α-Iminoperfluoronitriles

WILLIAM J. MIDDLETON AND CARL G. KRESPAN

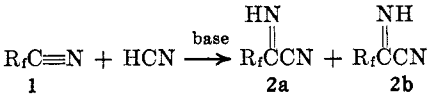
Contribution No. 1447 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received April 15, 1968

Hydrogen cyanide adds to perfluoronitriles in the presence of a basic catalyst to give α-iminoperfluoronitriles. These iminonitriles react with fluoro ketones to form oxazolines, with dienes to form Diels–Alder adducts, and with hydrogen cyanide to give imidazolines.

It has been well documented that the cyano group of an aliphatic perfluoronitrile is quite electrophilic and will add nucleophilic agents such as ammonia,[1] primary and secondary amines,[2] and mercaptans[3] with great ease to give imino compounds. Theoretically, either a *syn* or an *anti* isomer, or both, could be formed in these reactions. However, no geometrical isomers have been reported.

We have investigated the addition of hydrogen cyanide to aliphatic perfluoronitriles (1) to give α-iminoperfluoronitriles (2). The reaction occurs readily at 50° in the presence of an amine catalyst to give the adducts in yields of around 50%. The α-iminoperfluoronitriles are colorless liquids that are stable to distillation at atomsopheric pressure, but tend to polymerize upon storage for extended periods.

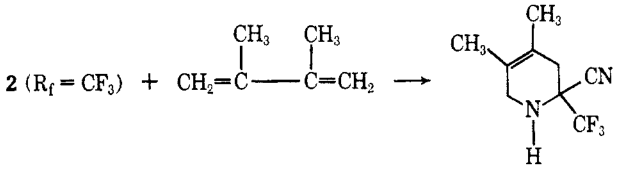


$$R_fC{\equiv}N + HCN \xrightarrow{\text{base}} R_f\overset{\overset{\large HN}{\|}}{C}CN + R_f\overset{\overset{\large NH}{\|}}{C}CN$$

1 2a 2b

Three nitriles were used in this study: trifluoroacetonitrile (1, $R_f = CF_3$), pentafluoropropionitrile (1, $R_f = C_2F_5$), and heptafluorobutyronitrile (1, $R_f = CF_3CF_2CF_2$). In each case, the α-iminoperfluoronitrile product was a mixture of two isomeric forms 2a and 2b, with one isomer predominating in the ratio of about 2:1. The composition of the isomeric mixtures could be determined easily by either proton or ^{19}F nmr spectra. The proton spectra showed two broad peaks for the two different imino hydrogens at extremely low field. This low-field position is consistent with the chemical shift observed for the imino hydrogen of hexafluoroacetone imine.[4] In the case of 2 ($R_f = CF_3$), the major isomer absorbed at τ −2.92, and the minor isomer absorbed at −2.46. The ^{19}F nmr spectrum of 2 ($R_f = CF_3$) indicated spin–spin coupling between the ^1H and the ^{19}F nuclei in both isomers. The stronger coupling ($J = 2.0$ Hz) was observed for the major isomer whose ^{19}F absorption was at the lower field position, and the weaker coupling ($J = 1.1$ Hz) was observed for the isomer at the higher field position. Since stronger coupling would be predicted for the isomer in which the CF_3 group and the H atom were *syn* to each other,[5] we have assigned this structure (2a) to the more abundant isomer. Attempts to separate the isomers by gas chromatography were unsuccessful.

The α-iminoperfluoronitriles were found to be reactive intermediates useful in preparing new heterocyclic compounds containing perfluoroalkyl groups. For example, they are reactive dienophiles and can be used in the Diels–Alder reaction to prepare tetrahydropyridines such as 3. In the presence of a basic



3

catalyst, the α-iminonitriles also form cyclic adducts with fluoro ketones, as illustrated by the reaction of 2 ($R_f = CF_3$) with hexafluoroacetone. This reaction is believed to occur as illustrated by Scheme I. The basic catalyst generates the anion 4, which adds across the carbonyl group of hexafluoroacetone to give anion 5. This anion then cyclizes to give 6, which in turn adds to the excess hexafluoroacetone present to give the anion 7. Protonation of 7 then gives 8, which is the 1:2 adduct actually isolated. This adduct is thermally unstable and can be pyrolyzed back to the 1:1 adduct 9 by distillation at atmospheric pressure. Related 1:1 adducts were also formed from the reaction of 2 ($R_f = CF_3$) with 1,3-dichlorotetrafluoroacetone and from 2 ($R_f = C_2F_5$) with hexafluoroacetone. In these cases, the 1:2 adducts were presumably formed but were not isolated or characterized since they decomposed to the 1:1 adducts upon distillation. No evidence was found that any of these iminooxazolines exist in two isomeric forms.

