Anal. Calcd for $C_{12}H_{10}O_5Cr$: C, 50.35; H, 3.52; O, 27.95; Cr, 18.18. Found: C, 50.51; H, 3.56; O, 27.75.

The filtrate was further concentrated to ~20 ml and treated with ceric ammonium nitrate followed by lithium aluminum hydride as described for run B. Glpc analysis showed a single product, identical with authentic 1-OH.

Run J.—Another sample (0.684 g, 2.03 mmol) of the methanesulfonate 2-OMs was treated in a similar manner with anhydrous buffered formic acid at 70° for 30 min. The product was isolated as described for run I, giving 0.405 g (70%) of 2-OCOH.

Formolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-ethyl-1,1-d_2 Methanesulfonate (4-OMs). Run K.—A solution of 0.355 g (1.05 mmol) of 4-OMs in 25 ml of deoxygenated formic acid[2a] buffered with 0.0491 *M* sodium formate was heated at 120° for 1 hr. The complexed formate 4-OCOH (0.209 g, 69%) was isolated as described in run I: mp 71–72°; ir ($CHCl_3$) 3090, 3035 (CH phenyl); 2980, 2945, 2920 (CH aliphatic); 2170 (CD aliphatic); 1980, 1890 (C≡O), 1730 (C=O ester), 1190 (CO); 660, 630 cm^{-1} (CrC); nmr ($CDCl_3$) δ 8.02, singlet (-OCOH); 5.30, broad singlet (π-C_6H_5-); 2.75, singlet ($C_6H_5CH_2$-). No signals were observed at δ ~4.4 (-CH_2O-). We estimate that ~5% of α-hydrogen-containing material could have been detected had it been present.

Anal. Calcd for $C_{12}H_8D_2O_5Cr$: C, 50.01; H, 2.80; D, 1.39; O, 27.76; Cr, 18.04. Found: C, 50.28; O, 27.70.

Formolysis Products of 2-[π-(Phenyl)chromium tricarbonyl]-1-propyl Methanesulfonate (*dl*-6-OMs). Run L.—A solution of 61.8 mg (0.176 mmol) of *dl*-6-OMs in 5 ml of deoxygenated formic acid[2a] was heated at 115° for 30 min. The reaction mixture was extracted, decomplexed with ceric ammonium nitrate, reduced with lithium aluminum hydride, and analyzed by glpc as described for run B. Two components were found to be present (relative abundance 17% and 83%) which were identified by their infrared spectra as alcohols *dl*-13-OH and *dl*-5-OH, respectively.

Registry No.—1-OMs, 20020-27-3; 2-OCOH, 38599-99-4; 2-OAc, 38600-00-9; 2-OMs, 38600-01-0; 3-OMs, 38605-70-8; 4-OMs, 38600-02-1; 4-OCOH, 38600-03-2; (±)-5-OMs, 38605-48-0; (±)-6-OMs, 38600-04-3; 7-OMs, 20020-28-4; (±)-8-OMs, 38637-45-5.

Acknowledgment.—It is a pleasure to acknowledge the finanical support given this work by the Directorate of Chemical Sciences of the Air Force Office of Scientific Research, Grant No. 991-66, and by the National Science Foundation, GP-11920, as well as helpful discussions with Professor Paul E. Peterson.

Kinetics of the Acid-Catalyzed Closure of Hydantoic Acids. Effect of 2-Aryl and 2-Alkyl Substituents[1]

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Ring closure of hydantoic acids to hydantoins studied under aqueous acid conditions in the pH range 0–2 at 50° shows a specific acid-catalyzed component at low pH as well as a spontaneous component at higher pH. The accelerating effect of substitution on the 2 carbon of hydantoic acids by alkyl or aryl groups is not always as large as can be expected on the basis of their bulk. The observed rates appear to be rationalizable, however, in terms of a competing acceleration–inhibition mechanism resulting from the substituents being able to interfere with the reaction center as well as assisting in the process.

Hydantoic acids are known to cyclize to their respective hydantoin under acid conditions and the effects of 2 substituents has been qualitatively observed.[2] The only data available for the attack of a ureido group at a carboxyl group are the kinetics of the acid-catalyzed closure of a para-substituted phenylthiocarbamoylleucine, but the closure resulted in a thiohydantoin.[3] More recently, Projarlieff, *et al.*,[4,5] have reported studies on the acid-catalyzed reversible cyclization of ureidopropionic acid to yield dihydrouracil which, although not a hydantoin, possesses chemical characteristics similar to hydantoins. Bruice, *et al.*, studied quantitatively the conversion of *O*-ureidobenzoic acid and its esters to 2,4-(1*H*,3*H*)-quinazolinedione, a hydantoin-like molecule, under basic conditions.[6,7] The effects of alkyl and aryl substituents in intramolecular closures has been well documented, with the results suggesting that, as the bulkiness of substituents in cyclization reactions was increased, the rates of cyclization increased.[8–20] However, exceptions to this rule do exist.[16,19]

Despite the large amount of work done on hydantoins, the kinetics of the acid-catalyzed cyclization of hydantoic acids and the effects of 2 substituents have not been quantitated. In the present study the kinetics of the cyclization and the effect of 2 substituents on the

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TABLE I

COMPOUNDS STUDIED WITH R^i (i = 1–3) REFERRING TO THE GROUPS IN SCHEME I

Registry no.	Full chemical name	Abbreviated name	R^1	R^2	R^3
462-60-2	Hydantoic acid	HA	H	H	H
18409-49-9[a]	2-Methylhydantoic acid	MHA	CH_3	H	H
38605-63-9	2,2-Dimethylhydantoic acid	DMHA	CH_3	CH_3	H
5616-20-6	2-Phenylhydantoic acid	PHA	C_6H_5	H	H
949-45-1[a]	2-Benzylhydantoic acid	BHA	C_7H_7	H	H
38605-65-1	2,3-Trimethylenehydantoic acid	TMHA	$-C_3H_6-$	H	H
26081-02-7[a]	2-Isopropylhydantoic acid	ISPHA	i-C_3H_7	H	H
6802-95-5	2,2-Diphenylhydantoic acid	DPHA	C_6H_5	C_6H_5	H
38605-67-3	2-Ethyl-5-methyl-2-phenylhydantoic acid	EMPHA	C_6H_5	C_2H_5	CH_3
38605-68-4	5-Methyl-2-phenylhydantoic acid	MPHA	C_6H_5	H	CH_3

[a] L isomer.

