Reactions of Epoxy-1,1,2-trichloroethane with Nucleophiles

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Epoxy-1,1,2-trichloroethane (**1**) was synthesized by the autooxidation of trichloroethylene and was characterized. It was shown to react readily with 2-mercaptobenzimidazole (**2**), 1-methyl-2-mercaptoimidazole (**3**), *p*-nitrothiophenol (**4**), and 3,4-dichlorothiophenol (**5**) forming 2-chloro-2-(benzimidazole-2-thio)acetic acid (**6**), 2-chloro-2-(1-methylimidazole-2-thio)acetic acid (characterized as methyl ester (**8**)), 2-chloro-2-(4-nitrothiothiophenoxy)-4-nitrophenylthioacetate (**9**), and 2-chloro-2-(3,4-dichlorothiophenoxy)-3,4-dichlorophenylthioacetate (**10**), respectively. Base hydrolysis of **9** yielded 2,2-di(4-nitrothiophenoxy)acetic acid (**11**). Adduct **9** decomposed on silica gel yielding *p*-nitrophenyldisulfide (**12**).

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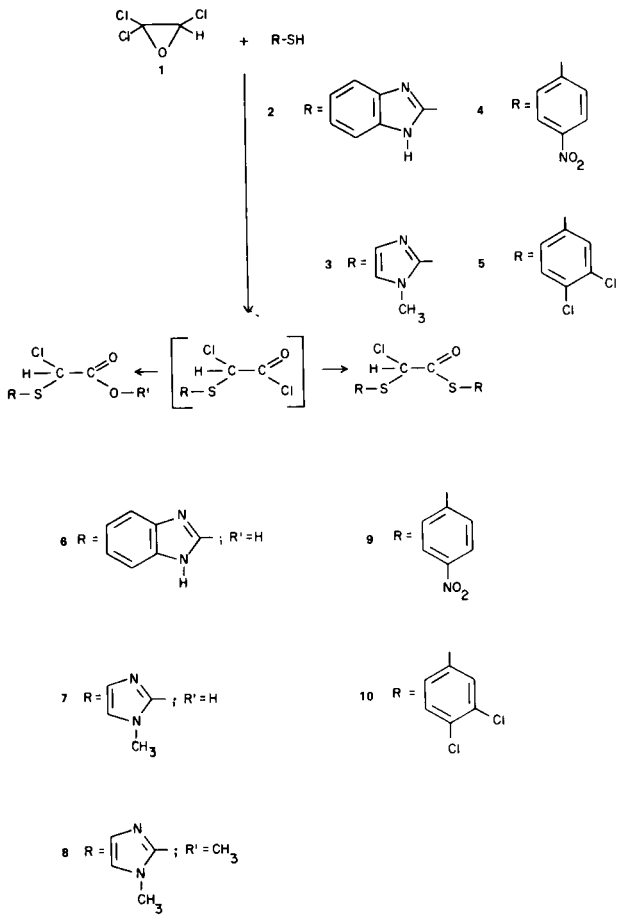
1,1,2-Trichloroethylene (TCE) has been widely used as an anesthetic, as a degreasing agent for metals and as an extractant of fats, oils and other materials in the food industry.

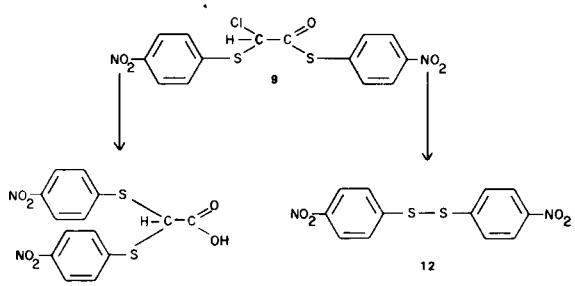
Based on its structural similarity to the known human carcinogen vinyl chloride (1a-b) and the possibility that both compounds are probably metabolized *via* an epoxide (2a-b), it was predicted that 1,1,2-trichloroethylene will be carcinogenic, particularly to the liver (2a). The epoxide intermediates were proposed as the activated carcinogenic intermediates for both compounds (2a) based on their structural similarity to known epoxide and chloro-ether carcinogens (3).