α-Iminotrifluoropropionitrile (2, $R_f = CF_3$) also reacts with hydrogen cyanide to give an imidazoline (10) in low yield. This same imidazoline was also isolated in low yield from the tarry residue of the reaction of trifluoroacetonitrile with hydrogen cyanide to give 2 ($R = CF_3$) and was formed when triethylamine was added to 2 ($R = CF_3$). We believe that Scheme II illustrates the course of this reaction. In the

---

(1) D. Husted, U. S. Patent 2,676,985 (1954).

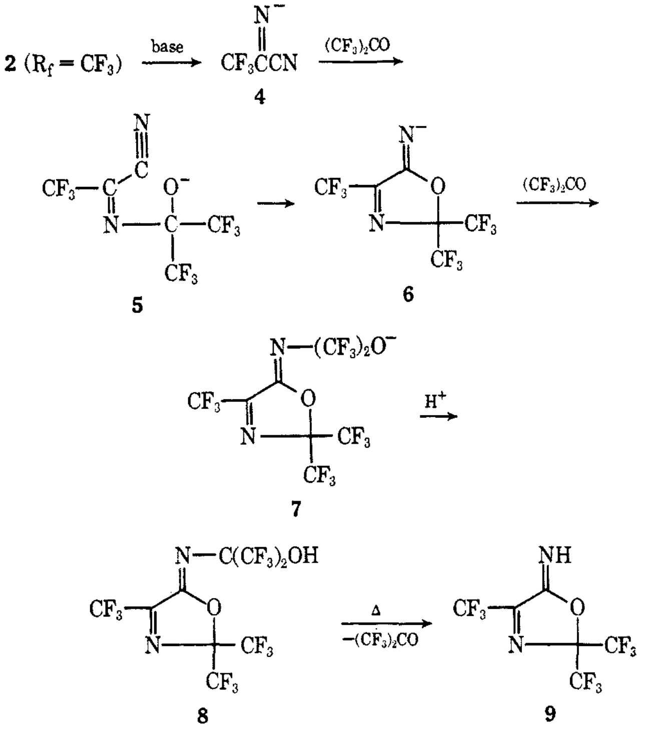
(2) W. L. Reilly and H. C. Brown, *J. Amer. Chem. Soc.*, **78**, 6032 (1956).

(3) H. C. Brown and R. Pater, *J. Org. Chem.*, **27**, 2858 (1962).

(4) W. J. Middleton and C. G. Krespan, *ibid.*, **30**, 1398 (1965).