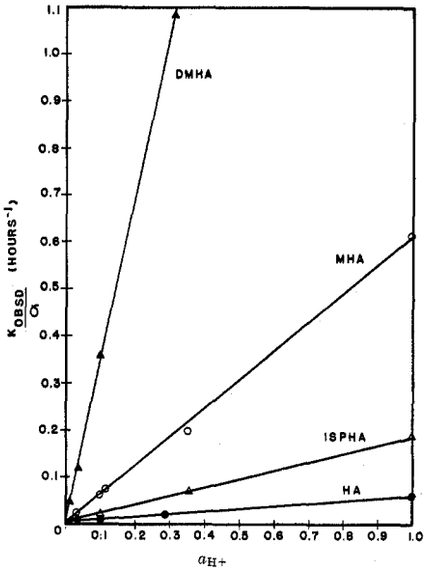
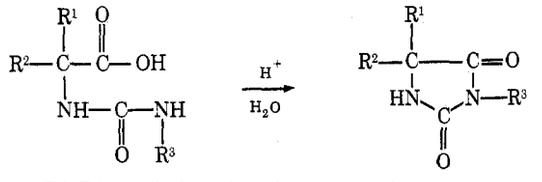


Figure 1.—Plot of k_{obsd} *vs.* a_{H^+} for the closure of HA, MHA, ISPHA, and DMHA to their respective hydantoin at 50° (μ 1.0, NaCl) from which k_1, a spontaneous rate constant, and k_2, a specific acid-catalyzed rate constant, can be determined. The intercept differences are significant and can be obtained by the use of expanded plots.

closure rate of a number of hydantoic acids were investigated in aqueous solution (μ 1.0) at 50° in the pH range 0–2. The reaction is represented as in Scheme I.

SCHEME I



R^1–R^3 = alkyl, aryl, or hydrogen substituent

Table I shows the ten acids that were studied. Included are 2,2-diphenylhydantoic acid (DPHA) and 2-ethyl-5-methyl-2-phenylhydantoic acid (EMPHA), which are the hydantoic acids of phenytoin and mephenytoin, respectively. Phenytoin and mephenytoin are two widely used anticonvulsive drugs.

Results

All the hydantoic acid closures followed first-order kinetics at constant pH and temperature. The reaction for all practical purposes appeared to be irreversible, as evidenced by spectral comparisons and by the absence of any observable reaction when the respective hydantoin was placed in the buffer.

The kinetic results obtained for the closures could be described in terms of eq 1 and 2

$$k_{obsd} = k_1\alpha + k_2\alpha a_{H^+} \quad (1)$$

$$\alpha = \frac{a_{H^+}}{K_a' + a_{H^+}} \quad (2)$$

where a_{H^+} = activity of hydrogen ions (obtained from pH measurements); α = fraction of the hydantoic acid present as the un-ionized acid; K_a' = the dissociation constant of the acid experimentally determined at 25° (μ 1.0) and corrected to 50°; k_1 = spontaneous rate constant; k_2 = specific acid catalyzed rate constant. Equation 1 predicts that a plot of k_{obsd}/α *vs.* a_{H^+} should give a straight line of slope k_2 and intercept k_1. Typical plots of k_{obsd}/α *vs.* a_{H^+} are shown in Figure 1. Actually, linear plots of k_{obsd} *vs.* $a_H{}^+$ adequately described most of the systems, since $K_a' \ll a_{H^+}$ and therefore $\alpha \cong 1$, throughout the pH range studied. However, in some of the cases, a plot of k_{obsd} *vs.* a_{H^+} showed a slight curvature as a_{H^+} approached K_a' but, more importantly, the k_1 value obtained from a linear approximate appeared too low when used to regenerate a curve to match the experimental points. The value of k_1 obtained from a plot of k_{obsd}/α *vs.* a_{H^+} was satisfactory.

Because of the low water solubility of DPHA and EMPHA, the kinetics of their closure was measured in a methanol–water mixture (1:1 v/v before mixing) with a hydrochloric acid concentration of 0.1 M. This was repeated for all the hydantoic acids. Table II gives the log $k_{2,rel}$, log $k_{pH1.0,rel}$, log $k_{pH2.0,rel}$, and log $k_{CH_3OH/H_2O,rel}$, where $k_{2,rel}$ is the relative specific acid-catalyzed rate constant in water (all rates relative to $R^1 = R^2 = R^3 = H$), $k_{pH1.0,rel}$ is the relative rate constant at pH 1.0 in water, $k_{pH2.0,rel}$ is the relative rate constant at pH 2.0 in water, and $k_{CH_3OH/H_2O,rel}$ is the relative rate constant in the methanol–water mixture. These data sets were sufficiently correlated to allow an estimation of k_2 and $k_{pH1.0}$ for DPHA and EMPHA and

TABLE II
DATA USED TO ESTIMATE k_2, $k_{pH1.0}$, AND $k_{pH2.0}$ FOR DPHA AND EMPHA

Acid	log k_{rel}[a] (k_2)	log k_{rel}[a] ($k_{pH1.0}$)	log k_{rel}[a] ($k_{pH2.0}$)	log k_{rel}[a] (k_{CH_3OH/H_2O})
HA	0.00	0.00	0.00	0.00
ISPHA	0.53	0.53	0.61	0.71
PHA	0.62	0.59	0.50	0.71
BHA	0.68	0.67	1.03	0.82
TMHA	1.04	1.03	1.05	1.22
MHA	1.05	1.02	0.97	1.21
DMHA	1.80	1.77	1.73	2.10
DPHA				1.61
EMPHA				3.23

[a] Rate data relative to where $R^1 = R^2 = R^3 = H$.

an approximate estimate of their rates of closure at pH 2.0. The results are shown in Table III. All the

TABLE III
ESTIMATED RATE CONSTANTS FOR DPHA AND EMPHA FROM METHANOL-WATER DATA

Acid	k_2, M^{-1} hr^{-1}	$k_{pH1.0}$, hr^{-1}	$k_{pH2.0}$, hr^{-1}
DPHA	1.30	1.41×10^{-1}	2.34×10^{-2}
EMPHA	32.5	3.39	4.79×10^{-1}

experimentally determined values of k_1, k_2, and pK_a' are shown in Table IV.