A recent report describes the finding that TCE causes liver cancer in mice (4). Preliminary evidence has been obtained suggesting that chloroethylene oxide is an intermediate in the *in vitro* microsomal oxidation of vinyl chloride (5a-b). Furthermore, biochemical studies, using rat liver microsomal preparations, have provided evidence for an epoxide intermediate in the metabolism of TCE (6).

The synthesis, characterization and reactivity of epoxy-1,1,2-trichloroethane was, therefore, of importance for the continuation of the latter studies. In particular, it was desirable to determine the reactivity of this compound toward sulfhydryl nucleophiles since the SH moiety is a likely target for its covalent reaction with protein. In addition, these compounds might ultimately be used to trap the epoxide in metabolic studies.

The epoxide of TCE, (**1**) has been reported but the compound was not properly characterized or purified (7). In the present work TCE was oxidized by reaction with oxygen initiated by either uv light or benzoyl peroxide. In the course of the oxidation TCE was converted into an approximately equimolar mixture of dichloroacetyl chloride and **1**. Methanolysis of the acid chloride was more facile than that of epoxide **1**. Therefore, the acid chloride





was converted to the higher boiling methyl ester of dichloroacetic acid by addition of a stoichiometric amount of methanol to the reaction products. Epoxy-1,1,2-trichloroethane was readily separated from the methyl ester by distillation. Elemental and mass spectral analyses confirmed the molecular formula C_2HCl_3O. Lack of either carbonyl or hydroxyl absorption bands and the presence of a characteristic epoxide absorption at 1260 cm^{-1} (8) in the infrared was consistent with structure **1**. The epoxide was rapidly hydrolyzed to dichloroacetic acid (7). At pH 7.4 it was found in the present work that this reaction follows pseudo first-order kinetics at a rate of 0.215 sec^{-1}, *ie.*, a half-life of 1.3 minutes.

The epoxide, **1**, reacted rapidly with a variety of thiols. Reaction with 2-mercaptobenzimidazole (**2**) and 1-methyl-2-mercaptoimidazole (**3**) yielded the chloroacetic acid derivatives **6** and **7**; the latter product was characterized as its methyl ester (**8**). The thiols, *p*-nitrothiophenol (**4**) and 3,4-dichlorothiophenol (**5**), each added two molecules of nucleophilic residue to epoxide **1** yielding the sulfide thioester derivatives **9** and **10**. Compounds **8** and **9** gave satisfactory elemental analyses and showed molecular ions consistent with their proposed structures. Elemental analysis of thioester **10** was not obtained; however, its molecular ion was consistent with the proposed structure. Compound **6** did not exhibit its molecular ion but lost a molecule of water; its elemental analysis was consistent with structure **6**. All these products showed a one-proton singlet in the nmr between δ 4 and 5 ppm indicative of a trisubstituted carbon. Compound **6** showed a carbonyl absorption compatible with a carboxylic acid. Compound **8** showed ir and nmr peaks as well as a mass spectral fragmentation pattern characteristic of a methyl ester. Compounds **9** and **10** both contained aromatic protons from two magnetically non-equivalent rings. Carbonyl absorptions observed for **9** and **10**, were consistent with thioesters.

When epoxide **1** was reacted with 1-methyl-2-mercaptoimidazole (**3**) in an aprotic solvent, chloroform, a new compound with an ir characteristic of an acid chloride was detected. Addition of methanol yielded the methyl ester **8**. When the reaction was carried out in methanol, **8** was isolated directly. Similarly, if **1** was reacted with less than a stoichiometric amount of **4** in methylene chloride, tlc revealed a new compound which reacted with an excess of thiol to form the thioester **9**. Thus, epoxide **1** probably reacted with the thiols **3** and **4** at the monochlorinated carbon forming intermediate acid chlorides. These, in turn, reacted with a second molecule of nucleophile forming the isolated products.

Attempts to isolate purified thioester **9** by preparative tlc resulted in the complete decomposition of this compound. The major product was a compound which showed a molecular ion peak at m/e = 308 in the mass spectrum. There was no carbonyl absorption in the ir which is consistent with *p*-nitrophenyldisulfide (**12**). Whether this reaction proceeds unimolecularly, perhaps with concomitant formation of chloroketene, or bimolecularly, has not been determined.

