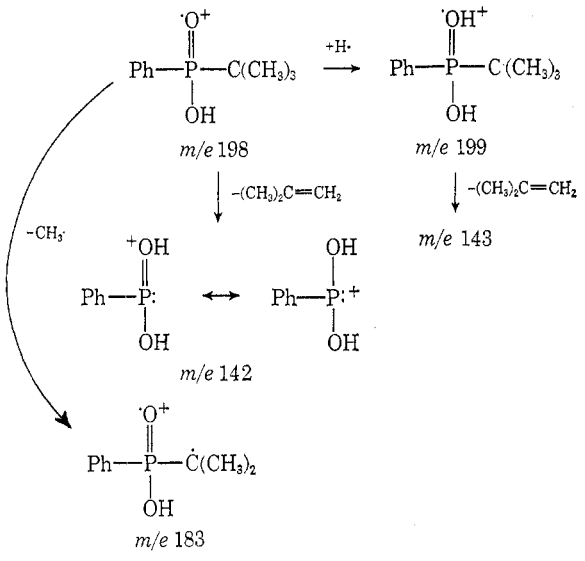
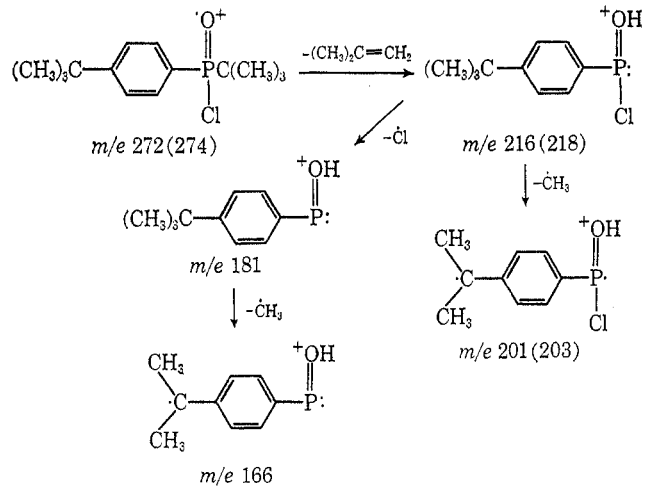
SCHEME IV



SCHEME V[a]



[a] The mass numbers in parenthesis denote the ion containing ^{37}Cl.

spectra of diarylphosphinic acids,[10] confirm that we isolated arylalkylphosphinic acids and not the compounds originally reported.[3]

The principal peaks of the mass spectrum of *p*-*t*-butylphenyl-*t*-butylphosphinyl chloride with sizes relative to the base peak 216 are 274 (11), 272 (30), 218 (43), 203 (24), 201 (83), 181 (6), and 166 (4%). Metastable ions are observed at 189, 187 with a broad peak at 171.8, and correspond to the transitions 218 → 203, 216 → 201 and 272 → 216, and 274 → 218, respectively. Scheme V illustrates this pattern.

Registry No.—III, 25097-42-1; IV, 4923-86-8; V, 25097-44-3; aluminum chloride, 7446-70-0; *t*-butylbenzene, 98-06-5; phosphorus trichloride, 7719-12-2.

Conformation of the Sodium Salts of 4-Phenylbutyric Acid and ω-Phenyloctanoic Acid in Aqueous Solution

JOHN F. SEBASTIAN[1] AND MILA TI

Department of Chemistry, Miami University, Oxford, Ohio 45056

Received October 23, 1969

The conformations of the sodium salts listed in the title have been investigated in deuterium oxide by nuclear magnetic resonance spectroscopy. The conformation of 4-phenylbutyric acid sodium salt has been found to exist in the *anti* form with respect to the β,γ carbon–carbon bond. The data do not permit the establishment of a unique conformation for sodium ω-phenyloctanoate, but possible conformations are delineated.

The nature and extent of the intermolecular and the intramolecular interaction of two or more apolar moieties in water continues to be a subject of extensive and lively investigation.[2-11] The elucidation of these interactions is crucial to an understanding of molecular conformations and reaction mechanisms in aqueous solution.

