The Kinetics of the Reaction of 1-Phenyl-1H-tetrazole-5-thiol Sodium Salt with Substituted 1,4-Naphthoquinone 2,3-Epoxides

D. F. O'BRIEN

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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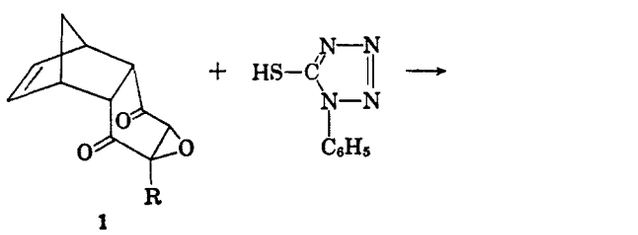
The kinetics of the reaction of 1-phenyl-1H-tetrazole-5-thiol sodium salt with 2,3-epoxides of Diels–Alder adducts of 1,4-benzoquinone were examined. The reaction was followed by determining the amount of unreacted mercaptide. Potentiometric titration with silver nitrate was utilized to analyze for mercaptan. The buffered reaction is first order in epoxide and first order in mercaptan. The reaction rates and activation parameters are discussed.

The reactions of 2,3-epoxides of 1,4-benzoquinone cyclopentadiene Diels–Alder adducts (**1**) with 1-phenyl-5-mercaptotetrazole (HPMT) give 2-thioether enediones (**2**).[1] When vigorous conditions are employed, the products are the isomeric 2-thioether hydroquinones (**3**). (See eq 1.) The configurations of the starting epoxide **1** and the enedione **2** are as shown.[2] The reaction proceeds smoothly in ethanol



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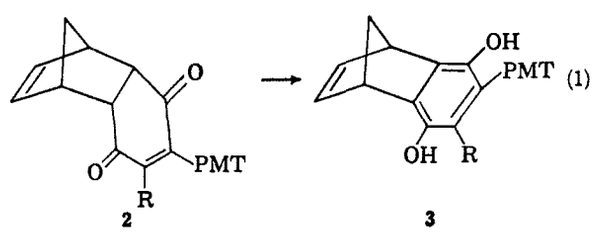
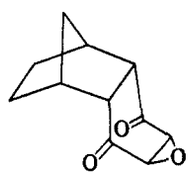


2 **3** (1)

a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = *i*-C_3H_7
e, R = *t*-C_4H_9

and somewhat slower in benzene.[1] The use of equimolar amounts of base accelerates the reaction and yields only **3**.[1] The reaction of **1a** with the triethylamine salt of HPMT in ethanol gave a 94% yield of **3a**.[1]

There are few studies of reactions of mercaptans with epoxides of conjugated 1,4 ketones.[1] No quantitative data are available. The kinetics of the reaction were examined to assist in understanding the mechanism and the effect of the carbonyls on the ring-opening reaction. For the study, seven epoxides, **1a–e**, **4**, and **5**, were examined. Epoxide **4** was obtained from **1a** by catalytic hydrogenation.[2] The *exo* adduct **5** resulted from the thermal isomerization of **1a**.[3]



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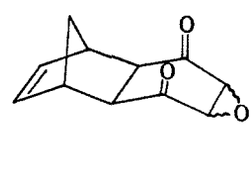

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Experimental Section

Epoxides.—The epoxides utilized in this study were prepared by the method reported previously.[2]

1-Phenyl-1H-tetrazole-5-thiol Sodium Salt (NaPMT).—The mercaptide, Eastman Grade, was oven dried to a constant weight and stored in a desiccator. A solution of the mercaptide in 90% ethanol (theoretical, 0.0215 *N*; found, 0.0212 *N* (standardized by iodine titration)) was stable for several months.

Buffer Solution.[4]—Lutidine, Eastman Grade, and lutidinium perchlorate, mp 110–111°, were dissolved in 90% ethanol to give a solution of 0.204 and 0.205 *N*, respectively.

Silver Nitrate Solution.—A standardized solution of silver nitrate in water (0.1006 ± 0.0002 *N*) was diluted to give 0.01002 *N* silver nitrate.