Alkaline hydrolysis of the *p*-nitrothiophenol diadduct **9** resulted in a rearrangement to carboxylic acid **11**. This compound contained no chlorine and mass spectral and elemental analyses were consistent with the molecular formula $C_{14}H_{10}N_2S_2O_6$. Compound **11** was soluble in aqueous base and had a carboxylic acid absorption in the ir. Nmr spectra showed that both aromatic rings were magnetically equivalent which supports the assigned structure. Similar rearrangements occur during solvolysis of β-chlorosulfides through the intermediacy of cyclic sulfonium ions (9a-b). Alternatively, hydrolysis of thioester **9** could liberate the nucleophilic thiolate ion which may displace chloride to form **11** (10).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 421 spectrophotometer and ultraviolet spectra were obtained with a Cary Model 14. Proton magnetic resonance spectra were recorded using a Varian Model A-60A spectrometer. Mass spectra of compounds **1**, **9** and **12** were obtained from the Morgan Schaffer Corp., Montreal, Canada. All others were obtained on a DuPont Model 21-492 double-focusing high resolution mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Analytical tlc was carried out on precoated silica gel G plates with fluorescent indicator. Preparative tlc was carried out on silica gel plates, 2000 microns thick without fluorescent indicator. Plates were visualized with short wavelength uv illumination. Gas chromatographic analyses were done on a Jarrel-Ash Model 28-710 gas chromatograph.

Uv Initiated Autoxidation of Trichloroethylene.

One hundred fifty ml. (1.14 moles) of TCE was heated to 60° in a photochemical immersion flask under a dry ice condenser. The liquid was irradiated through quartz with a Hanovia 250 W medium pressure mercury lamp while oxygen was bubbled through at a rate of 300 ml./minute. After 15 hours an nmr (neat) showed three singlets at δ 6.52 ppm, 6.19 ppm and 5.31 ppm in a respective ratio of 5:62:33. The peaks at 6.52 ppm and 6.19 ppm

corresponded to those of TCE and dichloroacetyl chloride, respectively.

Benzoyl Peroxide-catalyzed Autoxidation of Trichloroethylene.

Using a procedure similar to that described by McKinney, *et al.*, (7), 0.6 g. of benzoyl peroxide was dissolved in 300 ml. (2.28 moles) of TCE. The solution was heated to 70° under a dry ice condenser and oxygen was bubbled through at a rate of 300 ml./minute. After 60 hours an nmr (neat) showed the singlets corresponding to TCE, dichloroacetylchloride and **1** in a ratio of 4:53:43, respectively.

Epoxy-1,1,2-trichloroethane (**1**).

A mixture (65.4 g.) from the benzoyl peroxide-catalyzed autoxidation of TCE was found to contain 34.7 g. (0.235 mole) of dichloroacetic acid. This mixture was cooled to 0° and 10.0 ml. (0.247 mole) of methanol was added dropwise with stirring. After the vigorous gas evolution had stopped, an nmr (neat) showed five singlets at δ 6.52 ppm, 6.19 ppm, 6.09 ppm, 5.31 ppm and 3.92 ppm. The new peaks at 6.09 ppm and 3.92 ppm integrated 1:3, respectively, and were identical to those of methyldichloroacetate. The ratio of TCE:dichloroacetyl chloride:methyldichloroacetate:**1** was 3:7:49:41. This mixture was distilled at 127 mm keeping the pot temperature below 100° (11) and the fraction boiling at 48-53° was collected. This was redistilled collecting a colorless liquid, b.p. 48-49° at 135 mm; ir (salt plate): 3055, 1260 (epoxide (8)), 960, 861 and 798 cm^{-1}; nmr (neat): δ 5.31 ppm (s); mass spectrum: m/e, (relative intensity): 146 (10, Cl_3), 111 (17), 82 (100), 63 (28), 47 (49).

Anal. Calcd. for C_2HCl_3O: C, 16.30; H, 0.68; Cl, 72.15. Found: C, 16.31; H, 0.75; Cl, 72.14.

Hydrolysis of **1**.

A solution of 0.2 ml. of acetone in 1.5 ml. of 0.5 *M* sodium phosphate buffered at *p*H 7.4 was warmed to 37° and 20 μl. of **1** and 10 μl. of chlorobenzene were added. After shaking for various time intervals, 0.3 ml. of ether was added and the phases vigorously mixed for 45 seconds. An aliquot of the ether layer was immediately analyzed by glc (6′ x ¼″, 10% Apiezon on Chromosorb W, 88°) and the concentration of **1** after hydrolysis calculated from the ratio of its peak area to that of the chlorobenzene standard. The rate of hydrolysis of **1** was obtained from these data.