Over the past few years many investigators have examined the nature, structure, and the effect on reactivity of micelles.[5,7,12-15] However, the conformations of the molecular constituents of micelles have received relatively little attention. It has been fairly well established in a number of cases that at concentrations below the critical micelle concentration (cmc), intermolecular association can occur.[6,16] We have initiated a study of ω-phenylalkylcarboxylic acid salts in aqueous solution with the goal of obtaining information regarding the conformations of the anions at concentrations below the cmc. Our approach makes use of the phenyl ring as a conformational probe. The magnetic anisotropy arising from the ring current of the phenyl ring will affect the chemical shifts of any protons located in the

(1) To whom inquiries should be sent.
(2) W. Kauzmann, *Advan. Protein Chem.*, **14**, 1 (1959).
(3) G. Nemethy and H. A. Scheraga, *J. Phys. Chem.*, **66**, 1773 (1962).
(4) I. M. Klotz, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **24**, Suppl. 15, S-24 (1965).
(5) H. Inoue and T. Nakagawa, *J. Phys. Chem.*, **70**, 1108 (1966).
(6) P. Mukerjee, *ibid.*, **69**, 2821 (1965).
(7) N. Muller and R. H. Birkhahn, *ibid.*, **71**, 957 (1967).
(8) R. H. Conrad and L. Brand, *Biochemistry*, **7**, 777 (1968).
(9) D. M. Crothers and D. I. Ratner, *ibid.*, **7**, 1823 (1968).
(10) D. S. Olander and A. Holtzer, *J. Amer. Chem. Soc.*, **90**, 4549 (1968).
(11) M. P. Schweizer, A. D. Broom, P. O. P. Ts'O, and D. P. Hollis, *ibid.*, **90**, 1042 (1968).
(12) R. Haque, *J. Phys. Chem.*, **72**, 3056 (1968).
(13) R. B. Dunlap and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 4395 (1968), and references cited therein.
(14) L. R. Romsted and E. H. Cordes, *ibid.*, **90**, 4404 (1968).
(15) F. M. Menger and C. E. Portnoy, *ibid.*, **90**, 1875 (1968).
(16) P. Mukerjee, K. J. Mysels, and C. I. Dulin, *J. Phys. Chem.*, **62**, 1390 (1958).

TABLE I

CHEMICAL SHIFTS OF THE ACIDS IN DEUTERIUM OXIDE AND CARBON TETRACHLORIDE

Compd	Solvent (pD)	Concn, M[b]	Chemical shifts, ppm[a] $-C_6H_5$	$-CH_2C_6H_5$	$-CH_2-C(=O)$	$-CH_2-$	CH_3
Propionic acid	D_2O (1.6)	1.4×10^{-1}			2.40		1.08
	D_2O (9.8)	6×10^{-2}			2.17		1.04
	CCl_4	0			2.34[c]		1.14[c]
4-Phenylbutyric acid	D_2O (9.0)	1×10^{-1}	7.34	2.65	2.20	1.93	
	D_2O (9.4)	6×10^{-2}	7.33	2.64	2.21	1.91	
	D_2O (9.8)	2×10^{-2}	7.34				
	CCl_4	0	7.15[c]	2.67[c]	2.32[c]	2.07[c]	
Octanoic acid	D_2O (8.9)	1×10^{-1}			2.16	~1.3	0.85
	D_2O (9.1)	6×10^{-2}			2.17	~1.3	0.85
	D_2O (9.5)	2×10^{-2}			2.15	~1.3	0.84
	CCl_4	0			2.32	~1.3	0.89
ω-Phenyloctanoic acid	D_2O (8.5)	1×10^{-1}	7.05	2.43	2.15	~1.3	
	D_2O (8.6)	6×10^{-2}	7.11	2.47	2.14	~1.3	
	D_2O (9.2)	2×10^{-2}	7.31	2.64	2.12	~1.3	
	CCl_4	0	7.11[c]	2.57[c]	2.30[c]	~1.4	

[a] Based on first-order analysis and estimated to be reproducible to ± 0.02 ppm. TMS and DSS were used as internal references in CCl_4 and D_2O, respectively. [b] Zero values correspond to infinite dilution. [c] Value obtained from a plot of concentration *vs.* chemical shift extrapolated to infinite dilution.