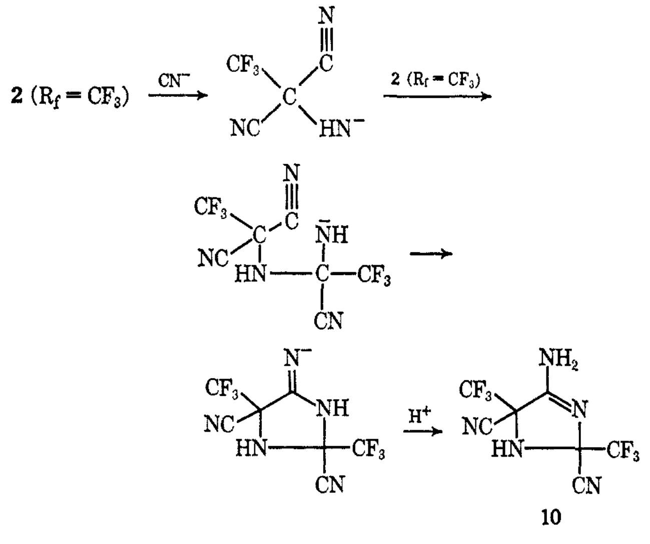
(5) D. J. Burton, R. L. Johnson, and R. T. Bogan [*Can. J. Chem.*, **44**, 635 (1966)] found that, for the two isomers of $CF_3CCl{=}CHCF_3$, $J_{H,CF_3,cis} = 1.2$ Hz while $J_{H,CF_3,trans}$ was negligible. For several olefins having CF_3 groups *cis* and *trans* to H, the ranges of coupling constants found are $J_{H,CF_3,cis} =$ 1.2–3 Hz and $J_{H,CF_3,trans} =$ 0–1 Hz (private communication from D. J. Burton). Extension of these results with olefins to coupling of substituents on the imine function seems reasonable, since consistency has already been observed in the order of coupling constants for *cis* and *trans* F attached to C=C, C=N, and N=N bonds as shown by the following references. J. W. Emsley, J. Feeney, and L. H. Sutcliffe ("High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, pp 908, 909) gave examples to show that the coupling of *trans* vinylic F atoms is much stronger than that of *cis* F atoms, $J_{FF,trans} =$ 112–124 Hz whereas $J_{FF,cis} =$ 30–60 Hz. For the N-fluoroiminofluoride case, A. L. Logothetis and G. N. Sausen [*J. Org. Chem.*, **31**, 3689 (1966)] reported the isomers of NCC(=NF)F to have $J_{FF,trans} = 265$ Hz and $J_{FF,cis} = 52$ Hz, assignments having been made on the basis of correlation with the olefinic systems. J. H. Noggle, J. D. Baldeschwieler, and C. B. Colburn [*J. Chem. Phys.*, **37**, 182 (1962)] found for the known *trans*- and *cis*-N_2F_2 that $J_{FF,trans} = 322$ Hz and $J_{FF,cis} = 99$ Hz.

SCHEME I



reaction of triethylamine with **2**, hydrogen cyanide is apparently formed from the decomposition of the hydrogen cyanide adduct to regenerate CF_3CN, which was isolated as an off-gas from the reaction. The low yield of **10** may be due to its instability in the presence of base. The loss of HCN would give an unstable intermediate that could polymerize, accounting for the tars that are observed.

SCHEME II



Experimental Section

α-Iminotrifluoropropionitrile (2, R_f = CF_3).—A mixture of 40 ml (*ca.* 1 mol) of liquid hydrogen cyanide, 95 g (1 mol) of trifluoroacetonitrile, and 2 ml of morpholine was heated with shaking in a 240-ml, corrosion-resistant bomb at 50° for 8 hr. The bomb was cooled and vented, and the contents were distilled to give 64.9 g (53%) of α-iminotrifluoropropionitrile as a colorless liquid: bp 71.5–72°; $n^{25}D$ 1.3301. α-Iminotrifluoropropionitrile was also prepared in somewhat lower yield by a similar reaction using triethylamine as catalyst in place of morpholine. The infrared spectrum shows bands at 3.07 (NH), 4.46 (C≡N), and 6.08 μ (C=N). The ^{1}H nmr spectrum shows two broad signals at τ −2.92 (relative area 2) and −2.46 (relative area 1) indicating both *syn* and *anti* isomers. The ^{19}F nmr spectrum shows a doublet (J_{FH} = 2.0 Hz) at +73.07 ppm (relative area 2) and a doublet (J_{FH} = 1.1 Hz) at +74.61 ppm (relative area 1) from trichlorofluoromethane used as an internal reference.

Anal. Calcd for $C_3HF_3N_2$: C, 29.52; H, 0.83; F, 46.70; N, 22.96. Found: C, 29.89; H, 1.19; F, 47.32; N, 22.93.

α-Iminopentafluorobutyronitrile (2, R_f = C_2H_5).—A mixture of 29.0 g (0.2 mol) of pentafluoropropionitrile, 10 ml (*ca.* 0.2 mol) of liquid hydrogen cyanide, and 0.5 ml of morpholine was heated in a 145-ml bomb at 50° for 8 hr. The bomb was cooled and vented, and the contents were distilled to give 18.3 g (53%) of α-iminopentafluorobutyronitrile as a colorless liquid: bp 83–83.5°; $n^{25}D$ 1.3180. The infrared spectrum showed bands at 3.07 (NH), 4.46 (C≡N) and 6.08 μ (C=N). The ^{1}H nmr spectrum showed broad singlets at τ −3.08 and −2.74 in a ratio of about 2:1 indicating the presence of two isomers. The ^{19}F nmr spectrum also showed the presence of two isomers. The major isomer had absorptions at +82.41 and +118.6 ppm for CF_3 and CF_2, respectively. The minor isomer had absorptions at +82.71 and +121.5 ppm for CF_3 and CF_2, respectively, from CCl_3F.

