[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

The Base-catalyzed Cleavage of β-Hydroxy Acids

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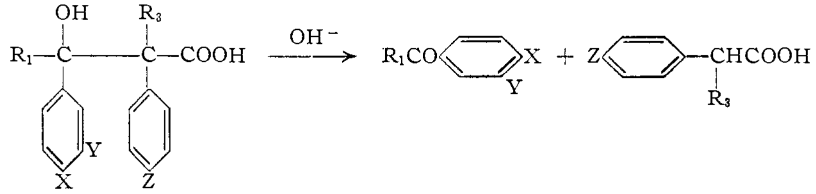
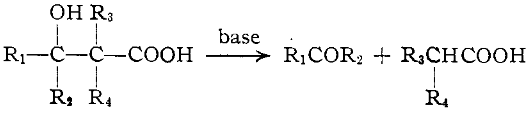
The effects of structural changes on the rate of cleavage of a series of substituted α,β-diaryl-β-hydroxypropionic acids were studied dilatometrically. As R_3 was increased in bulk, the rate increased. For variation of the substituent Z, the rate decreased in the order Cl > H > OCH_3, explainable in terms of stabilization of the carbanion $Ar\overset{\ominus}{C}HCOO^-$. As R_1 was increased in bulk, the rate decreased in the order H > CH_3 > C_2H_5 > C_6H_5; this effect is attributed to increasing hindrance to the approach of the base. For variation of the substituent X, the rate decreased in the order CH_3SO_2 > Cl > OCH_3 > H ≅ CH_3, which parallels the decreasing inductive effect. A small contribution from a resonance effect is seen in the order *p*-Cl > *m*-Cl ≅ *p*-OCH_3. The results are correlated by a concerted mechanism in which breaking of the C_α–C_β bond is essentially simultaneous with the breaking of the H–O bond, in contrast to the non-concerted cleavage of diacetone alcohol. Activation parameters are given, together with the effects of ionic strength and solvent composition (water:propanol ratio).



β-Hydroxy acids (and their esters, etc.) are frequently unstable to bases, being cleaved at the C_α–C_β bond to an aldehyde or ketone and an acid (or ester). This cleavage is often a source of annoyance. For example, esters of I may be formed



$$R_1-\overset{\overset{OH}{|}}{\underset{\underset{R_2}{|}}{C}}-\overset{\overset{R_3}{|}}{\underset{\underset{R_4}{|}}{C}}-COOH \xrightarrow{\text{base}} R_1COR_2 + R_3\underset{\underset{R_4}{|}}{C}HCOOH$$

I

by Reformatzky reactions, and attempts to hydrolyze them to the acids may be accompanied by decomposition. Also, attempts to prepare basic esters of I are frequently blocked by dissociation.[2]

Although the cleavage reaction was recognized over fifty years ago,[3] and although numerous examples are known,[4] there has been no systematic attempt to correlate the ease of cleavage with the structure of I. Much of the available information is due to the studies of Ivanov and his co-workers.[5] They heated various acids of type I with aqueous alkali and observed qualitatively the extent of cleavage. Ivanov reached the following conclusions, which hold with a few exceptions.

(1) When R_3 and R_4 are alkyl, cleavage is quantitative only when R_1 is aryl or both R_1 and R_2 are aralkyl.

(2) When R_3 is aryl, the acids are cleaved quantitatively.

(3) When R_3 is aryl, the cleavage of compounds where R_1 is hydrogen is slower than when both R_1 and R_2 are alkyl or aryl.[6]

The kinetic work on this reaction was carried out by Spassoff,[7] who cleaved four α,α′-diphenyl-β-alkyl-β-hydroxyglutaric acids at several temperatures. The first stage is the cleavage to phenylacetate ion and the ion of a β-keto acid; the latter subsequently undergoes very rapid decarboxylation. Because the reaction did not exhibit clean kinetics, Spassoff could conclude only that a β-phenyl group was more effective in promoting cleavage than a β-alkyl group.

A more recent qualitative study by Blicke and Cox[2,8] led to the following conclusions, based on their own work and data from the literature.

(1) If there is no α-aryl group, cleavage is slow. There is some indication that cleavage is accelerated by increasing bulk of groups R_3 and R_4. Cleavage is faster when R_3 is aryl.

(2) If both R_1 and R_2 are hydrogen, cleavage does not occur. If R_1 is alkyl and R_2 is hydrogen, cleavage is slower than when R_1 and R_2 both are alkyl groups. Cleavage is more rapid when R_1 is aryl, but it is still slow unless R_3 is also aryl. The effect of the size of R_1 and R_2 could not be deduced accurately from the qualitative data available.

(3) For esters of acids I, if R_1 and R_2 are hydrogen, cleavage is slow unless R_3 and R_4 are both aryl. If the β-carbon of the esters is alkylated or arylated, cleavage is much faster. Esters of I cleave faster than the acids, and cleavage by bases such as alkali, ammonia and hydrazine probably takes place before the ester function is attached.

As yet there are no quantitative data which permit generalizations about the mechanism of cleavage. The work reported in the present paper was designed to provide quantitative information about the effects of structure on reactivity for a

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[1] Abstracted from the Ph.D. Dissertation of M. E. Rowley, University of Michigan, 1956.

[2] F. F. Blicke and R. H. Cox, THIS JOURNAL, **77**, 5401, 5403 (1955).

[3] K. Michel and K. Spitzauer, *Monatsh.*, **22**, 1109 (1901).

[4] Complete literature surveys are given in the dissertations of M. E. Rowley (1956) and R. H. Cox (1954), University of Michigan.

[5] (a) D. Ivanov and J. Popov, *Bull. soc. chim. France*, [4] **49**, 1547 (1931); (b) D. Ivanov, M. Michova and T. Christova, *ibid.*, [4] **51**, 1321 (1932); (c) D. Ivanov, *ibid.*, [4] **53**, 321 (1933); (d) D. Ivanov and N. I. Nicolov, *ibid.*, [4] **51**, 1337 (1932); (e) D. Ivanov, *ibid.*, [5] **7**, 569 (1940); (f) D. Ivanov, *Atti X° congr. intern. chim.*, **3**, 209 (1939); *C. A.*, **33**, 8175 (1939); (g) D. Ivanov, *Ann. Univ. Sofia, Faculté phys.-math.*, [2] **33**, 241 (1937); *C. A.*, **32**, 3356 (1938); (h) D. Ivanov, *ibid.*, [2] **35**, 337 (1938–1939); *C. A.*, **34**, 2348 (1940).