Basic Conversion of 5,8-Methano-1-(1′-phenyl-5′-tetrazolylthio)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (2a) into 5,8-Methano-1-(1′-phenyl-5′-tetrazolylthio)-5,8-dihydro-1,4-naphthohydroquinone (3a).—A solution of **2a** (3.50 g, 0.01 mole) and 30 ml of ethanol was warmed to reflux, triethylamine (1.0 g, 0.01 mole) was added, and the mixture refluxed for 15 min. The initial yellow color changed to dark red-brown. After reflux, charcoal was added, and the mixture was warmed and then filtered into 300 ml of ice and water, which was acidified with 5 ml of acetic acid. The precipitate was collected, dried, and crystallized from acetic acid–water to give 1.7 g of 3a, 48% yield. Similar results were obtained with 2,6-lutidine as the base.

Reaction of Cyclohexene Oxide with NaPMT.—A solution of NaPMT (10.0 g, 0.080 mole, 0.23 *N*) in 220 ml of ethanol was outgassed with nitrogen. The solution was treated with cyclohexene oxide (5.0 g, 0.053 mole, 0.24 *N*). The mixture was stirred at room temperature under nitrogen for 17 hr. The white precipitate was collected and dried. Concentration of the filtrate to 100 ml gave more of the same solid. The white solid was acidified in solution, reisolated, and crystallized from ethanol to give 3.35 g (45% yield) with mp 187–188.5°. The infrared spectrum was the same as that of 1-phenyl-5-hydroxytetrazole. Treatment of the alcohol with base gave the original white solid. Further concentration of filtrate gave a crude product, whose infrared spectrum showed hydroxyl absorption, and its odor indicated it was a mercaptan, possibly 2-mercaptocyclohexanol.

Kinetic Procedure.—Temperature variation was no more than ±0.03°. Temperatures were checked with thermometers calibrated by the National Bureau of Standards.

The solutions were prepared with an ethanol–water solvent (90% by volume at 15.56°). Reactant solutions, epoxide, mercaptide, buffer, and neutral salt, of appropriate concentrations, were prepared. The required volumes of these solutions were combined by means of automatic delivery pipets calibrated with the ethanol–water solvent. The reaction mixture was kept at Dry Ice–isopropyl alcohol temperatures and outgassed with nitrogen. The cold, deoxygenated solution was distributed among

(1) H. S. Wilgus, III, E. Frauenglass, P. P. Chiesa, G. H. Nawn, F. J. Evans, and J. W. Gates, Jr., *Can. J. Chem.*, **44**, 603 (1966).

(2) D. F. O'Brien and J. W. Gates, Jr., *J. Org. Chem.*, **30**, 2593 (1965).

(3) M. J. Youngquist, D. F. O'Brien, and J. W. Gates, Jr., *J. Am. Chem. Soc.*, **88**, 4960 (1966).

(4) J. G. Pritchard and F. A. Long, *ibid.*, **79**, 2365 (1957).

10 to 14 nitrogen-flushed, ice–salt-cooled ampoules, each containing approximately 6 ml. These were carefully sealed and placed in the bath so that only the thin necks protruded above the surface of the oil. The cold ampoules were allowed approximately 15 min to come to thermal equilibrium. The time was taken first when the initial ampoule was removed from the bath and quenched in ice water. After the ampoules had been quenched, they were brought to 15°, the necks were scored and snapped off, followed immediately by removal of an exact aliquot (*ca.* 5 ml) with a calibrated, automatic delivery pipet. The aliquot was added to 100 ml of isopropyl alcohol to which a few drops of 1 *N* nitric acid had been added.

The extent of reaction was determined by analyzing the acidified alcohol solutions for unreacted mercaptan (HPMT). The mercaptan was measured by potentiometric titration with silver nitrate from a 10-ml microburet, with a silver electrode as the indicating electrode. The reference electrode was a Beckman No. 39270 fiber-type calomel electrode, connected to an external potassium nitrate salt bridge. A Beckman Model G pH meter served as the potentiometer. The silver electrode was thoroughly flushed with ethanol and water after each titration and repolished after each set of titrations.