Anal. Calcd for $C_4HF_5N_2$: C, 27.92; H, 0.59; F, 55.21; N, 16.28. Found: C, 28.13; H, 1.01; F, 55.09; N, 16.25.

α-Iminoheptafluorovaleronitrile (2, R_f = $CF_3CF_2CF_2$–).—A mixture of 39 g (0.2 mol) of heptafluorobutyronitrile, 10 ml (*ca.* 0.2 mol) of liquid hydrogen cyanide, and 0.5 ml of morpholine was heated in a 145-ml bomb at 50° for 8 hr. The bomb was cooled and vented, and the contents were distilled to give 15.8 g (36%) of α-iminoheptafluorovaleronitrile as a colorless liquid: bp 101–101.5°; $n^{25}D$ 1.3152. The infrared spectrum showed bands at 3.07 (NH), 4.46 (C≡N), and 6.07 μ (C=N). The ^{1}H nmr spectrum showed two broad signals at τ −31.6 and −2.74 (relative area 2:1). The ^{19}F nmr spectrum showed the presence of two isomers in approximately a 2:1 ratio. The major isomer had a triplet (J = 9.5 Hz) at +80.66 for CF_3, a singlet at +125.8 for one CF_2, and a quartet (J = 9.5 Hz) at +120.7 ppm for the other CF_2. The minor isomer had a triplet (J = 9.5 Hz) at +80.66 ppm, a singlet at +125.1 ppm, and a broad signal at +122.2 ppm for CF_3 and the two CF_2 groups, respectively.

Anal. Calcd for $C_5HF_7N_2$: C, 27.04; H, 0.46; F, 59.89; N, 12.62. Found: C, 27.47; H, 0.83; F, 59.30; N, 12.69.

1,2,3,6-Tetrahydro-4,5-dimethyl-2-(trifluoromethyl)-2-pyridinecarbonitrile (3).—A mixture of 3.5 g (0.043 mol) of 2,3-dimethyl-1,3-butadiene and 3.5 g (0.029 mol) of α-iminotrifluoropropionitrile was heated at 78° (reflux tempeature) for 1 hr and then distilled. There was obtained 4.65 g (80%) of **3** as a colorless liquid: bp 62–63° (1.25 mm), $n^{25}D$ 1.4316. The ^{19}F nmr spectrum showed a singlet at +80.3 ppm from CCl_3F, and the infrared spectrum showed a weak band at 4.49 (–CN) and a band at 3.01 μ (NH).

Anal. Calcd for $C_9H_{11}F_3N_2$: C, 52.93; H, 5.43; F, 27.92; N, 13.72. Found: C, 53.11; H, 5.46; F, 27.96; N, 13.84.

5-[2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)ethylimino]-2,-2,4-tris(trifluoromethyl)-3-oxazoline (8).—A 14-g sample (0.115 mol) of α-iminotrifluoropropionitrile was added dropwise over 10 min to 25 ml of hexafluoroacetone containing 6 drops of pyridine; the mixture was cooled to −78°. The mixture was warmed to room temperature and then distilled at reduced pressure to give 37 g (71%) of the oxazoline **8** as a colorless liquid: bp 40° (12 mm); $n^{25}D$ 1.3154. The ^{19}F nmr spectrum showed singlets at +69.3 (3 F), +76.9 (6 F), and +80.0 ppm (6 F) from CCl_3F. The ^{1}H spectrum showed a singlet at τ 5.88. The infrared spectrum showed a band at 5.70 μ.

Anal. Calcd for $C_9HF_{15}N_2O_2$: C, 23.80; H, 0.22; F, 62.76; N, 6.17. Found: C, 24.09; H, 0.60; F, 62.66; N, 6.50.