TABLE IV
THE VALUES OF k_1, k_2, AND pK_a' FOR THE ACIDS STUDIED

Acid	k_1, hr^{-1}	k_2, M^{-1} hr^{-1}	pK_a'
HA	3.5×10^{-4}	5.39×10^{-2}	3.52 ± 0.03
ISPHA	1.9×10^{-3}	1.81×10^{-1}	3.56 ± 0.03
PHA	1.1×10^{-3}	2.26×10^{-1}	3.04 ± 0.02
BHA	2.4×10^{-3}	2.58×10^{-1}	3.44 ± 0.02
TMHA	3.9×10^{-3}	5.99×10^{-1}	3.48 ± 0.04
MHA	2.4×10^{-3}	6.06×10^{-1}	3.55 ± 0.03
DMHA	6.5×10^{-3}	3.39	4.07 ± 0.03
MPHA		6.09×10^{-1}	
DPHA		1.30	3.01 ± 0.02
EMPHA		32.5	3.03 ± 0.03

Since the buffering species used was hydrochloric acid, the buffer concentration could not be varied without changing the pH. The effect of added acetic acid on the rate of cyclization at pH 1.0 was studied and the results are shown in Figure 2. The plot of k_{obsd} *vs.* acetic acid concentration shows that the acetic acid inhibits the rate of closure at high concentration, consistent with the findings of others on the effect of acetic acid on the rate of solvolysis of acetylsalicylic anhydride in hydrochloric acid buffer.[21,22] The inhibition was probably a solvent effect because it was not seen until the concentration of acetic acid was greater than 2% v/v.

Discussion

The results presented in the previous section can be rationalized in terms of a general mechanistic scheme for the reaction (Scheme II).

(21) E. R. Garrett, *J. Amer. Chem. Soc.*, **82**, 711 (1960).
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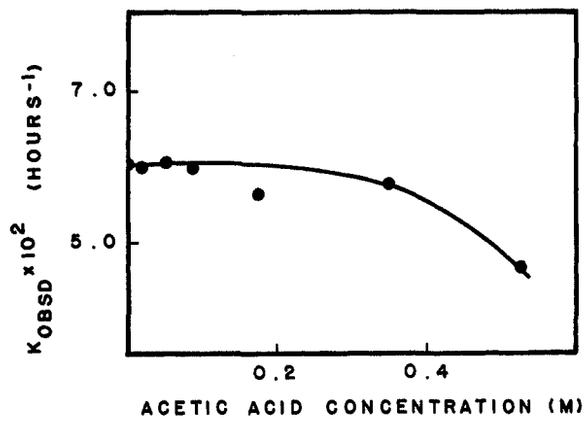
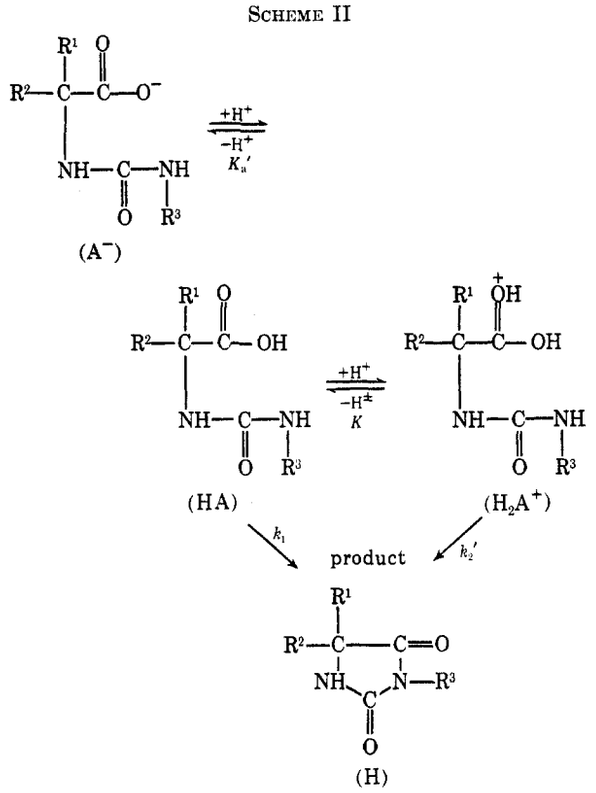


Figure 2.—Plot of k_{obsd} (pH 1.0) *vs.* acetic acid concentration (M) used to determine the effect of acetic acid on the closure rate of MHA to its hydantoin.

SCHEME II



The rate of product formation on the basis of Scheme II is

$$\frac{d[H]}{dt} = k_1[HA] + k_2'[H_2A^+] \quad (3)$$

The development of this equation leads directly to eq 1 and 2, where $k_2 = k_2'/K$. Figure 3 shows some representative plots of log k_{obsd} *vs.* pH, where, assuming Scheme II, the solid line is the path generated by the experimentally determined rate and equilibrium constants k_1, k_2, and pK_a'. As can be seen, Scheme II does appear to describe the system. k_1 corresponds to the spontaneous closure of the free hydantoic acid. However, the acid-catalyzed closure of the hydantoate anion, which is kinetically equivalent, cannot be totally discounted. It would appear, however, on a mechanistic basis that the latter route is highly unlikely.