2-Chloro-2-(1-methylimidazole-2-thio)methyl Acetate (**8**).

To a solution of 400 mg. (3.5 mmoles) of 1-methyl-2-mercaptoimidazole in 10 ml. of methanol, 0.40 ml. (4.5 mmoles) of compound **1** in 1.5 ml. of methylene chloride was added dropwise. After stirring at room temperature for 20 minutes, the solvent was removed under vacuum. The colorless foamy residue was triturated with ether and yielded a microcrystalline solid, the melting point of which was difficult to determine due to its hygroscopic nature. The product was water-soluble and gave a precipitate with aqueous silver nitrate indicating a hydrochloride salt; ir (potassium bromide): 1740, 1298 and 1271 cm^{-1}; nmr (deuteriochloroform): δ 7.20 (d, J = 6.0, 1), 7.18 (d, J = 6.0, 1), 5.80 (s, 1), 3.80 (s, 3), 3.74 (s, 3); mass spectrum: m/e (relative intensity) 220 (20), 185 (100), 161 (21), 125 (20), 113 (49), 83 (65), 72 (35), 59 (81).

Anal. Calcd. for $C_7H_9N_2SClO_2 \cdot HCl$: C, 32.70; H, 3.92; N, 10.89; S, 12.47; Cl, 27.57. Found: C, 32.68; H, 3.97; N, 10.92; S, 12.40; Cl, 27.64.

Reaction of **1** with 1-Methyl-2-mercaptoimidazole in Chloroform.

Ten μl. (0.11 mmole) **1** was added to a solution of 14 mg. (0.12 mmole) of 1-methyl-2-mercaptoimidazole dissolved in 0.4 ml. of chloroform. A precipitate immediately formed and an ir was quickly taken of the filtrate; ir in chloroform: 1803 cm^{-1} (acid chloride C=O). Two drops of methanol were added to this solution; ir in chloroform: 1740 cm^{-1}. Tlc (silica gel, benzene) showed the presence of a product with an R_f identical to methyl ester **8**.

Reaction of **1** with 1-Mercapto-2-methylimidazole in Water and Methylation of the Product.

Fifty μl. (0.56 mmole) of **1** dissolved in 1 ml. of acetone was added dropwise to a stirred solution of 50 mg. (0.44 mmole) of 1-mercapto-2-methylimidazole in 5 ml. of 0.1 *M* Tris buffered at *p*H 8.4. The resulting acidic solution was made basic with solid sodium carbonate and extracted with three 7 ml. portions of methylene chloride. The aqueous layer was acidified with 12 *N* hydrochloric acid and the water removed under vacuum at 20-22°. The residue was stirred in methanol, filtered and the filtrate evaporated leaving an oily residue. On tlc (silica gel, 30% methanol:chloroform) this product had an R_f of 0.2; ir (potassium bromide): 1710 cm^{-1} (carboxylic acid C=O). The residue was redissolved in 7 ml. of methanol and 5 ml. of a solution of diazomethane in ether was added and stirred at room temperature for 40 minutes. The solvent was removed, 10 ml. of a saturated sodium bicarbonate solution was added and the product was extracted with four 10 ml. portions of chloroform. Evaporation of the solvent left 23 mg. (24%) of an oil; its tlc properties and ir were identical to those of **8**.

2-Chloro-2-(benzimidazole-2-thio)acetic Acid (**6**).

Fifty μl. (0.56 mmole) of **1** in 1 ml. of methylene chloride was added dropwise to a stirred solution of 218 mg. (1.35 mmoles) of 2-mercaptobenzimidazole in 5 ml. of acetone. An exothermic reaction was followed by formation of a white precipitate. After stirring at room temperature for one hour the precipitate was filtered and washed with methylene chloride yielding 100 mg. (57%) of a yellow water-soluble solid which gave a precipitate with aqueous silver nitrate. The solid was triturated with three portions of ether, m.p. 134-141°; ir (potassium bromide): 1715 cm^{-1} (carboxylic acid C=O); nmr (deuteriochloroform): δ 7.89 (m, 2), 7.56 (m, 2), 4.75 (s, 1); mass spectrum: m/e (relative intensity): no molecular ion, 224 (50), 189 (18), 161 (25), 144 (24), 36 (100).

