benzyl-CH_2-, J = 5.5 Hz), δ 3.4 (m, 4H, -$COCH_2CO$- and α-CH_2- protons of $PhCH_2CH_2$-), δ 4.2 (q, 2H, ethyl-CH_2-, J = 6 Hz), δ 7.1 (d, 1H, thiazole proton, J = 4 Hz), δ 7.4 (s, 5H, phenyl protons), δ 7.6 (d, 1H, thiazole proton, J = 4 Hz), δ 7.8 (br, 1H, NH, exchanged with deuterium oxide).

N-Propyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**2d**).

From **1e** (500 mg, 2.6 mmoles) and propylamine (151 mg, 2.6 mmoles) in tetrahydrofuran (60 ml) there was obtained after 13 hours 450 mg (70%) of **2d**, mp 85-86° (tetrahydrofuran-petroleum ether); ir: 3320 NH), 1660 and 1640 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.0-1.5 (m, 6H, $2CH_3$), δ 3.0 (2H, -CH_2-N-), δ 3.6 (s, 2H, -$COCH_2CO$-), δ 4.2 (m, 2H, CH_3-CH_2-NH, J = 4 Hz), δ 7.3 (d, 1H, thiazole proton J = 4 Hz), δ 7.5 (d, 1H, thiazole proton J = 4 Hz), δ 8.2 (br, 1H, NH, exchanged with deuterium oxide).

N-Isopropyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**2e**).

From **1e** (500 mg, 2.6 mmoles) and isopropylamine (151 mg, 2.6 mmoles) in tetrahydrofuran (60 ml) there was obtained after 20 hours 611 mg (92%) of **2e** as white crystals, mp 123-125° (tetrahydrofuran-petroleum ether); ir: 3325 (NH), 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.3 (m, 9H, $3CH_3$), δ 3.4 (s, 2H, -$COCH_2CO$-), δ 4.2 (m, 3H, N(8)-CH_2- and methine proton of -CHN-CO), δ 7.2 (d, 1H, thiazole proton J = 4 Hz), δ 7.8 (d, 1H, thiazole proton, J = 4 Hz), δ 7.8 (br, 1H, NH, exchanged with deuterium oxide).

N-*t*-Butyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**2f**).

From **1e** (500 mg, 2.6 mmoles) and *t*-butylamine (187 mg, 2.6 mmoles) in tetrahydrofuran (60 ml) there was obtained after 27.5 hours 590 mg (85%) of **2f** as white crystals, mp 132-134° (tetrahydrofuran-petroleum ether); ir: 3340 (NH), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.2 (m, 12H, $4CH_3$), δ 3.3 (s, 2H, -$COCH_2CO$-), δ 4.3 (t, 2H, N(8)-CH_2-, J = 6 Hz), δ 7.3 (d, 1H, thiazole proton, J = 4 Hz), δ 7.5 (d, 1H, J = 4 Hz, thiazole proton), δ 7.8 (br, 1H, NH, exchanged with deuterium oxide).

N-Benzyl-*N'*-(2-thiazolyl)-*N'*-methylmalonamide (**2g**).

From **1a** (83 mg, 0.45 mmole) and benzylamine (50 mg, 0.45 mmole) in tetrahydrofuran (40 ml) there was obtained after 24 hours 124 mg (95%) of **2g**, mp 140-141° (tetrahydrofuran-petroleum ether); ir: 3300 (NH), 1670 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.7 (s, 2H, -$COCH_2CO$-), δ (s, 3H, CH_3), δ 4.8 (d, 2H, benzyl CH_2-, J = 4.5 Hz), δ 7.6 (d, 1H, thiazole proton, J = 4 Hz), δ 7.9 (s, 5H, phenyl protons), δ 8.1 (d, 1H, thiazole proton, J = 4 Hz), δ 8.3 (br, 1H, NH, exchanged with deuterium oxide).

N-Benzyl-*N'*-(2-thiazolyl)-*n'*-phenylmalonamide (**2h**).