As the titration progressed, silver mercaptide (AgPMT) precipitated and the potential slowly rose. A sharp break in the titration curve occurred in the range 1.5–3.0 mv. The midpoint of the break was taken as the end point. Titration of several aliquots of the same NaPMT sample under the same conditions showed that the titration curve was reproducible. Potentiometric titrations were performed on alcohol solutions of starting epoxide, buffer, and hydroquinone product, respectively. The blank titrations were zero.

The accuracy of the titration depended on the solvent. Weighed amounts of dry NaPMT were dissolved in water, ethanol, and isopropyl alcohol, respectively. The solutions were acidified with a few drops of 1 *N* nitric acid. Determination of the mercaptan gave 87% of theory in water, 95–96% in ethanol, and 98–99% in isopropyl alcohol.

The rate constants were determined from the integrated form of the second-order equation. The reactions were generally followed through two half-lives, eight to twelve points being used to determine each rate constant.

Data for a typical kinetic run is given in Table I.

TABLE I

DATA FOR A KINETIC RUN OF **1a** AND NaPMT[a]

(rate constant (0.90 ± 0.03) × 10^{-2} l. $mole^{-1}$ sec^{-1})

Time, sec	Titer, ml of 0.01 *N* $AgNO_3$	—Reactants × 10^3*N*— [NaPMT]	[Epoxide]	k_{obs} × 10^2, l. $mole^{-1}$ sec^{-1}
Initial		3.41	6.84	
0	1.60	3.30	6.73	
1800	1.42	2.93	6.36	0.88
3600	1.28	2.64	6.07	0.94
5460	1.16	2.39	5.82	0.92
7200	1.06	2.19	5.62	0.90
9000	0.97	2.00	5.43	0.91
10,800	0.89	1.83	5.26	0.92
14,400	0.76	1.57	5.00	0.90
18,000	0.66	1.36	4.79	0.87
21,960	0.55	1.14	4.57	0.89
25,200	0.47	0.97	4.40	0.90

[a] Reaction of **1a** and NaPMT was in 90% ethanol with lutidine (1.31 × 10^{-2}*N*), lutidinium perchlorate (1.32 × 10^{-2} *N*), and sodium perchlorate (3.37 × 10^{-2} *N*) at 45.00 ± 0.03°. The aliquot taken was 4.87 ml.

Results

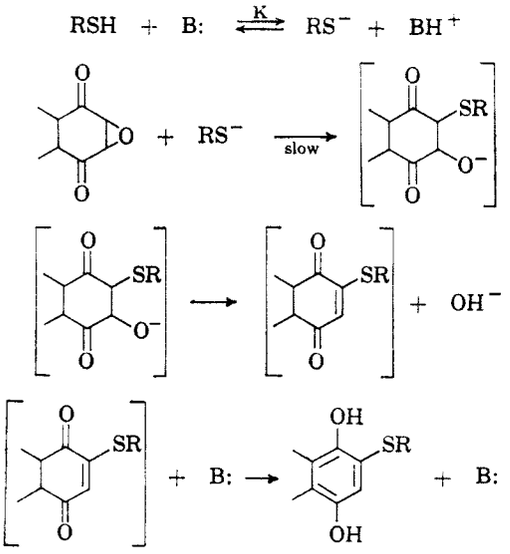
In Table II are listed the observed second-order rate constants determined in this work. The rates were followed by analysis of the unreacted mercaptan, by utilizing a modification of the procedure of Bishop[5] (see Experimental Section). The values of relative rates at 75.0°, the enthalpy of activation ΔH^*, and the entropy of activation ΔS^* are shown in Table III.

(5) C. A. Bishop, private communication, 1964.

Discussion

Treatment of the enedione **2a** with triethylamine or 2,6-lutidine yields the isomeric hydroquinone **3a**. This indicates that one function of the base is to enolize the intermediate enedione. A second function is to ionize the mercaptan to the more nucleophilic mercaptide. The pk_a of HPMT is approximately 3.5.[6] The proposed reaction is shown in Scheme I.