Inhibition of the closure owing to protonation of the ureido group was not observed, probably because studies

TABLE V

COMPARISON OF LOGARITHMS OF THE EXPERIMENTAL RELATIVE RATE DATA OF VARIOUS SUBSTITUENTS USED IN THE PRESENT STUDY WITH PERTINENT LITERATURE VALUES OF OTHER INTRAMOLECULAR CLOSURES WHERE STERIC EFFECTS WERE ALSO STUDIED

R^1, R^2	2-Substituted hydantoic acid (present study)	3-Substituted mono-*p*-bromophenylglutarates[b]	2-Substituted 4-bromobutyl amines[c]	3-Substituted phthalides[d]	3-Substituted dinitroanthranilic acid[e]
H, H	0.00	0.00	0.00		0.00
CH_3, H	1.05	0.68	1.10[a]		
C_2H_5, H	0.73[a]	1.13	1.39[a]		0.57
C_6H_5, H	0.63	1.21[a]	1.86[a]		
CH_3, CH_3	1.80 (0.42)	1.36	2.20	(0.47)	1.38
i-C_3H_7, H	0.53	1.52	1.98[a]		
C_2H_5, C_6H_5	1.35[a]	2.33	3.25[a]		
C_6H_5, C_6H_5	1.38 (0.0)	2.43	3.72	(0.0)	

[a] Data obtained assuming additivity, *e.g.*, for 2-ethylhydantoic acid, log k_{rel} (R^1 = C_2H_5, R^2 = R^3 = H) = log k_{rel} (R^1 = C_2H_5, R^2 = C_6H_5, R^3 = CH_3) − log k_{rel} (R^1 = H, R^2 = C_6H_5, R^3 = CH_3). [b] Reference 12. [c] Reference 8. [d] Reference 16. [e] Reference 11.

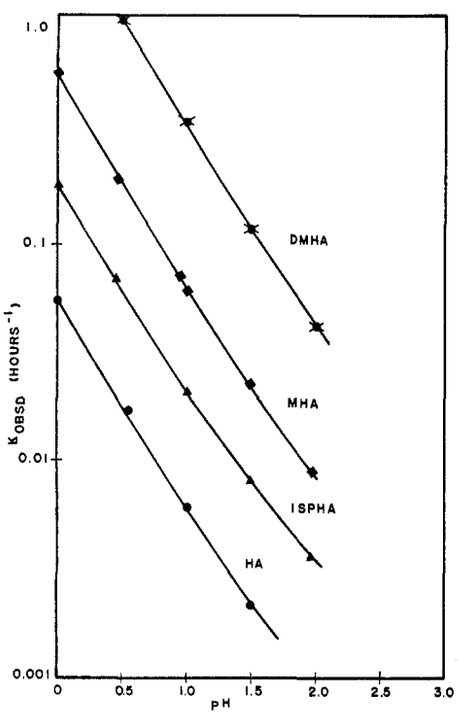
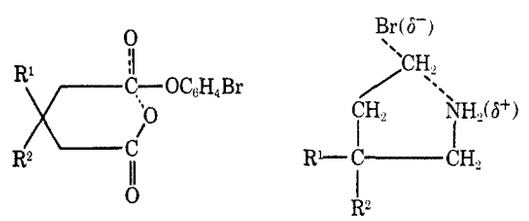


Figure 3.—pH–log k_{obsd} profile for the cyclization of HA, MHA, ISPHA, and DMHA to their respective hydantoin at 50° (μ 1.0, NaCl).

were not carried out in highly acidic systems. The protonation would have resulted in the loss of nucleophilicity by the ureido group.[4,5]

Steric Effects.—The study of steric effects of 2 substituents on the rate of intramolecular closure of hydantoic acids led to some unexpected results. The effect of steric substituents in other intramolecular closures[8-20] had generally shown that, as the bulkiness of the substituents in cyclization reactions was increased, the rate of reaction increased. It was predicted therefore that compounds like DPHA and EMPHA should close at very rapid rates. The experimental results of the present study, however, revealed that such was not the case. Substitution on the 2 carbon of hydantoic acid did increase the rate of the specific acid catalyzed and spontaneous closures, but only in partial agreement with data reported in the literature. Table V gives some pertinent literature comparisons.

Inspection of Table V shows that the effect of substitution appeared to be related to the size of the group. Bruice, *et al.*, investigated 3-substituted mono-*p*-bromophenylglutarate closures, while Brown, *et al.*, looked at 2-substituted 4-bromobutylamines. Their results were consistent with the hypothesis that substituent effects are directly related to their relative size, *i.e.*, isopropyl > phenyl > ethyl > methyl > hydrogen. A look at the possible transition states for their reactions shows that the R^1, R^2 groups are well separated from the reaction center and are unable to interfere with the reaction center in the transition state.



The rationale for the increased rates of cyclization with increased bulkiness of substituent presently has a number of schools of thought. First, the increase in bulk of R^1 and R^2 should decrease the volume in which the reactive ends of the molecule can exist. An increase in the size of R therefore should increase the rate of nucleophilic attack. That is the bulkiness cuts down the number of unprofitable rotamers.[12] Another approach attempts a quantitative analysis of the problem and discusses the rate increase in terms of gauche interactions, which are lessened in going from the ground state to the transition state. This quantitative approach, however, is limited to simple substituents but would predict *a priori* that the larger the group the faster the rate of reaction.[18] More recently Storm and Koshland,[19,23] as well as Bunnett and Hauser,[9] have suggested that the effect of the substituents may be due to orientational effects, where the substituent through interaction with the reaction center will favor certain orientations over others. The new orientation may be a favorable or an unfavorable one, so explaining the fact that substituents may occasionally lead to catalysis while at other times to inhibition. Cohen, *et al.*,[20b-d] have introduced the terms stereo population control and trimethyl lock to describe their findings on substituted *o*-hydroxycinnamic acids and their derivatives.

In the present study all the substituents cause a rate acceleration over the unsubstituted acid but the larger substituents have a smaller effect than their size

(23) D. R. Storm and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **94**, 5805 (1972).