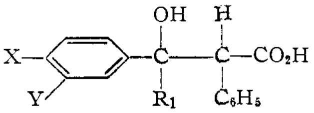
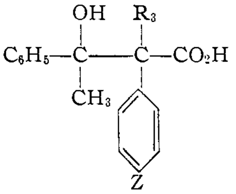
[6] This conclusion is not supported by rate data, and it is contrary to that reached in the present work.

[7] A. Spassoff, *Bull. soc. chim. France*, [5] **12**, 275 (1945); *Ann. Univ. Sofia, Faculté phys.-math.*, [2] **33**, 401 (1937); *C. A.*, **32**, 3359 (1938).

[8] R. H. Cox, Ph.D. Dissertation, University of Michigan, 1954.

TABLE I

PHYSICAL PROPERTIES OF β-HYDROXY ACIDS

						Neut. equiv.		Analyses,[e] %			
								Carbon		Hydrogen	
R_1	X	Y	M.p., °C.[b]	Yield,[c] %	Cryst. solv.[d]	Calcd.	Found	Calcd.	Found	Calcd.	Found
A. β-Aryl-β-alkyl-α-phenyl-β-hydroxypropionic acids[a] 											
CH_3	CH_3SO_2	H	175.0–179.0	21.6	AW	334.4	337	61.06	61.81	5.43	5.36
CH_3	Cl	H	213.0–214.5	20.7	BP	290.8	296	66.11	66.03	5.20	5.21
CH_3	Cl	H	202.0–202.5		BP	290.8	296	66.11	66.11	5.20	5.22
CH_3	CH_3O	H	153.0–155.0[f]	12.6	BP	286.0	289	71.31	71.23	6.34	6.21
CH_3	H	Cl	146.5–153.0	33.0	AW	290.8	287	66.11	66.03	5.20	5.16
CH_3	CH_3	H	192.0–193.0	23.0	BP	270.3	275	75.53	75.50	6.71	6.67
CH_3	CH_3	H	188.0–189.0		BP	270.3	271	75.53	75.50	6.71	6.51
CH_3	H	H	184.0–186.5[g]	31.3	BP	256.3	260				
C_2H_5	H	H	196.0–198.0[h]	14.1	EB	270.4	273				
i-C_3H_7	H	H	176.0–181.0		BP	284.4	280	76.03	76.00	7.09	7.08
C_6H_5	H	H	198.0–199.5[i]		BP	318.4	319				
B. α-Aryl-α-alkyl-β-phenyl-β-hydroxybutyric acids 											
R_3	Z										
C_2H_5	H		130.0–133.0	3.2	AW	284.4	288	76.03	76.07	7.09	7.00
H	Cl		166.0–170.0		N	290.8	290	66.11	65.93	5.20	5.25
H	OCH_3		197.0–198.5	21.7	BP	286.3	290	71.31	71.27	6.34	6.50

[a] The starting ketones and acids were obtained commercially, except as follows: *p*-methoxyphenylacetic acid, E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946); *m*-chloroacetophenone, J. C. E. Simpson, C. M. Atkinson, K. Schofield and O. Stephenson, *J. Chem. Soc.*, 646 (1945); *p*-methanesulfonylacetophenone, G. B. Bachman and C. L. Carlson, THIS JOURNAL, **73**, 2857 (1951). We acknowledge the assistance of Messrs. J. L. Spencer, R. P. Mayer, J. E. Robertson and U. Curtius in their preparation. [b] Melting points are uncorrected. [c] Yields reported are of materials having the purity indicated by the neutralization equivalents shown. This was generally the first crop of crystals from the second recrystallization. No attempt was made to increase the yields, since quality was more important. [d] B, butanone; P, petroleum ether (60–75°); A, acetic acid; W, water; N, nitromethane; E, ethanol. [e] All analytical samples were prepared by an additional recrystallization from either glacial acetic acid or acetic acid–water. Analyses by Anna Griffin of these laboratories. [f] Softened at 150°, melted with evolution of gas. [g] Ref. 8, m.p. 185–187°. [h] Ref. 8, m.p. 197–198°. [i] Ref. 5a, m.p. 186–187°.

group of α,β-diaryl-β-hydroxypropionic acids, and to obtain further information about the mechanism.

Experimental

Materials.—The β-hydroxy acids were prepared by the general method of Ivanov and Spassoff,[9] which involves metalating the α-arylacetic acid with two moles of isopropylmagnesium chloride[10] and condensing this "Ivanov reagent" with the desired ketone (or aldehyde) in ether–benzene solution. The physical properties of the new compounds and details of their preparation are given in Table I.

In two cases (Table I), it was possible to separate the mixtures of stereoisomers into pairs of racemates. After completion of the Ivanov reaction, hydrolysis of the reaction mixture with ice and dilute hydrochloric acid left one racemate as an insoluble solid which settled in the aqueous phase. This was collected and purified separately. The other racemate was isolated from the ether layer in the usual way.

Reagents and Solvents.—Distilled water was boiled at reduced pressure for 15 min. to remove dissolved gases. 1-Propanol (Eastman Kodak Co.) was distilled through an 18-inch Vigreux column. Aqueous sodium hydroxide (carbonate-free) was prepared in the conventional manner and standardized frequently. Sodium propoxide in propanol was prepared by dissolving clean sodium metal in dry[11] propanol; the solution was stored in a polyethylene bottle. All the solutions and solvents were protected from the atmosphere with Ascarite tubes; they were dispensed as needed by siphoning. Sodium perchlorate monohydrate (G. Frederick Smith Co., reagent) was heated at 140–150° for 2–3 hr., powdered, reheated for the same time, then stored in a desiccator.

Kinetic Method.—The rate of reaction was followed dilatometrically in a tap dilatometer. The uniformity of the capillary was checked by measuring length variations of a mercury thread. The dilatometers were cleaned after each run with hot potassium hydroxide–water–ethanol solution, and after every fifth run with dichromate cleaning solution. The stopcocks were relapped after every third or fourth run because of attack on the ground surfaces by the hot alkali. High-vacuum silicone grease was used as lubricant.