Anal. Calcd. for $C_9H_7N_2SClO_2 \cdot HCl$: C, 38.72; H, 2.89; N, 10.04; S, 11.49; Cl, 25.40. Found: C, 38.68; H, 3.36; N, 10.12; S, 11.56; Cl, 25.34.

2-Chloro-2-(4-Nitrothiophenoxy)-4-nitrophenylthioacetate (**9**).

Two hundred μl. (2.24 mmoles) **1** dissolved in 2 ml. of acetone was added dropwise to a solution of 296 mg. (1.53 mmoles) of *p*-nitrothiophenol and 1.33 mg. (1.58 mmoles) of sodium bicarbonate. A yellow suspension immediately formed. The mixture was stirred for 10 minutes at room temperature and extracted with five 10 ml. portions of methylene chloride. Evaporaton of the solvent yielded 347 mg. (88%) of a pale yellow oil which was recrystallized from 15% chloroform:ether, m.p. 99-100°; ir (potassium bromide): 1703 cm^{-1} (thio ester C=O); nmr (deuteriochloroform): δ 8.33 (d, J = 8.5, 2), 8.30 (d, J = 8.5, 2), 7.82 (d, J = 8.52), 7.50 (d, J = 8.5, 2), 5.98 (s, 1); uv (cyclohexane): λ max 289 mμ ($\epsilon = 1.51 \times 10^4$), 257 mμ ($\epsilon = 1.34 \times 10^4$); mass spectrum: m/e (relative intensity) 384 (2, Cl), 308 (31), 182 (64), 155 (100), 125 (40), 109 (59), 69 (62), 65 (67).

Anal. Calcd. for $C_{14}H_9ClS_2N_2O_5$: C, 43.70; H, 2.36; N, 7.28; S, 16.66; Cl, 9.21. Found: C, 43.92; H, 2.48; N, 7.54;

S, 17.08; Cl, 9.47.

Reaction of **1** with *p*-Nitrothiophenol in Methylene Chloride.

Ten μl. (0.11 mmole) of **1** dissolved in 0.5 ml. of methylene chloride was added to 5 mg. (0.03 mmole) of *p*-nitrothiophenol dissolved in 2 ml. of methylene chloride. Tlc (silica gel, benzene) showed a product with R_f 0.9. Upon addition of 30 mg. (0.18 mmole) additional *p*-nitrothiophenol, tlc showed that the spot at R_f = 0.9 had disappeared and a new spot appeared which had a R_f and an ir spectrum identical to **9**.

Decomposition of **9** on Silica Gel Tlc.

Compound **9** (15.2 mg., 0.038 mmole) was striped on a 10 x 20 cm preparative tlc plate and developed with benzene at room temperature. Uv visualization showed a weak band at the origin and a single band at R_f 0.7 which was eluted in acetone yielding 10.1 mg. (88%) of a white solid, m.p. 187-190°; mass spectrum: m/e (molecular ion) 308; ir (potassium bromide): no carbonyl absorption. The band remaining at the origin eluted on silica gel tlc (30% methanol:chloroform) to an R_f identical to that of **11**. When the tlc was carried out at 4°, this decomposition was slowed down.

2,2-Di(4-nitrothiophenoxy)acetic Acid (**11**).

Two hundred μl. (2.24 mmoles) of **1** dissolved in 2 ml. of acetone was added dropwise to a solution of 195 mg. (1.26 mmoles) of *p*-nitrothiophenol dissolved in 25 ml. of 1*N* potassium hydroxide and stirred at room temperature overnight. After extraction with five 10 ml. portions of methylene chloride, the aqueous layer was acidified with 12*N* hydrochloric acid and extracted into seven 10 ml. portions of methylene chloride. Evaporation of the solvent left 166 mg. (36%) of an orange solid which was recrystallized from ethyl acetate, m.p. 196-197°; ir (potassium bromide): 1715 (carboxyl C=O); nmr (deuteriochloroform): δ 8.27 (d, J = 8.7, 4), 7.79 (d, J = 8.7, 4), 5.79 (s, 1); uv (15% ethanol:chloroform): λ max 336 ($\epsilon = 1.66 \times 10^4$); mass spectrum: m/e (relative intensity) 366 (13), 321 (10), 307 (26), 212 (100), 194 (14), 166 (84), 155 (89), 138 (10), 121 (81), 109 (74), 97 (3), 69 (33), 63 (62).