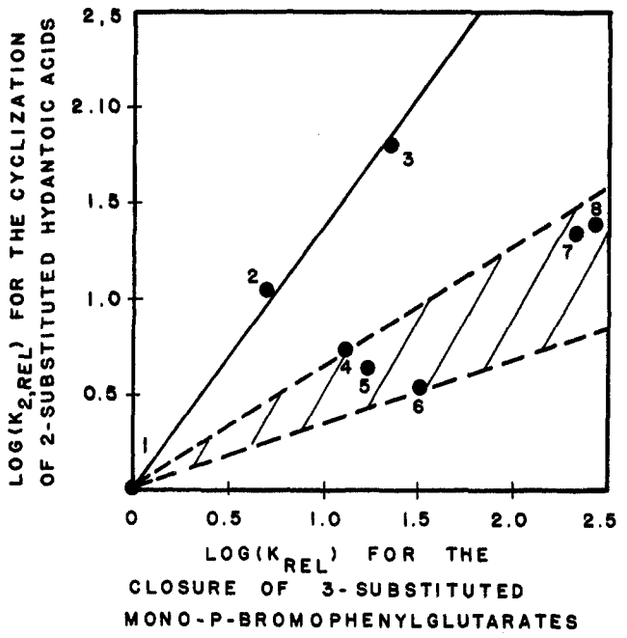
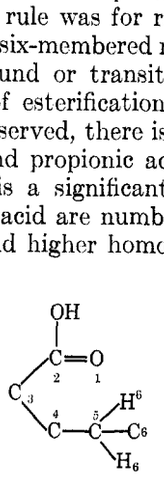


Figure 4.—Logarithms of the relative specific acid-catalyzed rate constants for the cyclization of 2-substituted hydantoic acids (present study) against the logarithms of the relative rates of closure of 3-substituted mono-*p*-bromophenylglutarates.[12] Rates are relative to $R_1 = R_2 = H$ for both the hydantoic acids and the glutarates. Key: 1 = H, H; 2 = CH_3, H; 3 = CH_3, CH_3; 4 = C_2H_5, H; 5 = C_6H_5, H; 6 = *i*-C_3H_7, H; 7 = C_2H_5, C_6H_5; 8 = C_6H_5, C_6H_5.

would predict. A plot of the logarithms of relative rate data from this study against that of 3-substituted mono-*p*-bromophenyl glutarate closure[12] is shown in Figure 4. The division into two groups is readily seen. The substituents which fall into the slower group—*i.e.*, isopropyl, phenyl, etc.—have a common property which is not shared with the methyl, dimethyl substituents. They are better able to interfere with the reaction center.

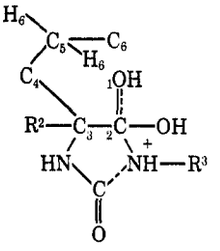
Newman[24] proposed an empirical rule called "The Rule of Six." This rule was for reactions where substituents can form a six-membered ring with some atom involved in the ground or transition state. For example, if the rates of esterification of a series of carboxylic acids are observed, there is little difference between acetic acid and propionic acid, but in going to butyric acid there is a significant drop in the rate. If the atoms in the acid are numbered, it can be seen that butyric acid and higher homologs have atoms in the six position.



This effect could be due to the blocking of the addition reaction and steric retardation owing to the increased spatial requirements in going from the ground state to the partial tetrahedral intermediate transition state.[24] The effect could also be due to solvation interference or an effect on K, the prereaction equilibrium protonation constant. Ingold has discussed steric effects in bimolecular reactions in a similar fashion but from a more energetic approach.[25]

The steric requirements discussed by Newman and Ingold, which are probably playing a role in the present work, have also been qualitatively noted by others in intramolecular reactions. In the case of 3-substituted mono-*p*-bromophenylglutarate closure,[12] moving the substituents to the 2 position[13] greatly decreased the effect of the substituent. Similarly, in the case of 2-substituted 4-bromobutylamine closures,[8] placing the substituent at the 1 or 3 position decreased the *gem*-dialkyl effect by moving the groups nearer the reaction center. With the 4-bromobutylamine closures, "substitution on the third carbon decreases the rate which is only about $^1/_6$ as fast as the parent. However, the bromine occupies a neopentyl position in this case and the observed rate represents a marked acceleration to such a hindered displacement reaction."[8]

In the present study, the transition state is probably very similar to that of the acid-catalyzed esterification of carboxylic acids. Below is a possible transition state which is susceptible to steric effects[24,26] for the acid-catalyzed closure of hydantoic acids.



A possible rate-determining transition state is the attack of the ureido group at the protonated carboxyl group with possibly some concerted leaving of a water molecule. Depending on R^1 and R^2, the coiled structure proposed by Newman as possibly causing inhibition can be superimposed on this system.

When the logarithms of the relative rate constants for the present study were plotted against those of Bruice, *et al.* (refer to Figure 4), HA, MHA, and DMHA may be assumed to be displaying relatively ideal behavior; *i.e.*, there is little steric inhibition by the substituents. The vertical distance between the line drawn through these three points (R^1, R^2; H, H; CH_3, H; CH_3, CH_3) and the experimental points for the other substituents may be taken as a measure of the inhibition by the other substituents. This distance in reality is a rough measure of the relative free energy of inhibition for the reaction assuming ideal behavior by the methyl, dimethyl substituents. Unfortunately, no effort was made to separate the catalytic and inhibitive effects into enthalpic and entropic contributions. These differences were then compared to the number of atoms in the 6 position (see Table VI). The order of inhibition was C_6H_5, $C_6H_5 > C_2H_5$, $C_6H_5 > i\text{-}C_3H_7 > C_6H_5 > C_2H_5$, and this order was qualitatively

(24) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1956, pp 203–213.

(25) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 544–557, 1155–1160.

(26) K. L. Loening, A. B. Ganett, and M. S. Newman, *J. Amer. Chem. Soc.*, **74**, 3929 (1952).