The appropriate amounts of standard alkali, 1-propanol, water and sodium perchlorate were mixed and heated to about 5° above the thermostat temperature. The β-hydroxy acid was added, the solution was boiled briefly under vacuum to remove dissolved gases, the dilatometer was loaded (with care to avoid air bubbles) with the aid of a water aspirator and then submerged in the thermostat, which was regulated to ±0.003°. About 10–12 minutes elapsed from the addition of the β-hydroxy acid to the time that temperature equilibrium was reached. The increase in height of the meniscus was measured to 0.005 cm. with a

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[9] D. Ivanov and A. Spassoff, *Bull. soc. chim. France*, [4] **49**, 19 (1931).

[10] F. F. Blicke, H. Raffelson and B. Barna, THIS JOURNAL, **74**, 253 (1952).

[11] Dried with magnesium propoxide by the method of Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 2nd ed., 1951, p. 166.

cathetometer. All runs were allowed to proceed until the meniscus height was essentially constant.

A given run obeyed first-order kinetics, because the concentration of alkali (after deducting the amount initially consumed by the conversion of I to its salt) remained constant during the run. Pseudo-first-order rate constants (k_{obs}) were calculated graphically either by the Guggenheim method [log ($V_{t+c} - V_t$) *vs.* t] or by the infinite time method [log ($V_\infty - V_t$) *vs.* t]. The slope of either plot is proportional to k_{obs}. The second-order rate constants reported in the tables were obtained by dividing k_{obs} by the base concentration. The agreement between the rate constants calculated by the two methods was very good at the lower temperatures; at higher temperatures, however, they differed appreciably because of errors in the infinity point caused by evaporation, formation of air bubbles, and side reactions such as base-catalyzed self-condensation of the ketone produced during the 24–48 hr. required to obtain the infinity reading. The values reported in the tables were all computed by the Guggenheim method,[12] which is believed to be more reliable.

For assurance that eq. 1 actually represented the reaction under study, the arylacetic acids produced by cleavage were isolated from runs with four different acids of type II. The recovery was 94% or better, the melting points of the crude acids were within 2–3° of those of the pure acids, and the neutralization equivalents agreed with the theoretical values within 2–5%. In three cases the identities of the ketones were established qualitatively through their dinitrophenylhydrazones. Cox[8] has demonstrated in many other cases that the arylacetic acids are formed quantitatively.

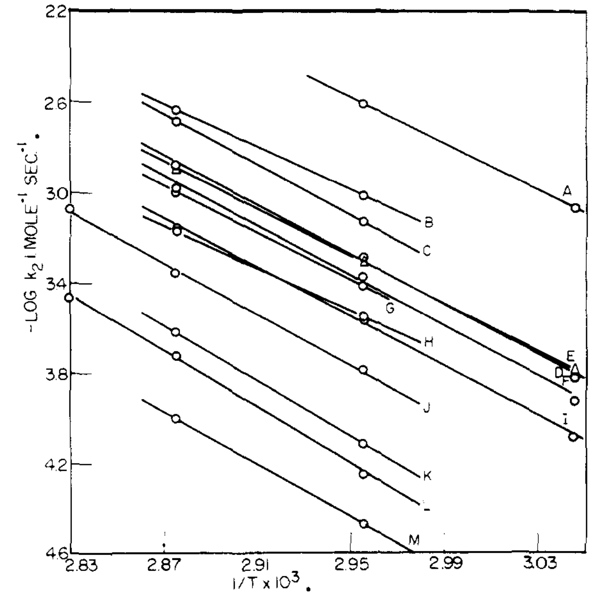


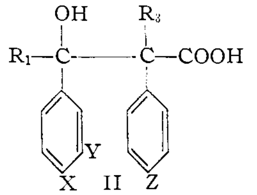
Fig. 1.—Arrhenius plot for activation energies: A, α-ethyl-α,β-diphenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = C_2H_5, X = Y = Z = H); B, α-*p*-chlorophenyl-β-phenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = X = Y = H, Z = Cl); C, α-phenyl-β-*p*-methanesulfonylphenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = Y = Z = H, X = CH_3SO_2); D, α-phenyl-β-*p*-chlorophenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = Y = Z = H, X = Cl), m. p. 213°; E, stereoisomer of D, m. p. 202°; F, α-phenyl-β-*p*-methoxyphenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = Y = Z = H, X = CH_3O); G, α-phenyl-β-*m*-chlorophenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = X = Z = H, Y = Cl); H, α-phenyl-β-*p*-tolyl-β-hydroxybutyric acid (II, R_1 = X = CH_3, R_3 = Y = Z = H); I, α,β-diphenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = X = Y = Z = H); J, α,β-diphenyl-β-hydroxyvaleric acid (II, R_1 = C_2H_5, R_3 = X = Y = Z = H); K, α-*p*-methoxyphenyl-β-phenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = X = Y = H, Z = CH_3O); L, α,β-diphenyl-β-hydroxyisocaproic acid (II, R_1 = $(CH_3)_2CH$, R_3 = X = Y = Z = H); M, α,β,β-triphenyl-β-hydroxypropionic acid (II, R_1 = C_6H_5, R_3 = X = Y = Z = H).

The Arrhenius energies of activation were calculated from the conventional plot (Fig. 1) of log k_2 *vs.* $1/T$. The enthalpy of activation was obtained from the equation $\Delta H^{\neq} = E_a - RT$ and the entropy of activation from the equation $k_2 = kT/h \exp(\Delta S^{\neq}/R) \exp(-\Delta H^{\neq}/RT)$.

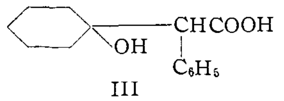
Duplicate runs gave values for k_2 agreeing within 4%. Probable errors were not calculated. An estimate for the errors in the activation quantities was obtained by using the deviation +4% at the lower temperature and −4% at the higher temperature. For enthalpies and entropies of activation obtained from two-temperature plots, the errors are estimated as ±1.8 kcal./mole and ±5.3 cal./mole/deg., respectively. From three-temperature plots, the respective errors are somewhat smaller, estimated to be ±0.7 kcal./mole and ±2.0 cal./mole/deg.

Results

A series of substituted α,β-diaryl-β-hydroxypropionic acids (II) was prepared, embodying variations in the groups R_1 and R_3 and in the substituents in the two phenyl groups (X, Y and Z). For comparison, phenyl-1-hydroxycyclohexylacetic acid (III) and its methyl ester[2,8] were also included.