SCHEME I



The rates should be independent of buffer concentration, but dependent on its composition. In Table II, runs 3 and 4, the effect on rate of altering the concentration of buffer is seen to be negligible. In Table II, runs 3 and 6, we note that a change of the buffer composition alters the *k*, presumably by changing the effective [RS^-]. In each case, care was taken to maintain a uniform ionic strength (μ = 0.050) by adjusting the concentration of the neutral salt, sodium perchlorate. In those cases where μ was allowed to deviate from 0.050, the reaction rate was affected. Higher salt concentrations accelerated the reaction (Table II, runs 3 and 7 and 9 and 10). The effect of the higher ionic strength can be interpreted as producing a greater concentration of mercaptide. This is apparently greater than the effect of the ionic strength on the activity coefficients of the reactants and transition state, which would tend to retard the reaction. These data, plus the lack of deviation of the rate data of the buffered reactions from a second-order plot, in one case to 91% completion, indicate that the scheme just given is valid.

The opening of an epoxide ring by an attacking nucleophile has been discussed in several reviews.[7–10] There are few reports of ring openings of α-epoxyketones. One by Sullivan and Williams describes the re-

(6) W. R. Ruby, C. G. Tremmel, and R. B. Pontius, unpublished observations.

(7) S. Winstein and R. B. Henderson in "Heterocyclic Compounds," Vol. 1, R. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, pp 22–46.

(8) A. Rosowsky in "The Chemistry of Heterocyclic Compounds," Vol. 19, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 173–349.

(9) R. E. Parker and N. S. Issacs, *Chem. Rev.*, **59**, 737 (1959).

(10) E. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 106–114.

TABLE II

REACTION OF NaPMT WITH SOME EPOXIDES IN 90% ETHANOL

Run No.	Compd	Temp, °C	Reactants × 10^3M [Epoxide]	Reactants × 10^3M [NaPMT]	Buffer × 10^2M[a] [Lut]	Buffer × 10^2M[a] [Lut·HClO4]	$k \times 10^2$, l. mole^{-1} sec^{-1}
1	1a	35.0	4.07	8.14	3.13	3.15	0.44 ± 0.02
2		45.0	4.07	8.12	3.13	3.15	0.83 ± 0.05
3		45.0	3.12	6.21	2.39	2.41	0.86 ± 0.04
4		45.0	3.12	6.21	1.20	1.21	0.89 ± 0.03
5		45.0	6.84	3.41	1.31	1.32	0.90 ± 0.03
6		45.0	3.12	6.21	4.49	2.41	1.12 ± 0.06
7[b]		45.0	3.12	6.21	2.39	2.41	0.74 ± 0.03
8		55.0	2.41	4.80	1.85	1.87	1.59 ± 0.04
9		55.0	2.41	4.80	1.85	1.87	1.56 ± 0.07
10[c]		55.0	2.41	4.80	1.85	1.87	1.33 + 0.05
11	1b	55.0	4.03	8.10	3.13	3.15	0.311 ± 0.009
12		65.0	4.03	8.15	3.13	3.15	0.57 ± 0.04
13		75.0	4.03	8.15	3.13	3.15	1.00 ± 0.06
14	1c	75.0	3.93	8.15	3.13	3.15	0.53 ± 0.03
15	1d	75.0	4.07	8.15	3.13	3.15	0.161 ± 0.004
16	1e	75.0	4.03	8.15	3.13	3.15	0.023 ± 0.002
17	4	35.0	3.12	6.24	2.39	2.41	1.95 ± 0.07
18		45.0	2.41	4.82	1.85	1.87	3.69 ± 0.17
19		55.0	2.41	4.80	1.85	1.87	6.74 ± 0.22
20	5	35.0	3.12	6.24	2.40	2.42	1.12 ± 0.09
21		45.0	2.41	4.82	1.85	1.87	2.16 ± 0.13
22		55.0	2.41	4.80	1.85	1.87	3.88 ± 0.11

[a] Unless otherwise noted, sufficient sodium perchlorate was added to bring the initial ionic strength, μ, to 0.050. Lut refers to lutidine, and Lut·HClO4 refers to lutidinium perchlorate. [b] No added $NaClO_4$, $\mu = 0.030$. [c] No added $NaClO_4$, $\mu = 0.023$.