TABLE VI

COMPARISON OF THE INHIBITING EFFECTS OF THE LARGE ALKYL AND ARYL SUBSTITUENTS TO THE NUMBER OF ATOMS IN THE 6 POSITION IN THE ACID-CATALYZED CLOSURE OF 2-SUBSTITUTED HYDANTOIC ACIDS

R^1, R^2	log (k_{rel})[a] I	log (k_{rel}) (exptl) II	Inhibiting[b] effect I − II	Number of atoms at 6 position
C_2H_5, H	1.56	0.73	0.83	3
C_6H_5, H	1.71	0.63	1.08	4
i-C_3H_7, H	2.10	0.53	1.57	6
C_2H_5, C_6H_5	3.21	1.35	1.86	7
C_6H_5, C_6H_5	3.36	1.38	1.98	8

[a] Obtained from Figure 4, where the individual groups would have fallen on the HA, MHA, DMHA line, *i.e.*, assuming that the HA, MHA, DMHA line represents relatively ideal behavior. [b] The difference (I − II) is really just the vertical distance from the HA, MHA, DMHA line to the experimental points, again referring to Figure 4.

identical with the number of atoms in the 6 position. If the assumption is made that the inhibition of the larger groups in the cyclization of hydantoic acids is identical with those seen in the intermolecular esterification mechanism of carboxylic acids, an inhibition factor, *IF*, can be defined

$$IF = \log \frac{k^{40°}_{CH_3CH_2COOH}}{k^{40°}_{RCOOH}}$$

where $k^{40°}_{CH_3CH_2COOH}$ is the specific acid catalyzed rate of esterification of the acid CH_3CH_2COOH;[24] $k^{40°}_{RCOOH}$ is the specific acid catalyzed rate of esterification of the acid RCOOH;[24] CH_3CH_2COOH is taken as the acid representative of hydantoic acid rather than CH_3COOH, because the terminal methyl replaces the ureido group. This means that, if HA is represented by CH_3CH_2COOH, MHA is represented by $(CH_3)_2CHCOOH$, DMHA by $(CH_3)_3CCOOH$, EHA by $CH_3CH_2CH(CH_3)COOH$, and ISPHA by $(CH_3)_2CHCH(CH_3)COOH$. Table VII gives the *IF* for the

TABLE VII

LOGARITHMS OF THE RELATIVE INHIBITION EFFECTS OF 2-ALKYL GROUPS ON THE ACID-CATALYZED ESTERFICATION OF CARBOXYLIC ACIDS

Carboxylic acid (RCOOH)	$k^{40°}_{CH_3CH_2COOH}/k^{40°}_{RCOOH}$	log $k^{40°}_{CH_3CH_2COOH}/k^{40°}_{RCOOH}$ (*IF*)
CH_3CH_2COOH	1.00	0.00
$(CH_3)_2CHCOOH$	2.52	0.40
$(CH_3)_3CCOOH$	22.5	1.35
$CH_3CH_2CH(CH_3)COOH$	8.49	0.93
$(CH_3)_2CHCH(CH_3)COOH$	106	2.03[a]

[a] Obtained by extrapolation from log $k_{CH_3CH_2COOH}/k_{RCOOH}$ *vs* the number of atoms in the 6 position. For R = CH_3CH_2COOH, $CH_3CH_2CH(CH_3)COOH$, $(CH_3)_3CCH(CH_3)COOH$ gives excellent correlation, allowing the estimation of $k_{(CH_3)_2CHCH(CH_3)COOH}$.

acids used. If the rates of the acid-catalyzed intramolecular cyclizations of hydantoic acids are now corrected by the respective *IF* and again compared to the works of Bruice, *et al.*, and Brown, *et al.*, the correction eliminated some of the inconsistencies in the experimental results (see Table VIII). Further data to allow the correction for all the acids was not available.

In summary these results show that the small steric acceleration effect seen with the large groups in the present study is probably due to competing acceleration–inhibition effects resulting from the groups being able to interfere with the reaction center as well as assisting in the process. The actual mechanism of the catalysis is difficult to interpret because, as stated by Thornton,[27] the use of substituents results in changes in the electronic energy surfaces of substituted *vs.* unsubstituted molecules, giving rise to different molecular geometries as well as force constants. This means that the effect of the substituents can be broken down into the effect of the substituent on the rest of the molecule including the reaction center, but we cannot forget about the effect of the rest of the molecule on the energetics of the substituent.

TABLE VIII

COMPARISON OF CORRECTED LOGARITHMS OF RELATIVE RATE DATA FOR THE PRESENT WORK WITH PERTINENT LITERATURE VALUES

R^1, R^2	2-Substituted hydantoic acids (corrected)	Brown, *et al.* 2-Substituted 4-bromobutyl amines[a]	Bruice, *et al.* 3-Substituted mono-*p*-bromophenyl glutarates[b]
H, H	0.00	0.00	0.00
CH_3, H	1.45	1.10	0.68
C_2H_5, H	1.56	1.39	1.13
CH_3, CH_3	3.15	2.20	1.35
i-C_3H_7, H	2.56	1.98	1.52

[a] Reference 8. [b] Reference 12.

The steric effect of the benzyl group, not discussed so far because no comparison data was available, appears to fall in line with other groups studied. The steric effect of the 2,3-trimethylene substitution has a log k_{rel} of 1.05, which is identical with that of a methyl group. At first this does not appear inconsistent because the cyclopentyl group is directed away from the reaction center in the transition state and so in reality acts as a methyl group. An anomaly arises, however, in that the cyclopentyl group has frozen rotation about the 2–3 bond and such an effect in intramolecular reaction usually results in rate increases in the order of 160-fold,[28] whereas here an increase of 11.5-fold is seen. Eliel[29] explains that the most important factors to be considered in ring closures are the case of having the ends of the acylic structure meet and a strain factor. The closure of 2,3-trimethylenehydantoic acid results in two adjacent five-membered rings with a common bond. The situation is similar to the case of succinic compared to maleic acid in the rate of cyclization of their phenyl esters,[28] where the rate increase is only 43-fold because of strain introduced into the system by a double bond. If 2,3-trimethylenehydantoic acid is corrected in a similar manner to the other substituents (refer to Tables VII and VIII) by the data of Newman,[24] the corrected rate increase over hydantoic acid is 11.5 × 3.4 or 39-fold. The apparent small increase in rate with the freezing of the 2,3 bond is due to strain imposed on the system by the added cyclopentyl group. The terminal methyl group (5-methyl) gives a log k_{rel} of 1.43, identical with that of a corrected methyl group at the 2 position. However, the mecha-

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(28) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 8–15.