II



III

All of the acids and esters were cleaved at 65.07° with constant ionic strength and concentrations. α,β-Diphenyl-β-hydroxybutyric acid (II, R_1 = CH_3, R_3 = X = Y = Z = H) was selected for study of the effect of concentration variations. All runs were accurately first-order in acid anion (the base concentration does not vary during a run). Varying the base concentration caused nearly proportional changes in the rate of cleavage (Table II), although a plot of k^c_{ob} *vs.* [OH^-] did not quite pass through the origin. The small positive intercept on the k-axis suggested that the carboxylate anion itself could catalyze cleavage, although the rate was so slow at low hydroxide concentration that an experimental test of this possibility could not be made. These results indicate that the rate is given by the equation

$$\text{rate} = k_2[OH^-][\text{II anion}] + k_2'[\text{II anion}]^2$$

TABLE II

EFFECT OF CONCENTRATION ON CLEAVAGE OF α,β-DIPHENYL-β-HYDROXYBUTYRIC ACID[a]

[Acid anion]	[NaOH][b]	10^4k_2, l. mole^{-1} sec.$^{-1}$	10^5k_1, sec.$^{-1}$
0.0737	0.0737	3.05	2.25
.0737	.2213	2.69	5.94
.0737	.3686	2.41;2.31	8.89;8.53
.0369	.1474	2.86	4.22
.0737[c]	.1474[c]	2.79[c]	4.11
.1474	.1474	3.03	4.47

[a] Temperature 65.07°; solvent 50% (vol.) aqueous 1-propanol; ionic strength 0.5897. [b] After deducting that consumed in neutralizing the acid. [c] Interpolated from plot of k_{obs} *vs.* [OH^-] for the first three values.

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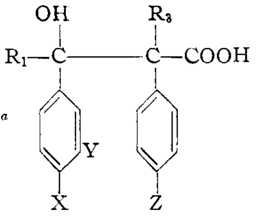
(12) The values calculated from the infinity plots are given in Mr. Rowley's thesis.[1]

Table III

Effects of Structural Variation on Cleavage of α,β-Diaryl-β-hydroxypropionic Acids[a]



	$10^4 k_2$, l. mole^{-1} sec.$^{-1}$ 55.20°	65.07°	74.68°	79.90°	E_a,[b] kcal./mole	$\Delta H^{\neq}$,[b] kcal./mole	$\Delta S^{\neq}$,[b] cal./mole/deg.
	A. α-Alkyl variation, $X = Y = Z = H$; $R_1 = CH_3$						
$R_3 = CH_3CH_2$	8.50	24.4	....	..	22.9	22.2	− 5.1
$R_3 = H$	0.828	2.69	6.90	..	24.7	24.1	− 4.0
	B. α-Aryl variation, $X = Y = R_3 = H$; $R_1 = CH_3$						
$Z = Cl$	...	9.63	23.1	..	21.9	21.2	−10.0
$Z = H$	0.828	2.69	6.90	..	24.7	24.1	− 4.0
$Z = OCH_3$	...	0.766	2.40	..	28.3	27.6	4.1
	C. β-Alkyl variation, $X = Y = Z = R_3 = H$						
$R_1 = CH_3$	0.828	2.69	6.90	..	24.7	24.1	− 4.0
$R_1 = CH_3CH_2$	...	1.64	4.39	8.46	26.0	25.3	− 1.3
$R_1 = (CH_3)_2CH$	...	0.565	1.86	3.45	28.8	28.2	5.1
$R_1 = C_6H_5$	...	0.339	0.992	..	26.4	25.8	− 0.9
	D. β-Aryl variation, $R_1 = CH_3$; $Z = R_3 = H$						
$X = Y = H$	0.828	2.69	6.90	..	24.7	24.1	− 4.0
$X = CH_3$; $Y = H$[c]	...	2.81	6.74	..	21.7	21.0	−12.9
$X = CH_3$; $Y = H$[d]	...	3.06	....	..	..	..	....
$X = H$; $Y = Cl$	...	3.89	10.1	..	22.3	21.6	−10.4
$X = OCH_3$; $Y = H$	1.19	4.22	10.5	..	25.4	24.8	− 1.1
$X = Cl$; $Y = H$[e]	1.51	5.03	13.2	..	25.6	24.9	− 0.3
$X = Cl$; $Y = H$[f]	1.57	4.92	12.7	..	24.4	23.7	− 3.8
$X = CH_3SO_2$; $Y = H$	...	7.32	20.7	..	25.6	24.9	0.4

[a] [Acid anion] = 0.0737; [NaOH] = 0.2213; [NaClO₄] = 0.2949. Solvent is 50% (vol.) aqueous 1-propanol. [b] Computed at 65.07°. [c] Racemate m.p. 192–193°. [d] Racemate m.p. 188–189°. [e] Racemate m.p. 213–214.5°. [f] Racemate m.p. 202–202.5°.

which reduces to the observed second-order equation

$$\text{rate} = k_2[\text{OH}^-][\text{II anion}]$$

at moderate hydroxide concentrations.

The effects of ionic strength and solvent composition (water : propanol ratio) upon the rate of cleavage of α,β-diphenyl-β-hydroxybutyric acid were investigated briefly. Each acid was also cleaved at one or two other temperatures to permit the computation of the activation parameters.

The numerical values of the rate constants are recorded in the following tables. The compounds are grouped in such a way as to present the trends observed as a function of structure.

Table IV

Effect of Ionic Strength on Cleavage of α-Phenyl-β-aryl-β-hydroxybutyric Acids[a]

$ArC(OH)(CH_3)CH(C_6H_5)COOH$

Ar	[NaClO₄] added	$10^4 k_2$, l. mole^{-1} sec.$^{-1}$ 65.07°	74.68°
Phenyl	None	2.22	4.61
Phenyl	0.2949	2.69	6.90
p-Anisyl	None	2.96[b]	..
p-Anisyl	0.2949	4.22	..

[a] [Acid anion] = 0.0737; [NaOH] = 0.2213; solvent 50% (vol.) aqueous propanol. [b] Duplicate 2.96.