From **1b** (110 mg, 0.45 mmole) and benzylamine (50 mg, 0.45 mmole) in tetrahydrofuran (20 ml) there was obtained after 12 hours 155 mg (98%) of **2h** as light tan crystals, mp 144-145° (tetrahydrofuran-petroleum ether); ir: 3300 (NH), 1690 and 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.6 (s, 2H, $-COCH_2CO-$), δ 4.8 (d, 2H, benzyl CH_2-, J = 4.5 Hz), δ 7.6 (d, 1H, thiazole proton, J = 4 Hz), δ 7.9-8.1 (m, 11H, phenyl and thiazole protons), δ 8.3 (br, 1H, NH, exchanged with deuterium oxide).

N-Benzyl-*N'*-(2-thiazolyl)-*N'*-*p*-methoxyphenylmalonamide (**2i**).

From **1c** (51 mg, 0.19 mmole) and benzylamine (20 mg, 0.19 mmole) in tetrahydrofuran (20 ml) there was obtained after 16 hours 72 mg (99%) of **2i** as off-white crystals, mp 160-163° (tetrahydrofuran-petroleum ether); ir: 3310 (NH), 1690 and 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.6 (s, 2H, $-COCH_2CO-$), δ 4.2 (s, 3H, OCH_3), δ 4.8 (d, 2H, benzyl CH_2-, J = 4.5 Hz), δ 7.2 (d, 1H, thiazole proton, J = 4 Hz), δ 7.4 (s, 9H, ArH), δ 7.6 (d, 1H, thiazole proton, J = 4 Hz), δ 8.3 (br, 1H, NH, exchanged with deuterium oxide).

N-Benzyl-*n'*-(2-thiazolyl)-*N'*-*p*-chlorophenylmalonamide (**2j**).

From **1d** (45 mg, 0.16 mmole) and benzylamine (18 mg, 0.16 mmole) in tetrahydrofuran (20 ml) there was obtained after 24 hours 55 mg (90%) of **2j**, mp 190-192° (tetrahydrofuran-petroleum ether); ir: 3320 (NH), 1700 and 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.7 (s, 2H, $-COCH_2CO-$), δ 4.7 (d, 2H, benzyl CH_2-, J = 4.5 Hz), δ 7.3 (d, 1H, thiazole proton, J = 4 Hz), δ 7.5 (s, 9H, ArH), δ 7.7 (d, 1H, thiazole proton, J = 4 Hz), δ 8.4 (br, 1H, NH, exchanged with deuterium oxide).

N,N-Diethyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**2k**).

From **1e** (500 mg, 2.6 mmoles) and diethylamine (187 mg, 2.6 mmoles) in tetrahydrofuran (60 ml) there was obtained after 33 hours a pale brown oil. The oil was distilled at 88-90°/1.5 mm to yield 687 mg (99%) of **2k** as a colorless liquid which darkened on standing; ir: (neat) 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.5 (m, 9H, $3CH_3$), δ 3.3 (q, 4H, diethyl-CH_2-, J = 6 Hz), δ 3.6 (s, 2H, $-COCH_2CO-$), δ 4.2 (q, 2H, ethyl-CH_2-, J = 6 Hz) δ 7.2 (d, 1H, thiazole proton, J = 4 Hz) and δ 7.5 (d, 1H, J = 4 Hz, thiazole proton).

N,N'-Dibenzylmalonamide (**3a**). Method A.

Compound **2b** (1 g, 3.3 mmoles) and benzylamine (300 mg, 3.3 mmoles) in tetrahydrofuran (100 ml) were heated under reflux for 17 hours. The solvent was removed under reduced pressure and the residue was recrystallized from tetrahydrofuran-hexanes forming white crystals 840 mg (90%), of **3a** as white crystals, mp 140-142°; ir: 1670 and 1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.5 (s, 2H, $-COCH_2CO-$), δ 4.7 (d, 4H, benzyl protons, J = 4 Hz), δ 7.8 (s, 10H, phenyl protons), δ 8.3 (br, 2H, NH, exchanged with deuterium oxide).

Method B.