(29) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 198.

TABLE IX

CALCULATED VALUES, ASSUMING ADDITIVITY, COMPARED TO THE EXPERIMENTALLY DETERMINED VALUES FOR THE EFFECT OF 2 SUBSTITUENTS ON THE CLOSURE OF HYDANTOIC ACIDS

R^1	R^2	R^3	log k_{rel} expti	log k_{rel} calcd
CH_3	CH_3	H	1.80	2.10
C_6H_5	C_6H_5	H	1.38	1.26
C_6H_5	C_2H_5	CH_3	2.78	2.73[a]
CH_3	CH_3	H	3.15[b]	2.90[b]

[a] Assuming that the effect of benzyl is approximately the same as that of ethyl. The assumption was made considering the fact that their Taft steric parameters are identical, *i.e.*, when considered as $C_6H_5CH_2CH_2$ *vs.* $C_2H_5CH_2$. [b] Using the corrected values of Table VIII.

nisms for the rate increases are probably not the same. The 5-methyl group can, by induction, increase the nucleophilicity of the ureido group and stabilize any positive charge built up on the terminal nitrogen in the transition state. The acceleration could also be due to the greater relief of the gauche carboxyl–methyl amido ($-CONHCH_3$) interaction compared to carboxyl–amido ($-CONH_2$) interaction.[18]

Additivity of the Steric Effects.—The trend toward additivity among the logarithms of the relative rates of closure is interesting. This phenomenon was also observed by Bruice, *et al.*[12] The calculation of log (k_{rel}) for $R^1 = C_2H_5$, $R^2 = R^3 = H$ and $R^1 = C_2H_5$, $R^2 = C_6H_5$, $R^3 = H$ used in the discussion so far have asssumed additivity; and, as could be observed from those results, the values obtained did seem to be in the right order of magnitude. Table IX gives the calculated values compared to the experimentally determined values for some substituents where the additivity phenomenon could be checked.

Experimental Section

Equipment.—A Cary 14 recording spectrophotometer was used for all spectroscopic measurements. The pH measurements were carried out using a Corning Model 12 research pH meter standardized with potassium tetraoxoalate standard buffer (pH 1.679, 12.61 g/l.). Infrared spectra were measured on a Perkin-Elmer 70 infrared spectrometer.

Materials.—All chemicals used were of analytical or reagent grade. Mephenytoin was supplied by Sandoz Drug Co. Buffers were made from triply distilled water and analytical grade concentrated hydrochloric acid with the ionic strength adjusted to 1.0 with sodium chloride.

The hydantoic acids were prepared from their amino acids by treatment with potassium cyanate or methyl isocyanate, or by the hydrolysis of the corresponding hydantoin.[2] The amino acids for the formation of the hydantoic acids were commercially available or, in the case of 2,2-diphenylglycine, were prepared from the hydrolysis of the corresponding hydantoin (hydrolysis of the hydantoin in this case did not allow the isolation of the hydantoic acid). Analysis of the compounds prepared, method of synthesis, infrared data, and melting points (reported melting points)[30-37] are shown in Table X. Examples of the various synthetic procedures used are listed below.

Method I. 2,2-Diphenylglycine (DPG).—To 300 ml of 20% sodium hydroxide was added 5,5-diphenylhydantoin (17 g, 0.07 mol). The solution was placed in a plunging autoclave under nitrogen at 180° for 30 hr. This was then charcoal filtered, diluted to 800 ml with water, and neutralized with acetic acid. Product was collected, washed with successive portions (100 ml) of water, ethanol, and ether, and dried in a vacuum hot air oven. DPG gave mp 258° dec (yield 10.7 g).

TABLE X

ANALYSIS,[a] METHOD OF SYNTHESIS, INFRARED DATA, AND MELTING POINTS OF COMPOUNDS STUDIED

Compd	Method of synthesis	Wavenumber for C=O stretch, cm^{-1} (NaCl cells, solvent THF)	Wavenumber for C=O stretch, cm^{-1} (KBr pellet)	Mp (dec), °C	Reported mp (dec), °C	Ref
HA	II	1680, 1720		178–179	180	30
MHA	II	1680, 1720		182–183	185	30
DMHA	II	1680, 1730		186–187	184	31
PHA	IIa	1690, 1730		195–196	181, 196.5	30, 32
BHA	IIa	1690, 1725		192–193	188–190	33
TMHA	II	1675, 1740		200–202		
ISPHA	II	1680, 1720		200–201	187, 176	34, 35
DPHA	IIa	1680, 1730	1625, 1710	190–191		
EMPHA	III	1680, 1710		189–190	177–178	32
MPHA	IIb	1680, 1720		166–167	164–165	32
DPG	I		1630	261–263	242, 263	36, 37

[a] Satisfactory combustion analytical data (±0.3%) were provided for all new compounds. Ed.

Method II. 2-Isopropylhydantoic Acid (ISPHA).—To *dl*-valine (3 g, 0.025 mol) was added an excess of potassium cyanate (3 g, 0.037 mol) in 15 ml of water. The solution was heated in a hot water bath at 90–100° for 1.5 hr. After cooling in ice water, the solution was acidified with concentrated hydrochloric acid. The precipitate was collected, washed with ice water and then with ether, and dried. After two recrystallizations from an ethanol–water mixture, a product with mp 200–201° was obtained.

Method IIa.—If the amino acid was very water insoluble, a slight variation of method II was used. The amino acid was solubilized in basic solution by the addition of some sodium hydroxide (enough to effect solution) and then the excess potassium cyanate was added.

Method IIb.—When methyl isocyanate was used as the carbamoylating agent, the amino acid was again dissolved in slightly alkaline solution and the excess methyl isocyanate was added dropwise to the reaction mixture at room temperature, not at elevated temperatures.

Method III. 2-Ethyl-5-methyl-2-phenylhydantoic Acid (EMPHA).—To 45 ml of 1 *N* sodium hydroxide was added mephenytoin (5 g, 0.02 mol). The solution was heated at 90–100° for 0.75 hr and then cooled. After extraction with 3 × 50 ml of ether and filtering, the aqueous alkaline portion was acidified. The precipitate was collected and, after recrystallization from an ethanol–water mixture, was found to decompose at 189–190°, consistent with EMPHA.