Pyrolysis of 8 to Form 9.—A 22.7-g sample of **8** was distilled at atmospheric pressure through a 24-in. packed column. There was obtained 15.1 g (92%) of 5-imino-2,2,4-tris(trifluoromethyl)-3-oxazoline as a colorless liquid: bp 90–91°; $n^{25}D$ 1.3212; $\lambda_{max}^{cyclohexane}$ 227 mμ (ε 4400). The ^{19}F nmr spectrum showed singlets at +69.4 (3 F) and +77.0 (6 F) ppm from CCl_3F. The ^{1}H nmr spectrum showed a broad singlet at τ 0.83.

Anal. Calcd for $C_6HF_9N_2O$: C, 25.01; H, 0.35; F, 59.35; N, 9.73. Found: C, 25.29; H, 0.35; F, 59.32; N, 9.63.

5-Imino-4-pentafluoroethyl-2,2-bis(trifluoromethyl)-3-oxazoline.—α-Iminopentafluorobutyronitrile (4.3 g, 0.025 mol) was added dropwise to 10 ml of stirred hexafluoroacetone containing

3 drops of pyridine; the mixture was cooled to −78°. It was warmed to 25° and then distilled at atmospheric pressure to give 2.8 g of the iminooxazoline as a colorless liquid: bp 103–104°; n^{25}D 1.3168; $\lambda_{\max}^{\text{cyclohexane}}$ 230 mμ (ε 3800); infrared spectrum, 5.80 and 3.03 μ. The ^{19}F nmr spectrum showed singlets at +77.2 (6 F), +81.7 (3 F), and +118.5 ppm (2 F) from CCl_3F. The ^{1}H nmr spectrum showed a broad singlet at τ 0.84.

Anal. Calcd for $C_7HF_{11}N_2O$: C, 24.87; H, 0.30; F, 61.82; N, 8.29. Found: C, 24.94; H, 0.65; F, 61.47; N, 8.53.

5-Imino-2,2-bis(chlorodifluoromethyl)-4-trifluoromethyl-3-oxazoline.—α-Iminotrifluoropropionitrile, 6.1 g (0.05 mol), was added dropwise to 25 g (0.12 mol) of stirred 1,3-dichlorotetrafluoroacetone containing 0.05 ml of pyridine; the mixture was cooled to 0°. Distillation of this gave 9.2 g (57%) of the iminooxazoline as a colorless liquid: bp 84–85° (100 mm); n^{25}D 1.3814; $\lambda_{\max}^{\text{cyclohexane}}$ 237 mμ (ε 4740); infrared spectrum, 5.80 and 3.02 μ. The ^{19}F nmr spectrum showed an A_2B_2 pattern (four principal peaks) centered at about +61.2 ppm (4 F) and a singlet at +69.2 ppm (3 F). The ^{1}H nmr spectrum showed a broad singlet at τ 0.74.

Anal. Calcd for $C_6HCl_2F_7N_2O$: C, 22.45; H, 0.31; Cl, 22.09; F, 41.43; N, 8.73. Found: C, 22.79; H, 0.62; Cl, 22.90; F, 41.16; N, 8.80.

4-Amino-2,5-dicyano-2,5-bis(trifluoromethyl)-3-imidazoline (10).—Triethylamine (0.5 ml) was added dropwise over 2 min to a solution of 14.0 g (0.115 mol) of α-iminotrifluoropropionitrile in 15 ml of benzene. An exothermic reaction occurred, and a gas (CF_3CN) was evolved. The reaction mixture was cooled to keep the temperature between 30 and 40°. After 30 min, the solid that formed was filtered off and washed with benzene to give 2.9 g of an off-white solid. Sublimation at 130° (1.0 mm), recrystallization from benzene, and resublimation gave 1.3 g (12.5%) of 4-amino-2,5-dicyano-2,5-bis(trifluoromethyl)-3-imidazoline as a white crystalline solid, mp 187–190° (with some decomposition). The infrared spectrum showed bands at 2.94, 3.02, 3.15 and 6.20 (NH and NH_2), 4.44 (C≡N), and 5.86 μ (C=N). The ^{19}F nmr spectrum in acetone indicated the presence of two isomers. The major isomer (88%) showed a pair of quartets (*J* = 2.7 Hz) of equal area centered at +76.1 and +81.9 ppm from CCl_3F. (This is probably the isomer with the CF_3 groups on the same side of the ring.) The minor isomer (12%) showed two singlets of equal area at +76.3 and +82.0 ppm. The ^{1}H nmr spectrum in $(CD_3)_2CO$ showed broad absorptions at τ 2.38 (NH_2) and 3.13 (NH).