TABLE III

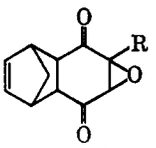
RELATIVE RATES AND ACTIVATION PARAMETERS

Compd	Rel rate[a] (75.0°)	ΔH^*, kcal/mole	ΔS^*, eu
1a	(1.00)[b]	12.3 ± 0.8	−29.6 ± 2.6
1b	0.408	12.6 ± 1.0	−31.8 ± 3.1
1c	0.216		
1d	0.066		
1e	0.009		
4	(4.17)[b]	11.8 ± 0.7	−28.0 ± 2.5
5	(2.15)[b]	11.1 ± 0.8	−30.4 ± 2.7

[a] Statistically corrected. [b] Estimated from the rate data at 35.0, 45.0, and 55.0°.

TABLE IV

RELATIVE RATES OF SOME NUCLEOPHILIC DISPLACEMENTS



R	RCH(O)CH2 + NH3, 20°[a]	RCH2CH2Cl[b] + I−, acetone, 60°	+ NaPMT, EtOH, 75°
H	1.00	1.00	(1.00)[d]
CH_3	1.05	0.37	0.408
C_2H_5	0.79	0.52	0.216
i-C_3H_7	0.33	0.33	0.066
t-C_4H_9	0.19	(0.02)[c]	0.009

[a] The data were taken from ref 9, p 768; S. Anderson, Ph.D. Thesis, University of Lund, Sweden, 1955. [b] J. B. Conant and R. E. Hussey, *J. Am. Chem. Soc.*, **47**, 476 (1925); A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 11–13. [c] Estimated for this series from the data of P. D. Bartlett and L. J. Rosen, *J. Am. Chem. Soc.*, **64**, 543 (1942), for the reaction of RCH_2CH_2-Br + I^- in acetone at 25°. The relative rates for R = C_2H_5 and t-C_4H_9 are 474 and 20, respectively. [d] Estimated from the rate data at 35.0, 45.0, and 55.0°.

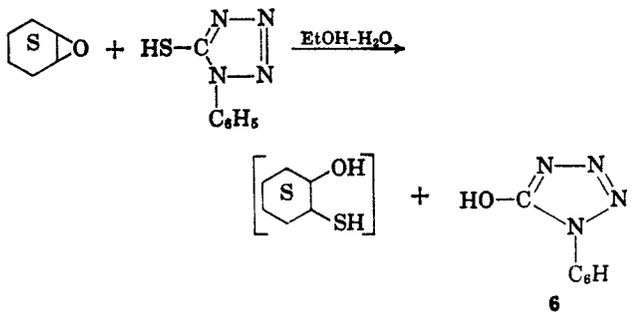
action of H_2S adjacent to the carbonyl in mesityl oxide epoxide.[11] Another notes the reaction of amines with chalcone epoxide at the position β to the carbonyl.[12]

The rate of epoxide opening is less influenced by steric effects than the rate of nucleophilic displacement of halides.[10] This is reflected in the relative rate of epoxide opening by ammonia, as the substitution in the 2 position is successively changed from hydrogen to t-butyl (Table IV). The rate of the t-butyl-substituted compound is one-fifth that of the unsubstituted epoxide. This compares with a rate for neohexylchloride with iodide of one-fiftieth that of ethyl chloride in a classic Finkelstein displacement (Table IV). The rate of epoxide opening in the system reported herein is affected by substitution at the 2 position similarly to the halide displacement. Since the rate of reaction of the more nucleophilic mercaptide would be expected to show less dependence on steric hindrance than the reactions of the less nucleophilic ammonia, some factor(s) must outweigh the effect of nucleophilicity. Two effects may contribute to the observed rate. First, the reaction may be facilitated by activation due to the carbonyl groups in a manner analogous to that proposed by Bartlett and Trachtenberg for phenacyl compounds.[13] Another possible explanation for the effect of 2-substitution on the 1,4-diketoepoxide opening is dependent on the relative sizes of the attacking nucleophiles. If PMT^- is significantly larger than I^- or NH_3, the observed relative rates could be due to interference of the substituent with the approaching nucleophile. Unfortunately, there is no present assessment of the steric requirements of PMT^-, relative to I^- and NH_3.