Kinetic Measurements.—All aqueous reactions were carried out at 50.0 ± 0.1° in tightly stoppered 50-ml volumetric flasks suspended in an oil bath. Samples (5 ml) were withdrawn at

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(31) C. J. West, *J. Biol. Chem.*, **34**, 187 (1918).
(32) H. Aspelund, *Acta Acad. Aboenisis, Math. Phys.*, **23**, 1 (1962).
(33) H. D. Dakin, *J. Biol. Chem.*, **6**, 235 (1909).
(34) W. J. Boyd, *J. Biochem.*, **27**, 1838 (1933).
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(36) H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, **49**, 3105 (1953).
(37) R. Duschinsky (to Hoffmann-La Roche Inc.), U. S. Patent 2,593,860 (1952).

appropriate times, placed in screw-capped vials, quickly cooled in ice water, and then stored in a freezer (−15°). Analysis of the samples was carried out at 230 nm for hydantoic acids without aryl substitution, and at 242.5 nm for the acids with aryl substitution. The extinction coefficients of the hydantoic acids are about one-third those of the respective hydantoin. The rate constants were obtained by plotting log $(A_\infty - A_t)$ *vs.* time, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively. Reactions carried out at 50.0 ± 0.1° in the methanol–water mixture were done in ampoules to prevent evaporation problems. The reverse of the ring-closure reactions was studied under identical conditions, but no visible reactions were noted, suggesting that the reactions were for all practical purposes irreversible under the conditions employed. Similarly, the spectrum of the reaction product for the ring-closure reactions was identical with that of an equimolar solution of the respective hydantoin.

pK_a Measurements.—pK_a's were measured in a water-jacketed cell maintained at 25° under nitrogen. The apparatus and method of determination, with slight modification, was that described by Albert and Sargent[38] for carboxylic acids with low water solubility. The hydantoic acids (~0.001 mol) were dissolved in 100 ml of standard sodium hydroxide solution (0.01909 *M*, μ 1.0 with NaCl) and then back-titrated with standard hydrochloric acid solution (0.1090 *M*, μ 1.0 with NaCl). The first end point gave the concentration of the dissolved acid and the remaining points were used to calculate the pK_a, correcting for the concentration of hydrogen ions. The reactions studied were carried out at 50°, but the pK_a's were determined at 25°. King[39] has determined the thermodynamic pK_a's of some hydantoic acids at 25 and 50°, and the average variation in the pK_a's in going from 25 to 50° was 0.02. Estimation of the pK_a' values at 50° was accomplished by the addition of 0.02 to each pK_a value determined at 25°.

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3-Substituted Propionaldehyde Derivatives. A Study of the Chemistry of 2-Hydroxymethylglyceraldehyde Acetonide[1]

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The reaction of glyceraldehyde acetonide with formaldehyde gave the 4-hydroxy-1,3-dioxolane II. Distillation of II gave hydroxymethylglyceraldehyde acetonide VI, characterized as its dimethylhydrazone V, dimethylacetal VII, and *N*-methyloxazolidine derivative X. The latter compound proved to be stable to acetylation and mesylation, and the protecting group could be removed under very mild acidic conditions, allowing the synthesis of aldehydomesylate IX and aldehydothioacetate XIIa.

The replacement of the alcohol function of a β-hydroxyaldehyde is a difficult undertaking because of the ease of polymerization of such compounds. We would like to report on the synthesis and some reactions of 2-hydroxymethylglyceraldehyde acetonide, and its transformation to the 3 mesylate and 3 thioacetate in both a protected and unprotected form. Some of these compounds were required in large quantities in connection with a cepham synthesis.

Glyceraldehyde acetonide I[3] was treated with formaldehyde in aqueous methanolic potassium carbonate. Crystallization of the reaction mixture gave II in 70% yield. Its structure was determined from its reactions and from analytical and spectroscopic data. Also, 4-hydroxy-1,3-dioxanes are known to arise from the reaction of aldehydes with aldols.[4]

The acetate IIa was prepared, but was difficult to obtain in crystalline form. This was due to the fact that two isomers were present in the reaction mixture, as evidenced by the nmr spectrum, which showed two singlets for the anomeric proton at 5.65 and 5.85 ppm in a ratio of 3:1. A method was devised to achieve selective hydrolysis of the acetonide function of the acetate mixture IIa, and the diol mixture IIIa was obtained in very good yield. The method consisted of treatment of the acetonide IIa with 90% aqueous trifluoroacetic acid for 2 min. The resulting diol acetate IIIa was converted to an oily mesylate IVa, but no further work was done on it, since it could not be obtained crystalline.

However, the mixture of epimeric *p*-nitrobenzoates IIb was easily prepared in crystalline form, even though two isomers were obtained (two singlets for the anomeric proton at 6.3 and 6.5 ppm, ratio 3:1). It is evident from the nmr spectrum that the isomer in which the *p*-nitrobenzoate is equatorial is favored.[5] Compound IIb could be converted to a crystalline mixture of epimeric diols IIIb and a crystalline mixture of epimeric mesylates IVb. Attempts to displace the mesylate with potassium thioacetate or with sodium hydrogen sulfide, and to extrude formaldehyde in order to regenerate a hydroxyaldehyde, failed.

While carrying out these reactions, we noticed that high-temperature distillation of compound II gave the aldehyde VI, which we had wanted in the first place. The ir spectrum indicated the presence of an aldehyde (1730 cm^{-1}) and a hydroxyl group (3400 cm^{-1}). The nmr spectrum was consistent with the proposed structure. Upon standing at room temperature for a few hours, the hydroxyaldehyde became very viscous and the carbonyl absorption in the ir decreased considerably. Aldols are known[4] to polymerize or dimerize on standing. It was thus necessary to protect the alde-

(1) We wish to thank the National Research Council of Canada and Bristol Laboratories, Syracuse, N. Y., for financial support.

(2) Abstracted from part of the Ph.D. thesis of Phillip Rossy.

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