Anal. Calcd for $C_7H_3F_6N_5$: C, 31.01; H, 1.11; F, 42.05; N, 25.83; mol wt, 271. Found: C, 31.31; H, 1.21; F, 41.79; N, 25.83; mol wt, 272.

Registry No.—**2a** (R_f = CF_3), 17244-08-5; **2b** (R_f = CF_3), 17244-09-6; **2a** (R_f = C_2F_5), 17244-10-9; **2b** (R_f = C_2F_5), 17244-11-0; **2a** (R_f = $CF_3CF_2CF_2$–), 17244-12-1; **2b** (R = $CF_3CF_2CF_2$–), 17244-13-2; **3,** 17244-18-7; **8,** 17244-19-8; **9,** 17244-14-3; $C_7HF_{11}N_2O$, 17244-15-4; $C_6HCl_2F_7N_2O$, 17244-16-5; **10** (CF_3 groups *cis*), 17244-17-6; **10** (CF_3 groups *trans*), 17244-47-2.

Conformations of Alkylpiperidine Amides

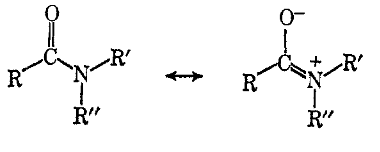
Roy A. Johnson

Biochemical Research Division, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 8, 1967

The nuclear magnetic resonance signals of the C-2 and C-6 protons of a series of alkylpiperidine benzamides coalesce at a temperature lower than that for the same protons in similar alkylpiperidine acetamides. This leads to the conclusion that the energy barrier to rotation about the C—N amide bonds is lower in the benzamides than in the acetamides as a result of increased steric interactions between the phenyl ring and the C-2 and C-6 substituents in the planar benzamide conformation. Such steric interactions between the amide and C-2 and C-6 alkyl substituents in both acetamides and benzamides are sufficient to cause conformational bias in the piperidine ring, resulting in the preference for axial configurations for the alkyl groups. These examples are a special case of the general concept of $A^{(1,3)}$ strain. The piperidine-containing molecule 3-benzoyl-3-azabicyclo[3.3.1]nonane has been found to have a chair–chair conformation. The nmr spectrum of 1-benzoyl-*trans*-decahydroquinoline shows no variation with temperature change, suggesting that the amide group in this molecule has no preferred conformation.

Our interest in the behavior of the benzamides of azacycloalkanes in biological systems raised the question of what the conformation of the amide functional group will be in these molecules at physiological temperatures. Simple amides, such as dimethylformamide, have been shown by nmr spectroscopy to have a preferred conformation at room temperature.[1] This conformation results from an energy minimum due to overlap of the π-electron orbitals of the carbonyl with the orbital of the lone pair of electrons on the nitrogen. This preferred conformation is the one in which the O=C—N bonds lie in a plane. The familiar resonance



forms also may be used to illustrate this conformation. One type of evidence that such a preferred conformation exists in dimethylformamide is the presence of two distinct signals for the $-CH_3$ protons in the nmr spectrum of this compound when taken at room temperature.[1] The different environments in which the methyl groups are found in this conformation result in the observation of the two nmr signals. When the nmr spectrum is taken at increasingly higher temperatures, the two methyl signals are seen to coalesce into a single signal. This effect is attributed to an increase in the rate of rotation around the C—N amide bond as the temperature is raised until the environments of the two methyl groups become equivalent as detectable by nmr spectroscopy. Others have enlarged upon the initial experiments,[2] have determined relative ratios of the two possible conformations when R′ ≠ R″,[3] have studied solvent effects on "*cis*" and "*trans*" forms,[3] and have examined similar effects in various types of amides.[4]

---

(1) (a) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955); (b) H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956).

(2) M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962).

(3) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).

(4) (a) R. M. Moriarty and J. M. Kliegman, *J. Org. Chem.*, **31**, 3007 (1966); (b) D. M. Lynch and W. Cole, *ibid.*, **31**, 3337 (1966); (c) T. H. Siddall, III, *ibid.*, **31**, 3719 (1966); (d) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967); (e) J. P. Chupp and J. F. Olin, *J. Org. Chem.*, **32**, 2297 (1967); (f) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967).