Table V

Effect of Solvent and Nature of Base on Cleavage of α,β-Diphenyl-β-hydroxybutyric Acid (A) and Phenyl-1-hydroxycyclohexylacetic Acid (B)[a]

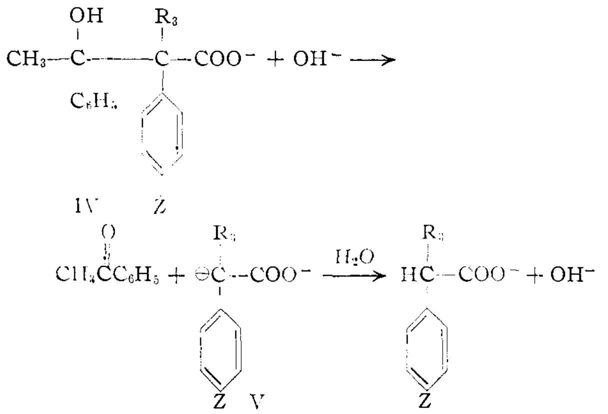
Acid	% Water[b]	[NaOH]	$10^4 k_2$, l. mole^{-1} sec.$^{-1}$
A	100	0.2213	2.46
A	50	.2213	2.69 (6.90[g])
A	5	.2173[c]	89.8
A	1	.2173[c]	129[e]
A	0	.2763[d]	>129[f]
B	50	.2213	(0.07[g])[h]
B	0	.3306[d,i]	0.840; (3.02[g])

[a] [Acid anion] = 0.0737; [NaClO₄] = 0.2949 except where noted; temperature 65.07° except where noted. [b] Balance of solvent is 1-propanol. [c] [NaClO₄] = 0.2985. [d] Base is sodium propoxide. [e] Taken from infinity plot. [f] Lower limit; too fast to measure. [g] At 74.68°. [h] Upper limit; too slow to measure. [i] No NaClO₄ added.

Discussion

Any discussion of the effects of structural variations on reactivity must consider the inductive and resonance effects of the groups and their steric influences, any of which may accelerate or retard the reaction. The problem in analyzing our data then becomes one of determining the ascendancy of one or another effect.

Effects of Structure on the Rate of Cleavage. A. α-Alkyl Variation.—By far the largest change observed in this work is wrought by replacing the α-hydrogen of the reference compound (α,β-diphenyl-β-hydroxybutyric acid (IV), $R_3 = Z = H$) by an ethyl group. This increases the rate roughly tenfold. It cannot be ascribed to the electrical effect of the ethyl group; its electron-releasing tendency (either inductive or hyperconjugative) should oppose the acquisition of the C_α–C_β bonding electrons by $C\alpha$ and also should destabilize the carbanion V, thereby retarding cleavage.


IV

V

The accelerating effect of an α-ethyl group can be explained by relief of steric compression (F-strain) by cleavage. Models show that considerable crowding results from the introduction of the α-ethyl group. Further testimony for the existence of steric crowding is found in the low yield (3%) of the α-ethyl acid obtained from the Ivanov synthesis. In fact, an attempt to extend this series to α,α,β-triphenyl-β-hydroxybutyric acid (IV, $R_3 = C_6H_5$; $Z = H$) was foiled by the utter failure of the Ivanov synthesis; although the chloromagnesium derivative of chloromagnesium diphenylacetate formed readily, as expected, it would not condense with acetophenone, and diphenylacetic acid was recovered quantitatively. We obtained a low yield of impure adduct from the Ivanov reaction of diphenylacetic acid with cyclohexanone, but it dissociated to the components on attempted recrystallization.[13] These synthetic failures do not stem from any unreactivity of the Ivanov reagent from diphenylacetic acid, since Blicke and Raffelson[14] have prepared α,α-diphenyl-β-hydroxypropionic acid in good yield from this reagent and formaldehyde; the acid is quite stable to alkali.[15]

Acceleration of a reaction by relief of steric compression in passing to the transition state is well-known; for example, highly branched tertiary halides solvolyze much faster than the parent *t*-butyl halide.[16]

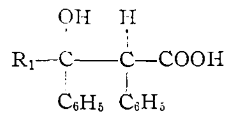
This concept affords an explanation of the otherwise mysterious results of Ashworth and Dubois.[17] In the base-catalyzed dealdolization of β-hydroxy ketones, they found that $Et_2C(OH)CH(CH_3)COEt$ was cleaved some 20% faster than diacetone alcohol. We feel that the α-methyl group is responsible for the faster rate by virtue of the increased F-strain it provides.

B. **α-Aryl Variation.**—The electrical effects of α-substituents were separated from the steric effects by studying *p*-substituted acids IV in which Z was varied from Cl to H to OCH_3; $R_3 = H$. The rates decreased in the order given.

Acquisition of the bonding electron pair by C_α should be promoted by electron-withdrawing groups Z and opposed by electron-releasing groups. The explanation can also be phrased in terms of the effect of the substituent on the acidity of the α-hydrogen of phenylacetic acid. It was found, for example, that the Ivanov reagent from *p*-chlorophenylacetic acid was formed much more rapidly than that from *p*-methoxyphenylacetic acid. The anion V from *p*-chlorophenylacetic acid is therefore of lower energy than those from the other two acids, hence its formation by cleavage should be easier than formation of the other two.

In keeping with this explanation, it was found that the rates of these three reactions ($Z = Cl, H, OCH_3$) fitted a Hammett plot (Fig. 2) of log (k_2/k_2°) *vs. sigma*, using the values for the σ-constants given by Hammett.[18] It is therefore probable that the rates of cleavage of other α-(*meta*- or *para*-substituted phenyl) acids IV could be estimated from tabulated σ-constants, using the measured $\rho = 2.16$. Further measurements are planned to check the validity of this treatment.

C. **β-Alkyl Variation.**—The rates of cleavage decrease steadily as R_1 (structure VI) increases in size from methyl to ethyl, isopropyl and phenyl.[19]


VI

$$R_1—\overset{OH}{\underset{C_6H_5}{C}}——\overset{H}{\underset{C_6H_5}{C}}—COOH \qquad VI$$

If the observed rate changes resulted from the inductive effect, the larger alkyl groups should retard cleavage but phenyl should increase it. Any alteration in the electron density at C_β should be reflected in the acidity of the hydroxyl group. If conjugation of R_1 with the developing carbonyl were rate-influencing, the ethyl and isopropyl compounds would be cleaved more slowly than the methyl compound, but phenyl should be cleaved much faster. Electrical effects are thus seen not to be dominant, and the observed rate differences must largely result from steric factors.

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(13) Other attempts to condense the Ivanov reagent from diphenylacetic acid with ketones have been unsuccessful; F. F. Blicke and R. H. Cox, private communication. In fact, there appears to be no successful preparation of these compounds recorded in the literature.

(14) F. F. Blicke and H. Raffelson, THIS JOURNAL, **74**, 1730 (1952).

(15) H. E. Zaugg, *ibid.*, **72**, 3001 (1950).