A solution of **1e** (200 mg, 1 mmole) and benzylamine (100 mg, 1 mmole) in *p*-dioxane (60 ml) was heated at reflux for 24 hours. The solvent was removed *in vacuo*. Recrystallization of the product from tetrahydrofuran-hexanes, gave 280 mg (99%) of **3a** as white crystals, mp 140-142°.

Method C.

Bis(2,4,6-trichlorophenyl)malonate (600 mg, 1.2 mmoles) and benzylamine (400 mg, 3.7 mmoles) were heated in an oil bath at 160° until a clear melt resulted (1 minute). The 2,4,6-trichlorophenol formed and the excess benzylamine were removed during the heating period by passing a slow stream of nitrogen through the flask. The residued oil was triturated with anhydrous diethyl ether. The product was collected by filtration and recrystallized from tetrahydrofuran-hexanes to give 330 mg (98%) of **3a**, mp 140-142°.

N,N-Diphenethylmethylmalonamide (**3b**). Method A.

A mixture of **1f** (350 mg, 1.7 mmoles) and benzylamine (24.2 g, 203 mmoles) was heated at reflux (180°) for 24 hours. The pale orange mixture was filtered. Addition of petroleum ether-anhydrous diethyl ether (10 ml, 1:1) to the filtrate produced slightly off-white crystals. Recrystallization from tetrahydrofuran-petroleum ether yielded 10 mg (18%) of **3b** as white crystals, mp 184-185°; ir: 3300 (NH), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.4 (d, 3H, CH_3, J = 5 Hz), δ 2.7 (m, 5H, methine proton and α-CH_2- protons of $PhCH_2CH_2$-), δ 3.3 (t, 4H, benzyl-CH_2-, J = 6 Hz), δ 6.8 (s, 10H, phenyl protons), δ 7.6 (br, 2H, NH, exchanged with deuterium oxide).

Method B.

Compound **3b** was prepared in a manner similar to that employed for **3a** using method C above. From 500 mg (1.05 mmoles) of bis(2,4,6-trichlorophenyl)methylmalonate and 380 mg (3.15 mmoles) of phenethylamine there was obtained, after recrystallization from tetrahydrofuran-petroleum ether, 337 mg (99%) of white crystals, mp 184-185° (tetrahydro furan-petroleum ether).

N,N'-Dibenzylethylmalonamide (**3c**). Method A.

A mixture of **1g** (938 mg, 4.2 mmoles) and benzylamine (500 mg, 4.2 mmoles) in diphenyl ether (45 ml) was heated at 130° for 19 hours. Most of the solvent (40 ml) was distilled off under reduced pressure. Addition of anhydrous diethyl ether (8 ml) to the cooled residue gave a slightly off white crystalline solid. Recrystallization from tetrahydrofuran-hexanes gave 1.3 g (90%) of **2c** as white crystals, mp 136-138°; ir: 3300 (NH), 1670 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.0 (t, 3H, CH_3, J = 4.5 Hz), δ 1.9 (m, 2H, ethyl CH_2-), δ 3.2 (t, 1H, methine proton, J = 5 Hz), δ 4.5 (d, 4H, benzyl CH_2-, J = 4 Hz), δ 7.4 (s, 10H, phenyl protons), δ 7.8 (br, 2H, NH, exchanged with deuterium oxide).

Method B.

Compound **3c** was prepared in a manner similar to that employed for **3a** using method C above. From 400 mg (0.8 mmole) of bis(2,4,6-trichlorophenyl)ethylmalonate and 250 mg (2.3 mmoles) of benzylamine there was obtained, after recrystallization from tetrahydrofuran-hexanes, 240 mg (96%) of **3c** as white crystals, mp 136-138°.

Kinetic Studies. Materials.