vicinity of the ring.[17,18] If intramolecular hydrophobic (or hydrotactoid) forces are strong enough, the ω-phenylalkyl moiety of a sodium ω-phenylalkylcarboxylate may assume a conformation in which the distance between the phenyl ring and the carbon atom α to the carboxylate group is less than the theoretical distance of maximum extension.[8] Two nmr methods have been employed to examine this possibility. The first approach (method 1) involves the determination of the nuclear magnetic resonance spectra of the ω-phenylalkylcarboxylic acids (specifically 4-phenylbutyric acid and ω-phenyloctanoic acid) at infinite dilution in CCl_4 where, since hydrophobic bonding is not possible, the hydrocarbon moiety will assume a more or less extended conformation.[8] The spectra are then compared, with respect to the chemical shifts of the methylene protons (especially the protons α to the carboxyl group), with the spectra of the sodium salts of the acids in D_2O. A correction to the proton chemical shift resulting from salt formation is estimated by noting the effect of converting propionic acid to its sodium salt on the α-proton resonances. Now if the α-methylene protons are indeed located in the near vicinity (6–8 Å or less) of either the shielding or deshielding regions of the phenyl ring, then the observed chemical-shift difference $\Delta\delta_{CCl_4-D_2O}$ for the phenyl-substituted acid and its sodium salt should be significantly different (≥ 0.1 ppm) from $\Delta\delta'_{CCl_4-D_2O}$, the shift difference for propionic acid and its sodium salt. If the protons lie in or very near the region where the diamagnetic and paramagnetic effects exactly cancel one another or if the protons are farther than 6–8 Å from the phenyl ring, then one would expect a shift difference ($\Delta\delta_{CCl_4-D_2O} - \Delta\delta'_{CCl_4-D_2O}$) of 0.0 ± 0.1 ppm. Method 2 is based on the direct comparison of the phenylalkylcarboxylic acid salts in D_2O with sodium propionate. Assuming that sodium propionate is a good choice for a reference compound, this method should yield shift data similar to method 1 data.

(17) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(18) J. W. Emsley, J. Feeney and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 595.

Results

The chemical-shift data for the various acids and their sodium salts in CCl_4 and D_2O are summarized in Table I. Propionic acid, which has a relatively simple nmr spectrum, was chosen as the model compound for determining the effect of solvent (CCl_4 and D_2O) and pD on the chemical shift of the protons α to the carboxyl group. In addition, propionic acid should exhibit (in the nmr at room temperature) no conformational changes as the solvent is varied. Klevens has determined the critical micelle concentration of a number of potassium salts of aliphatic carboxylic acids.[19] At 25° the cmc of the C_6 carboxylate was 1.55 M, 0.098 M for the C_{10} salt, and 0.0255 M for the C_{12} salt. These data suggest that the concentrations listed in Table I for the sodium salts of propionic acid and 4-phenylbutyric and octanoic acid in D_2O are below the critical micelle concentrations of the respective salts. Further evidence bearing on this point is provided by the chemical shift of the aromatic protons of the phenyl-substituted salts. The chemical shift of the phenyl protons of ω-phenyloctanoate in D_2O at a concentration of 2×10^{-2} M (pD 9.2) was 7.31 ppm (Table I), which shifted 0.20 ppm upfield (to 7.11 ppm) when the salt concentration was increased to 6×10^{-2} M (pD 8.6). Similar phenyl proton shifts (with respect to direction and magnitude) have been observed for a series of ω-phenylalkyltrimethylammonium bromides when the cmc was reached upon increasing the bromide concentration.[20] The chemical shift of the phenyl protons of 4-phenylbutyrate in D_2O showed virtually no change over the concentration range of 1×10^{-1} to 2×10^{-2} M (Table I). However, the chemical shift of the phenyl protons of ω-phenyloctanoate at the lowest concentration (2×10^{-2} M, D_2O) examined and the shift of the aromatic protons of 4-phenylbutyrate at all concentrations measured, in D_2O, yielded essentially the same values (7.31 ppm for ω-phenyloctanoate and 7.34 ppm for 4-phenylbutyrate, Table I). These results indicate

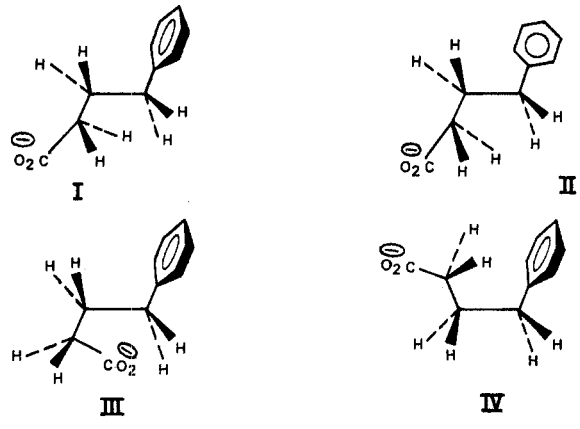
(19) H. B. Klevens, *J. Phys. Chem.*, **52**, 130 (1948).