(16) H. C. Brown and R. S. Fletcher, *ibid.*, **71**, 1845 (1949).

(17) M. R. F. Ashworth and J. E. Dubois, *Bull. soc. chim. France*, 147 (1955).

(18) L. P. Hammett, "Physical-Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 188. *Cf.* H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(19) Compounds where $R_1 = H$ could not be studied quantitatively because they did not follow straightforward kinetics. Plots of log $(V_{t+c} - V_t)$ *vs.* time exhibited a pronounced curvature after 10–15% reaction. From the slopes of the initial straight portions of the curves it appeared that they cleaved 2–3 times as fast as the corresponding compounds where $R_1 = CH_3$. The nature of the competing reaction was not investigated; a reasonable conjecture is the Cannizzaro reaction of the aldehyde.

The compound where R_1 = *t*-butyl was not included because it seemed likely that it would have cleaved more slowly than the isopropyl compound whose rate already was inconveniently slow.

An alkyl group at the α-position caused a sharp rate increase, explained above by relief of F-strain. *A priori*, a β-alkyl group would be expected to have the same effect—but this is contrary to observation. A clue to the mystery is furnished by examination of scale models. The β-alkyl group interferes with the approach of the hydroxide ion, the more so as R_1 increases in size. The data suggest that hindrance to the approach of the base is sufficiently important to exercise dominance over the rate, that it outweighs the predicted rate-enhancing effect of increasing F-strain.[20]

This hypothesis may be applied to the data of Ashworth and Dubois.[17] In their study of the rates of dealdolization of ketols $RC(CH_3)(OH)CH_2COR'$ ($R = R'$), they observed a steady decrease in rate as group R was increased in bulk from methyl to *n*-propyl, *n*-amyl, isopropyl, and *t*-butyl. The magnitudes of the changes approximated those observed in the present work. They attributed the observed sequence of reactivities to the diminishing ability of R′ to hyperconjugate with the existing carbonyl group. Unfortunately, groups R and R′ were varied simultaneously. Since their results can be explained just as well by invoking steric hindrance to the approach of the base, an experimental attempt to distinguish these two explanations should be conducted in which only one group is varied.

A somewhat similar example of steric hindrance to an approaching base controlling a reaction is found in "Hofmann elimination" from onium salts. Here it is believed that the least hindered proton is selected for removal, not the one which would give the more stable olefin (resonance control, Saytzeff Rule).[21]

D. β-Aryl Variation.—The influence of the electrical effects of β-substituents upon the rate of cleavage was studied by varying substituents in the β-phenyl group; the steric factor remains constant. As *para*-substituents are introduced into the β-phenyl group of α,β-diphenyl-β-hydroxybutyric acid, the rate of cleavage increases in the order hydrogen < methoxyl < chlorine < methanesulfonyl. Since the methoxy derivative cleaves *faster* than the reference compound, the result cannot be explained solely in terms of a resonance effect. Instead, the observed order of cleavage for this group of compounds parallels the inductive effects estimated from the ionization constants of the corresponding substituted acetic acids. It is believed that the primary influence of these *para*-substituents arises from increasing the acidity of the β-hydroxyl by withdrawing electrons inductively from its vicinity.

A further postulate is required to account for the fact that a *m*-chloro substituent is less effective than *p*-chloro. Consideration of the inductive effect alone would lead to the opposite prediction, since the inductive effect is strongly damped by increasing the distance.[22] Thus, the respective σ-constants for *m*-chloro and *p*-chloro are +0.373 and +0.227.[18] We suggest, therefore, that a small contribution to the rate is made by resonance of the β-aryl group with the developing carbonyl group. A *para*-substituent with unshared electrons can resonate with the incipient carbonyl, a *meta* substituent cannot. This possible resonance cannot be of primary importance, however, since the methoxyl group, which has the greatest ability to resonate, has a much smaller rate-enhancing effect than chlorine or methanesulfonyl.

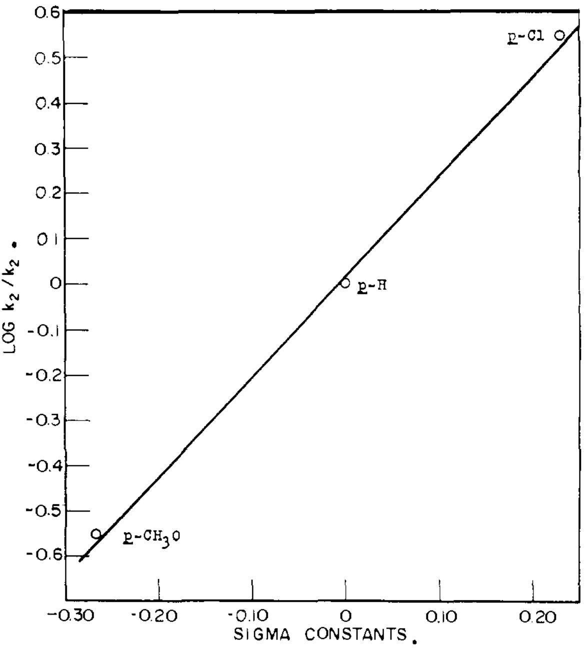

Fig. 2.—Hammett plot of cleavage rates of α-(*p*-substituted phenyl)-β-phenyl-β-hydroxybutyric acids by NaOH in 50% aqueous 1-propanol at 65.07°.

These hypotheses can be tested by studying a wider variety of substituents in the *meta* and *para* positions. Although the Hammett relationship fails to correlate the observed rates for the *para*-substituents in the β-phenyl group, *meta*-substituents should fit this equation. When more data become available, a more accurate assessment of the importance of resonance in the transition state of this reaction can be made.

The *p*-methyl group exerts no influence on the rate, within experimental error. If the inductive effect is solely responsible, this is not surprising; a methyl group substituted in acetic acid has only a slight effect on the acidity compared to the powerful effects of chlorine and the other substituents. A *t*-butyl group may demonstrate a sufficiently greater inductive electron-release to cause a measurable retardation.

E. Esters of III.—The cleavage of III and its methyl ester was investigated briefly. Aqueous propanol could not be used as a solvent because of the likelihood of ester hydrolysis, hence these compounds were cleaved in dry propanol with sodium propoxide. The acid cleaved at a convenient

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(20) It would be desirable to disentangle the various steric and electrical effects, all of which probably exert some influence. One approach to the solution would be a study of the cleavage of these compounds with a series of bases of equal basicity but graded steric requirements, such as amines or alkoxide ions.