Anal. Calcd. for $C_{14}H_{10}N_2S_2O_6$: C, 45.90; H, 2.75; N, 7.65; S, 17.50. Found: C, 46.23; H, 2.41; N, 7.56; S, 17.24.

Alternatively 75 mg. (0.195 mmole) of **9** was dissolved in 4 ml. of 1*N* potassium hydroxide and stirred for 20 minutes at room temperature. The solution was extracted with three 15 ml. portions of chloroform, acidified with 12*N* hydrochloric acid and extracted into four 10 ml. portions of chloroform. Evaporation of the solvent left 54 mg. (76%) of an orange solid which was recrystallized from ethyl acetate yielding **11**.

When 30 mg. of **9** was dissolved in 5 ml. of acetone and stirred for 2 hours with 5 ml. of saturated aqueous sodium carbonate, a product formed which had tlc properties and an ir identical to **11**.

2-Chloro-2-(3,4-dichlorothiophenoxy)-3,4-dichlorophenylthioacetate (**10**).

Two hundred μl. (1.79 mmoles) of 3,4-dichlorobenzenethiol was added to a solution of 155 mg. (1.84 mmoles) of sodium bicarbonate in 4 ml. of water and dissolved by addition of acetone. To this was added 200 μl. (2.24 mmoles) of **1** in 1.5 ml. of acetone. The resulting suspension was made basic with additional sodium bicarbonate solution and extracted with four 7 ml. portions of chloroform. The solvent was evaporated to yield 268 mg. (70%) of a pale yellow oil uncrystallizable in common solvents which gave a single spot at R_f 0.7 on tlc (silica gel, 50% benzene:cyclohexane); ir (chloroform): 1700 cm^{-1}; nmr (deuteriochloroform): δ 7.38 (m, 6), 5.69 (s, 1); mass spectrum: m/e (relative intensity) 430 (45, isotopic cluster consistent for Cl_5S_2), 395 (1), 367 (4), 225 (100), 217 (9), 189 (24), 155 (14), 109 (13), 79 (13).

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REFERENCES AND NOTES

(1a) P. L. Viola, A. Bigotti, and A. Caputo, *Cancer Res.*, **31**, 516 (1970); (b) C. Maltoni and G. Lefemine, *Environ. Res.*, **7**, 387 (1974)

(2a) B. L. Van Duuren, *Ann. N. Y. Acad. Sci.*, **246**, 258 (1975); (b) J. F. Powell, *Brit. J. Ind. Med.*, **2**, 142 (1945).

(3) B. L. Van Duuren, *Ann. N. Y. Acad. Sci.*, **163**, 633 (1969). and earlier references cited therein.

(4) U. S. Dept. of Health, Education and Welfare, NCI, Carcinogenesis Technical Report Series No. 2, Washington, D. C., U. S. Government Printing Office, 1976.

(5a) R. Göthe, C. J. Calleman, L. Ehrenberg, and C. A. Wachtmeister, *Ambio*, **3**, 234 (1974); (b) A. Barbin, H. Brésil, A. Croisy, P. Jacquignon, C. Malaveille, R. Montesano, and H. Bartsch, *Biochem. Biophys. Res. Commun.*, **67**, 596 (1975).

(6) B. L. Van Duuren and S. Banerjee, *Cancer Res.*, **36**, 2419 (1976).

(7) L. L. McKinney, E. H. Uhing, J. L. White, and J. C. Picken, Jr., *Agri. Food Chem.*, **3**, 413 (1955).

(8) L. L. Bellamy, "The Infra-red Spectra of Complex Molecules", John Wiley and Sons, New York, N.Y., 1960, pp. 118-119.

(9a) R. C. Fuson, C. C. Price, and D. M. Burness, *J. Org. Chem.*, **11** 475 (1946); (b) S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948).

(10) G. E. Wilson, Jr. and J. G. Riley, *Tetrahedron Letters*, 379 (1972).

(11) Yu. Ya. Mekhryushev and V. A. Poluektov, *Russian J. Phys. Chem.*, **47**, 959 (1973).