(20) H. Inoue and T. Nakagawa, *ibid.*, **70**, 1108 (1966), and references cited therein.

that 2×10^{-2} M sodium ω-phenyloctanoate in D_2O and 2×10^{-2} to 1×10^{-1} M sodium 4-phenylbutyrate are below their respective critical micelle concentrations under the conditions studied.

Discussion

Consider first the preferred conformation of sodium 4-phenylbutyrate in D_2O. Conformers I–IV represent limiting conformations of this acid salt as determined from Corey–Pauling–Koltum (CPK) molecular models



and consideration of the calculated effect of the relative orientation of the phenyl ring, with respect to the aliphatic protons, on the chemical shifts of the α and β protons. Another possibility is that two or more conformers may be in equilibrium with one another. The shift of the α-proton resonance resulting from the magnetic anisotropy of the phenyl ring is estimated (from the data presented in Tables II and III) to be −0.04 to −0.06 ppm. For conformer I, the Johnson–Bovey tables[18] predict that the phenyl ring should cause a shift of the α protons of − 0.144 ppm; for II, a shift of −0.153 ppm; for III, a shift of −0.035 ppm; and finally, for IV, a shift of 1.46 ppm is calculated. The average error between the shifts observed by Johnson and Bovey[17] for various phenyl derivatives and the calculated values was 0.07 ppm (the actual error values ranged from 0.01 to 0.15 ppm). Hence, the observed shift for the α protons of sodium 4-phenylbutyrate (−0.04 to −0.06 ppm) rules out only conformer IV as a significant contributor to the preferred conformation of sodium 4-phenylbutyrate. Since conformer IV allows the maximum apolar interaction possible (as determined from CPK models), it is concluded that hydrophobic (or hydrotactoid) forces are not the predominant forces determining the conformation of sodium 4-phenylbutyrate.

TABLE II

α-PROTON SHIFTS RELATIVE TO SODIUM PROPIONATE[a]

Compd	Concn, M	pD	Shift,[b] ppm
4-Phenylbutyric acid	6×10^{-2}	9.8	−0.04
Octanoic acid	2×10^{-2}	9.5	+0.02
ω-Phenyloctanoic acid	2×10^{-2}	9.2	+0.05

[a] Concentration 6×10^{-2} M, pD 9.8, DSS internal reference. [b] Positive sign indicates upfield shifts relative to the α protons of sodium propionate.

TABLE III

α-PROTON SHIFTS ($\Delta\delta_{CCl_4-D_2O}$) OF THE ACIDS

Compd	Solvent (pD)	Concn, M[a]	$\Delta\delta_{CCl_4-D_2O}$[b]
Propionic acid	CCl_4	0	
	D_2O (9.8)	6×10^{-2}	+0.17
4-Phenylbutyric acid	CCl_4	0	
	D_2O (9.4)	6×10^{-2}	+0.11
Octanoic acid	CCl_4	0	
	D_2O (9.5)	2×10^{-2}	+0.17
ω-Phenyloctanoic acid	CCl_4	0	
	D_2O (9.2)	2×10^{-2}	+0.18

[a] Zero values correspond to infinite dilution. [b] In parts per million; individual chemical shifts were taken from Table I. Positive sign indicates an upfield shift.