(21) *Cf.* H. C. Brown and I. Moritani, THIS JOURNAL, **75**, 4112 (1953); C. H. Schramm, *Science*, **112**, 367 (1950).

(22) *Cf.* for example, G. E. Hall, R. Piccolini and J. D. Roberts THIS JOURNAL, **77**, 4540 (1955).

rate under these conditions. The ester cleaved much more rapidly, although accurate rate constants could not be obtained.[23] Moreover, an attempt to prepare *n*-propyl α,β-diphenyl-β-hydroxybutyrate came to nought when the Reformatzky reaction product dissociated on attempted distillation.

The greater rate of cleavage of β-hydroxy esters compared to the acids has been observed by others. Zaugg found that esters of α,α-diphenyl-β-hydroxypropionic acid were split readily by base, although the free acid was quite stable.[14] Blicke and Cox reported that several esters of β-hydroxy acids were cleaved at room temperature by such weak bases as ammonia and hydrazine, even though the corresponding acids were not.[2,8]

It is not surprising to find the esters more readily split than the acids. The approach of the negative hydroxide ion to the neutral ester is easier than the approach to the negatively charged anion of the acid. Furthermore, cleavage of the ester leads to the carbanion of an arylacetic ester, while cleavage of the acid anion produces a less stable doubly-charged anion. In other words, as is well known, the α-hydrogen of an ester is more acidic than the α-hydrogen of a carboxylate anion.

F. **Stereochemical Variations.**—Both diastereoisomeric racemates of α-phenyl-β-*p*-chlorophenyl- and α-phenyl-β-*p*-tolyl-β-hydroxybutyric acid were isolated by taking advantage of a fortunate difference in their ether solubilities. It is probable that the diastereoisomers of the other β-hydroxy acids studied in this work could also have been separated, although no such attempt was made. Table III shows that the diastereoisomers were cleaved by base at the same rate, within experimental error.

A greater difference in the rate of cleavage would have been anticipated. In the ground state of the molecule, the rotational conformation of lowest energy should be that involving minimum steric interaction between the α- and β-substituents.[24] In comparing models of the two diastereoisomers in their assumed preferred conformations, there is a perceptible difference in the ease of bringing up the base to the β-hydroxyl group. On the other hand, the transition state of lowest energy should be that in which the negative carboxylate ion lies as far as possible from the β-hydroxyl group being attacked by the negative hydroxide ion.

Apparently the various stereochemical factors compensate each other in the systems studied. Further experiments are planned in which more reactive compounds will be cleaved at lower temperatures so as to magnify the differences in rotational conformation. The use of neutral and negatively charged bases of different steric requirements will demonstrate the relative importance of charge interaction and steric hindrance.

Environmental Variations. A. Salt Effect.—Addition of sodium perchlorate as an inert salt increased the rate markedly. Since the reaction at hand occurs by attack of hydroxide ion on the negatively-charged β-hydroxy carboxylate ion, the positive salt effect observed is in agreement with theory which predicts that magnifying the ionic atmosphere decreases the mutual repulsions between ions of similar charge.

B. **Effect of Solvent and Base Strength.**—Most of the data accumulated in this research were obtained in a 1:1 solvent mixture of water and propanol. The reference compound, α,β-diphenyl-β-hydroxybutyric acid, cleaved somewhat more slowly in pure water. In 95% propanol, the rate is thirty times faster than in 50% propanol; in 99% propanol, it is fifty times faster; in dry propanol at 65°, the rate was too fast to measure. A comparison of the effect of the dry solvent was also performed for phenyl-1-hydroxycyclohexylacetic acid (III) at 75°; in 50% propanol the rate was too slow to measure, while in dry propanol it proceeded fairly rapidly, at least forty times as fast.

A somewhat similar effect of solvent was noted by Åkerlof in his study of the dealdolization of diacetone alcohol.[25] When the solvent was changed from pure water to 50% propanol (by weight), the rate decreased 22%. In 80% propanol, it was about the same as in pure water, and in 99% propanol, it was two and one-half times as fast as in water. These changes were interpreted as "solvent effects," since the cleavage of diacetone alcohol is considered to be specifically catalyzed by hydroxide ion.[26]

It is inconceivable that changes of the magnitude observed here could result simply from a "solvent effect." The most reasonable explanation for our results is that the cleavage of β-hydroxy acids is catalyzed both by hydroxide ion and propoxide ion, the latter being the more effective since it is a stronger base.[27] As the proportion of water in the solvent is decreased, the equilibrium below is shifted to the right. It is surprising to find such a

$$\mathrm{OH^- + PrOH \rightleftarrows PrO^- + H_2O}$$

large effect in view of the probably small differences in basicity. Further study with a wider range of bases, solvents and β-hydroxy acids will be needed to unravel the relationship between base strengths and cleavage rates.

The Mechanism of Cleavage of β-Hydroxy Acids.—A "concerted" or "synchronous" mechanism best explains the data thus far collected. The rapid neutralization of the carboxyl group is obviously the first step. The remainder of the cleavage is

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[23] The volume increase was much smaller than that noted with any of the free acids studied. The volume increase stopped after about 3 hours, and thereafter a slow *decrease* was noted. Obviously some side reaction was taking place. This was not ester interchange, since this reaction would be extremely rapid at 65°. Self-condensation of the phenylacetate ester produced by cleavage also was not responsible for the volume decrease, since a separate experiment with ethyl phenylacetate, sodium propoxide and propanol showed that this Claisen condensation proceeded with a volume increase. The nature of the side reaction was not further investigated. An attempt to measure the cleavage of methyl α,β,β-triphenylpropionate was frustrated by the low solubility of this ester in sodium propoxide solution.

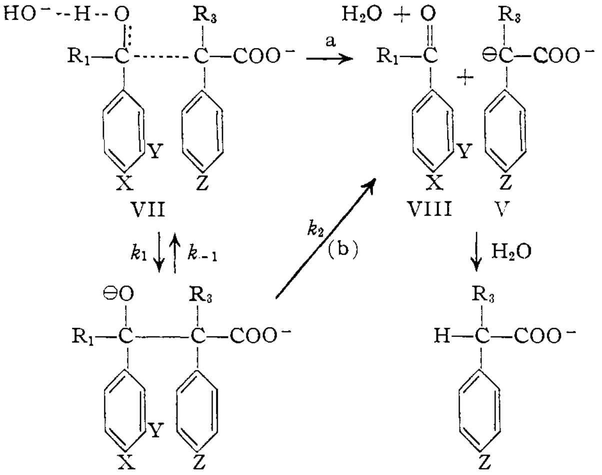
[24] *Cf.* D. J. Cram, F. D. Greene and C. H. Depuy, THIS JOURNAL, **78**, 790 (1956).