If the carbonyl is activating the reaction by interacting with the nucleophile, this should be reflected in the activation parameters and as an increase in reac-

(11) W. J. Sullivan and P. H. Williams, *J. Org. Chem.*, **25**, 2128 (1960).
(12) N. G. Baker and N. H. Cromwell, *J. Am. Chem. Soc.*, **73**, 1051 (1951).
(13) P. D. Bartlett and E. N. Trachtenberg, *ibid.*, **80**, 5808 (1958).

tion rate over that of suitable model compounds. The *exo* isomer **5** reacts twice as fast as **1a**, whereas the saturated *endo* isomer **4** reacts approximately four times as fast as **1a**. Thus, if we are to choose a model compound such as cyclohexene oxide, we must correct its rate relative to that of **1a** by the effect of the norbornene group and the double bond, a combined factor of nine. The epoxide opening of cyclohexene oxide with NaPMT under the reaction conditions gives **6**,



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the oxygen analog of HPMT. Since the presence of **6** interferes with the analysis, the apparent rate decreases with time (Table V). A value for the observed

TABLE V

KINETIC DATA FOR THE REACTION OF CYCLOHEXENE OXIDE WITH NaPMT[a]

Time, sec	$k_{obs} \times 10^3$, l. mole^{-1} sec^{-1}	Time, sec	$k_{obs} \times 10^3$, l. mole^{-1} sec^{-1}
1800	9.20	10,800	6.80
3600	8.32	14,400	5.82
5400	7.81	18,000	5.68
7200	7.75	21,600	5.13
9240	7.15		

[a] Reaction conditions are as follows: cyclohexene oxide (4.03×10^{-3} *N*) and NaPMT (8.10×10^{-3} *N*) in 90% ethanol with lutidine (3.13×10^{-2} *N*), lutidinium perchlorate (3.15×10^{-2} *N*), and sodium perchlorate (1.04×10^{-2} *N*), at 55.00 ± 0.03°.

second-order rate of cyclohexene oxide was estimated from the initial data, at 55.0°, $k_i = 1.0 \times 10^{-2}$ l. mole^{-1} sec^{-1}. The relative rate of **1a** to that of cyclohexene oxide at 55.0° corrected for the factors discussed is 15. This comparison indicates that activation by the carbonyls adjacent to an epoxide in the compounds studied is small at best when compared to effects reported for α-halo ketones, *e.g.*, the relative rates of reaction of chloroacetone and *n*-butyl chloride with potassium iodide in acetone at 50° are 35,700 and 1.00,[14] respectively.

The entropy of activation (Table III) for the ring opening is a large negative number of the order of −28 to −32 eu. The large ΔS^* is due to a highly ordered transition state. This ordering may be due to the carbonyls. To assess this, we consider the parameters for the opening of propylene oxide with thiocyanate. The ΔH^* and ΔS^* were found to be 14.3 kcal/mole and −19.4 eu, respectively.[15] In a study of the reaction of mercaptans with ethylene oxide, Danehy and Noel[16] found the ΔH^* to vary from 10.9 to 10.2 kcal/mole and the ΔS^* from −26.5 to −32.6 eu, on going from β-mercaptopropionic acid to 2-mercaptoethanol to 2-mercaptoethylamine.[16] The entropy of activation for the reaction is comparable to that observed in other nucleophilic displacements on epoxides, and does not require participation by the carbonyls. The present data favor an epoxide ring opening, which is not facilitated by the carbonyls and in which the 2 substituent interferes with the approach of the nucleophile.

Registry No.—**1a**, 15052-12-7; **1b**, 15052-13-8; **1c**, 15052-14-9; **1d**, 15052-15-0; **1e**, 15052-16-1; **4**, 15052-17-2; **5**, 15052-18-3; NaPMT, 15052-19-4; cyclohexene oxide, 286-20-4.

Acknowledgment.—We are indebted to Dr. C. A. Bishop, of the Research Laboratories, and to Dr. S. G. Smith, of the University of Illinois, for their helpful suggestions with regard to many of the details of the kinetic procedure.

(14) F. B. Hoffman, *J. Org. Chem.*, **15**, 430 (1950).
(15) P. L. Nichols and J. D. Ingham, *J. Am. Chem. Soc.*, **77**, 6547 (1955).
(16) J. P. Danehy and C. J. Noel, *ibid.*, **82**, 2511 (1960).