The preparation of the various mesoionic compounds **1a-g** is described herein or has been described previously. Benzylamine (99 + % grade) obtained from Aldrich Chemical Co., was distilled before use, and a middle fraction of bp 40° at 5 mm pressure was used. All solvents employed for kinetic measurements were purified by literature methods [27]. Spectrograde *p*-dioxane (Aldrich) was refluxed for 7 hours over sodium hydroxide pellets and then distilled at atmospheric pressure (bp 100-101°). The distillate was stored over Fischer Scientific Co. 4A molecular sieves. Dimethyl-d_6 sulfoxide (DMSO-d_6) obtained from Wilmad Glass Co., was distilled from potassium hydroxide and the middle distillate (bp 72°/10 mm) was collected over Fischer 4A molecular sieves. Tetrahydrofuran (99 + % grade, Aldrich) was distilled at atmospheric pressure. The distillate was allowed to stand 48 hours over sodium hydroxide pellets and 24 hours over sodium chips. It was distilled from sodium and stored over 4A molecular sieves. Kinetic studies were performed in a water bath maintained at ±0.1° by means of a Haake-51 thermostat.

Procedure.

A. Control Experiment.

In order to check the accuracy of the quenching method to be used in the kinetic measurements, a 0.24 *M* solution, equimolar in benzylamine and **1e**, was prepared in DMSO-d_6. Samples of the solution were left in a refrigerator (0°) and at room temperature for a period of 24 hours. There was no detectable change in the ^1H nmr spectra of these two samples at the end of the test period.

B. Proton NMR Method.

In a typical experiment, a stock solution of **1e** (47 mg/ml) and benzyl-

amine (25 mg/ml) was prepared in DMSO-d_6 at room temperature using a 10-ml volumetric flask. At the beginning of each run, 0.4 ml of solution containing the amine and the mesoionic compound was transferred to each of six ^{1}H nmr tubes using a 1-ml pipette. The tubes were immediately cooled in an ice-water mixture and then sealed with a hand torch. When the tubes returned to room temperature, they were simultaneously placed in the constant temperature bath (60°, 65°, 70°, 75°). After the tubes had been withdrawn at appropriate intervals and quenched in an ice-water mixture, they were again allowed to return to room temperature. The rate of reaction was then determined by measuring the integration curves for the disappearance of one of the AA', BB' doublet signals at δ 8.04 due to the thiazole protons of the mesoionic compound. The methyl signal (δ 1.2) of the mesoionic compound was used as an internal standard. Each experiment was performed in duplicate and each ^{1}H nmr signal was integrated six times and the averaged value was used for subsequent calculations.

C. UV Spectrophotometric Method.

The procedure used for the proton magnetic resonance technique was employed for the spectrophotometric method with slight modifications. One milliliter portions of sample solutions (0.15-0.6 *M* with respect to benzylamine and 1×10^{-2} *M* with respect to mesoionic compound) in *p*-dioxane at room temperature were pipetted into each of six Pyrex ampules. The ampules were immediately sealed with rubber septum caps and simultaneously placed in a constant-temperature water bath (70°). At appropriate intervals, ampules were removed and quenched by plunging them into ice-water mixture. After the quenched ampules returned to room temperature, a 50 μl aliquot was removed using a hypodermic syringe fitted with a 5 cm needle. For an optimum absorbance reading, the aliquot was diluted with *p*-dioxane in a 10-ml volumetric flask to 2.00×10^{-5} *M* with respect to the initial concentration of the mesoionic compound. The decrease in absorbance at 245 nm accompanying formation of the ring-opened product was measured as a function of time. Absorbance-time measurement was continued until the absorption peak of the ring-opened compound appeared at 255 nm. Each experiment was performed in duplicate. The uv absorbances were determined with a Beckman Acta MVII spectrophotometer using a 1-cm quartz cell covered by a Teflon stopper.

The best fit to the kinetic data was obtained in all cases by the method of least squares employing a Hewlett-Packard Company Teletype program. For the uv method, reactions were followed until the 255 nm absorbance due to the ring-opened product was the only observable signal. For the ^{1}H nmr technique, integration measurements were continued until it became impractical to analyze the spectra further. No corrections were made for concentration changes between room temperature and the reaction temperatures.

Acknowledgement.

The support of this research in part by the U. S. Public Health Service (grant No. HL-22566) and the School of Graduate Studies, Virginia Commonwealth University is gratefully acknowledged. We also thank Professor Fred M. Hawkridge for helpful discussions.

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[b] Present address: Department of Chemistry, Virginia State University, Petersburg, VA 23803.

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