[25] G. Åkerlof, *ibid.*, **50**, 1272 (1928).

[26] An extensive discussion of the diacetone alcohol cleavage is given in A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, New York, N. Y., 1953, pp. 283–297. A brief review is presented in J. Hine, "Physical-Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1956, pp. 252–254.

[27] J. Hine and M. Hine, THIS JOURNAL, **74**, 5266 (1952), showed that water is approximately three times as acidic as 1-propanol.

thought to proceed by removal of the proton from the β-hydroxyl group with essentially simultaneous fission of the C_α–C_β bond to form the ketone and the carbanion V (path a). The reaction is driven to completion by the irreversible acquisition of a proton from the solvent by V.



The alternative path b is deemed not to represent this reaction for the following reasons. If $k_1 >> k_{-1}$ and $k_2 < k_1$, we would have the cleavage of the C_α–C_β bond as the rate-determining step. This is the situation which obtains in the well-known dealdolization of diacetone alcohol.[26] Were this true with β-hydroxy acids, it would be difficult to see why changing the nature of the base and solvent should have such an overwhelming influence on the rate. As mentioned above, the diacetone alcohol cleavage is not nearly so sensitive to base strength. Secondly, a much smaller salt effect would have been predicted, since this rate-determining step would have involved a unimolecular dissociation of one doubly-charged anion to a second one (V) and a neutral molecule. Finally, it would be difficult to explain the effect of bulky β-substituents in decreasing the rate if the C_α–C_β bond cleavage were rate determining; the F-strain hypothesis would have led to the unqualified prediction that increasing bulk would promote dissociation.

The possibility that proton removal is rate-determining ($k_1 << k_2$) is excluded by the fact that substitution on the α-position, either an α-alkyl group or a *para*-substituent in the phenyl group, has a pronounced influence on the rate. The fairly large positive value of *rho* (2.16) shows that electron accession to C_α is involved in the transition state. This could scarcely be the case if the rate were controlled by removal of the proton from the remote β-hydroxyl group.

The arguments which show that neither separate step can be rate controlling provide powerful support for the idea that H–O and C_α–C_β bond-breaking both are important in the rate-determining step, and hence support the postulation of a synchronous mechanism.

The dealdolization of diacetone alcohol is considered to proceed by a two-step path, C–C bond cleavage being rate determining.[26] On the other hand, more complicated ketols are believed to dissociate by a concerted mechanism.[17] Perhaps someone will discover that certain β-hydroxy acids may also cleave by the two-step path.

Acknowledgment.—We are indebted to Professor F. F. Blicke for many helpful discussions.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF HUMBLE OIL AND REFINING CO.]

The Ozonolysis of Phenanthrene in Methanol

BY PHILIP S. BAILEY[1]

RECEIVED JANUARY 7, 1956

During ozonolysis in methanol, phenanthrene is attacked at the 9,10-double bond. The active oxygen containing ozonolysis products are characterized. The results support the Criegee mechanism for ozonolysis. The recently published Milas mechanism is criticized. By decomposition of the active oxygen containing products any one of the following substances can be obtained in good yield: 2,2′-biphenyldicarboxaldehyde, methyl 2′-formyl-2-biphenylcarboxylate, 2′-formyl-2-biphenylcarboxylic acid and diphenic acid.

This paper is the first of a series dealing with the course and mechanism of the ozonolysis reaction, especially in regard to aromatic type compounds.

The recent elegant work of Criegee and co-workers[2] concerning the mechanism of ozonolysis has dealt largely with aliphatic compounds. Wibaut and co-workers[3] have done a great deal of ozonolysis work with aromatic and heterocyclic compounds in which they have shown that the ozone attack is probably electrophilic in nature.

(1) Address requests for reprints to the author, Department of Chemistry, University of Texas, Austin, Texas.

(2) (a) R. Criegee and G. Wenner, *Ann.*, **564**, 9 (1949); (b) R. Criegee and G. Lohaus, *Chem. Ber.*, **86**, 1 (1953); (c) R. Criegee, G. Blust and G. Lohaus, *Ann.*, **583**, 2 (1953); (d) R. Criegee and G. Lohaus, *ibid.*, **583**, 6 (1953); (e) **583**, 12 (1953); (f) R. Criegee, P. deBruyn and G. Lohaus, *ibid.*, **583**, 19 (1953); (g) R. Criegee and M. Lederer, *ibid.*, **583**, 29 (1953); (h) R. Criegee, G. Blust and H. Zinke, *Chem. Ber.*, **87**, 766 (1954); (i) G. Lohaus, *ibid.*, **87**, 1708 (1954); (j) R. Criegee, A. Kerckow and H. Zinke, *ibid.*, **88**, 1878 (1955). See also (k) P. S. Bailey, *ibid.*, **87**, 993 (1954); (l) P. S. Bailey, *ibid.*, **88**, 795 (1955); (m) J. Meinwald, *ibid.*, **88**, 1889 (1955).

(3) P. W. Haayman and J. P. Wibaut, *Rec. trav. chim.*, **60**, 842 (1941); J. P. Wibaut and E. C. Kooijman, *ibid.*, **65**, 141 (1946); J. P. Wibaut and J. Van Dijk, *ibid.*, **65**, 413 (1946); E. C. Kooijman and J. P. Wibaut, *ibid.*, **66**, 705 (1947); J. Van Dijk, *ibid.*, **67**, 945 (1948); J. P. Wibaut, F. L. J. Sixma, L. W. F. Kampschmidt and H. Boer, *ibid.*, **69**, 1355 (1950); H. Boer, F. L. J. Sixma and J. P. Wibaut, *ibid.*, **70**, 509 (1951); F. L. J. Sixma, H. Boer and J. P. Wibaut, *ibid.*, **70**, 1005 (1951); J. P. Wibaut and F. L. J. Sixma, *ibid.*, **71**, 761 (1952); F. L. J. Sixma, *ibid.*, **71**, 1124 (1952); L. W. F. Kampschmidt and J. P. Wibaut, *ibid.*, **73**, 431 (1954); J. P. Wibaut and H. Boer, *ibid.*, **74**, 241 (1955).