The observed chemical shift of the β protons of 4-phenylbutyric acid in CCl_4 (at infinite dilution) minus the chemical shift of the salt in D_2O (6×10^{-2} M) yields a shift difference of 0.16 ppm (see Table I). From the data listed for propionic acid in Table I the effect of salt formation on the β-proton resonances is estimated to be 0.10 ppm. Therefore, the observed shift due to the phenyl's influence on the β protons is approximately 0.06 ppm. The predicted shift (from the Johnson–Bovey tables) due to the phenyl's influence of the β protons in conformer I (and III) is estimated to be 0.065 ppm; the predicted shift of the β protons in conformer II is −0.380 ppm. Therefore, the β-proton data exclude conformer II. Clearly, the shift data presented so far exclude conformers II and IV as significant contributers to the average conformation of sodium 4-phenylbutyrate. These data do not exclude I, III, or I $\rightleftharpoons$ III. However, CPK models indicate that there is considerable steric interaction between the carboxylate carbon atom and the benzylic protons in conformer III. The models also suggest the possibility of steric inhibition to solvation of the carboxyate moiety for this conformer. It is therefore concluded that conformer I best represents the preferred conformation of sodium 4-phenylbutyrate.

The shifts of the α protons of ω-phenyloctanoic acid determined by methods 1 and 2 are 0.01 and 0.05 ppm, respectively. If octanoic acid is used as the model compound in method 2, the shift obtained is +0.03 ppm. Figure 1 shows the ±0.10 ppm limits which define that region of space the α protons may occupy, with respect to the center of the phenyl ring, and still yield shifts consistent with the observed data. Unfortunately, the extended form of the acid salt and a conformation which allows the α protons to approach to within 2.9 Å of the phenyl ring (determined from Corey–Pauling–Koltun models) are both consistent with the observed shifts and consequently, within the limits previously delineated, no concrete conclusions regarding the major conformers of this acid salt can be supplied.

The use of sodium 4,4-dimethyl 4-silapentane-1-sulfonate (DSS) as an internal standard in aqueous solutions containing aromatic solutes and/or micelles has been criticized.[20,21] However, 4-phenylbutyric acid in D_2O showed virtually no change in the phenyl proton chemical shift over the concentration range of 1×10^{-1} M to 2×10^{-2} M (Table I). The studies[21] which demonstrated that the DSS signal could be shifted in aqueous solution by the presence of aromatic solutes involved an aromatic solute concentration of 0.8 M and a DSS concentration of 1.5–3.0 wt %. The salt concen-

(21) E. S. Hand and T. Cohen, *J. Amer. Chem. Soc.*, **87**, 133 (1965).

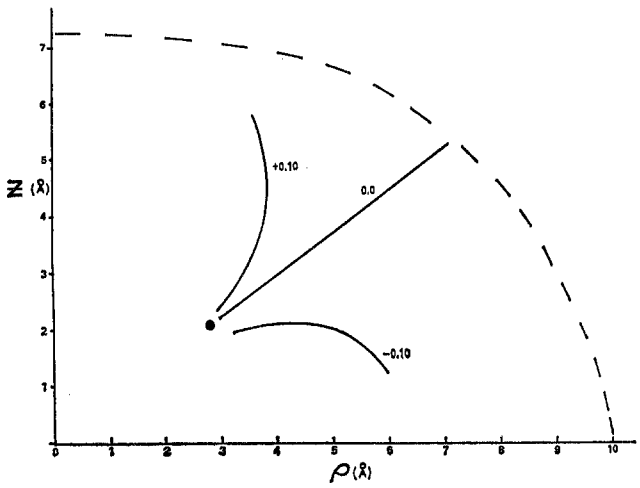


Figure 1.—The +0.10-, 0.00-, and −0.10-ppm isoshielding lines about a phenyl ring. Z is the axis perpendicular to the phenyl nuclear plane and passing through the center of the ring, and ρ is the axis perpendicular to Z and passing through the center of the phenyl ring. The dotted line represents the maximum possible distance of the α protons of sodium ω-phenyloctanoate from the center of the phenyl ring. The origin is at the center of the phenyl ring. The point on the graph represents the distance of closest approach of the α protons to the phenyl ring.

trations listed in Table I are considerably lower than 0.8 *M;* the DSS internal reference constituted no more than 1% by weight of the D_2O solutions used (Table I). The downfield shift of the phenyl protons of ω-phenyloctanoic acid sodium salt (Table I) upon dilution is opposite to that expected if DSS complexed with the carboxylate salt. All of these considerations suggest that the chemical shifts listed in Table I are real and do not reflect a perturbation of the DSS resonance position.

Experimental Section

Proton magnetic resonance spectra were obtained on a Jeolco C-60H nmr spectrometer operating at 60 MHz with an ambient probe temperature of approximately 29°. Tetramethylsilane (TMS) was used as an internal reference in carbon tetrachloride solutions and sodium 4,4-dimethyl 4-silapentane-1-sulfonate (DSS) was used as an internal reference in D_2O solutions. Chemical shifts were found to be reproducible to within ±0.02 ppm. Chemical shifts were estimated by first-order analyses and are believed to be accurate to <0.1 ppm. The D_2O solutions were 0.2 *M* in NaCl. The listed pD values are the readings obtained directly from the pH meter.

Materials.—Solvents and internal reference compounds were obtained from Nuclear Magnetic Resonance Specialties, Inc. Propionic acid (Baker Analyzed reagent), 4-phenylbutyric acid (Eastman), and ω-phenyloctanoic acid (Pfaltz and Bauer) were used without further purification. Octanoic acid (Matheson Coleman and Bell) was distilled under reduced pressure, bp 83–85° (0.25 mm).

Registry No.—4-Phenylbutyric acid sodium salt, 1716-12-7; sodium ω-phenyloctanoate, 24867-14-9.

Acknowledgment.—We gratefully acknowledge support by grants from the Research Corporation and the Miami University Research Committee.

An Efficient Synthesis of Selected Indenones

M. BRAWNER FLOYD AND GEORGE R. ALLEN, JR.

Process and Preparations Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

Received September 18, 1969

An efficient, apparently general synthesis of 2-alkylindenones is described. This procedure is dependent on the Friedel–Crafts acylation of α-alkyl-β-aryl-β-chloropropionyl chlorides (**5**) to furnish 2-alkyl-3-chloroindanones (**6**), dehydrochlorination of which affords the 2-alkylindenones (**7**). The method is also applicable to the preparation of indenone **7a**. The requisite acid chlorides **5** are prepared by the action of thionyl chloride on β-arylhydracrylic acids **4**, the esters of which are available conveniently by application of the Reformatsky procedure to the appropriate benzaldehyde **1** and α-bromo ester **2**. Selected examples of the reaction of the indenone system with electrophilic and nucleophilic reagents are presented. Isomerization of the alkylindenone system into the 2-alkylideneindanone system was noted to a small extent under certain conditions.

In the course of another investigation, we required a procedure for the synthesis of 2-alkylindenones. Several methods for their preparation have been reported, but none appeared to be uniformly general. Among the potential procedures, dehydrobromination of 2-alkyl-2-bromoindanones, available by bromination of the corresponding 2-alkylindanones, has been studied most extensively. Despite the apparent general nature of this sequence for the preparation of 2-methylindenones,[1] its applicability to the synthesis of higher homologs is questionable. Thus, dehydrobromination of 2-ethyl-2-bromoindanone affords a mixture of 2-ethylindenone and 2-ethylideneindanone, the latter predominating.[2] Yet, treatment of 2-bromo-2-butylindanone with dimethylamine is reported to give 2-butyl-3-dimethylaminoindanone, apparently *via* Michael addition of the amine onto the intermediate 2-butylindenone.[1a] Cyclization of *cis*-cinnamic acids is a second procedure that has been studied.[3] This method appears limited in that the *trans* isomer results from most syntheses, and conversion into the required *cis* isomer is not uniformly successful.[2,4]

Two additional methods for the preparation of 2-alkylindenones have received limited attention. Vilsmeier–Haack formylation of an acetophenone is reported to give a 3-amino-1-chloroindene, which was converted into a 2-methylindenone in two stages.[5] The general utility of this procedure has not been ascer-

(1) (a) S. Allisson, J. Büchi, and W. Michaelis, *Helv. Chim. Acta*, **49**, 891 (1966); (b) J. G. Topliss and L. M. Konzelman, *J. Pharm. Sci.*, **57**, 737 (1968).

(2) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1452 (1960).

(3) (a) R. Stoermer and G. Voht, *Justus Liebigs Ann. Chem.*, **409**, 36 (1915); (b) S. Goszczynski and E. Salwinska, *Zesz. Nauk. Politech. Slask., Chem.*, **24**, 235 (1964); *Chem. Abstr.*, **63**, 11415e (1965).

(4) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968).

(5) K. Bodendorf and R. Mayer, *Chem. Ber.*, **98**, 3565 (1965).