β-acetylacrylate and 25.4 g. (0.14 mole) of ethyl α-bromopropionate in 100 cc. of a mixture of dry benzene and toluene, which contained equivalent amounts of benzene and toluene, was added dropwise with stirring. The reaction started after gentle warming; however, the reaction mixture soon set to a gel and failed to reflux spontaneously. The mixture was then maintained at reflux by means of an oil-bath, and the remainder of the reactants was added dropwise with stirring. Stirring and refluxing were continued for three hours after all the benzene–toluene solution had been added.

The reaction mixture was poured into iced sulfuric acid, and the benzene–toluene layer was separated. The aqueous layer was extracted with ether. The ether and benzene–toluene extracts were combined, washed with 5% sodium carbonate solution, and dried over anhydrous sodium sulfate. Removal of the solvents under diminished pressure left an oil which was distilled: colorless liquid, b. p. 121–122° (2 mm.); $n^{20}D$ 1.4579; yield, 10.5 g. (30%).

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 59.02; H, 8.25. Found: C, 59.40; H, 8.18.

Attempts to transform the product into diethyl α,β-dimethylmuconate by means of phosphorus oxychloride or phosphorus pentoxide in benzene resulted in recovery of the material unchanged.

Summary

1. It has been demonstrated that under proper conditions, monocrotalic acid can be esterified with methanol and hydrogen chloride. Methyl monocrotalate and its derivatives, methyl anhydromonocrotalate and methyl dihydroanhydromonocrotalate, react very readily in the cold with aqueous ammonia to give the corresponding amides. These two reactions lead to the deduction that monocrotalic acid contains a primary carboxyl group.

2. Monocrotalic acid forms with thionyl chloride monocrotalyl chloride which gives methyl monocrotalate with methanol. With diazomethane the acid chloride gives the diazoketone. This product with hydrogen chloride gives the chloroketone but could not be made to rearrange with silver oxide to the homologous acid.

3. Prolonged heating of monocrotalic acid with thionyl chloride gives anhydromonocrotalic acid. In turn this could be esterified with diazomethane to methyl anhydromonocrotalate.

4. Oxidation of monocrotalic acid with nitric acid gives dimethylmaleic anhydride and traces of acetic acid. Acid permanganate gives acetic acid.

5. Treatment of methyl dihydroanhydromonocrotalate with potassium cyanide in order to convert it to an adipic acid derivative gives apparently merely a stereoisomer of the original compound.

6. By the condensation of the monoethyl ester monoacid chloride of dimethyl succinic acid with ethyl cyanoacetate, the ethyl-δ-carbethoxy-δ-cyano-α,β-dimethyllevulinate presumably was formed but could not be hydrolyzed to the monocrotalic acid amide.

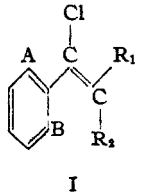
URBANA, ILLINOIS RECEIVED JULY 2, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

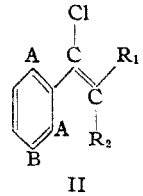
Restricted Rotation in Aryl Olefins. VII. A New Synthesis of Hindered β-Substituted-β-Arylacrylic Acids

BY ROGER ADAMS AND C. W. THEOBALD[1]

Recent work on the study of optical activity resulting from restricted rotation has led to the preparation and resolution of several acrylic acid derivatives of types I and II,[2] in which R_1 or R_2 is a carboxyl and A and B represent a variety of groups.



I



II

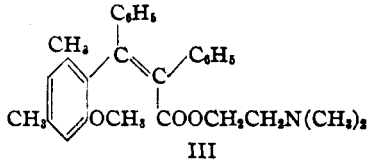
The same general synthetic procedure has been used in preparing all of these compounds. It is, however, not adaptable to the preparation of compounds in which the chlorine atom in I or II is replaced at will by other atoms or groups. The last step in the method consists in the conversion of a β-keto acid by means of phosphorus pentachloride to the corresponding β-chloroacrylic acid. Preliminary experiments to convert the keto acid to the β-bromoacrylic acid by means of phosphorus tribromide failed. With the exception of the introduction of the methoxyl group in the β-position of the acrylic acid, no feasible reactions are available for conversion of β-keto acids to β-substituted acrylic acids with varying β-substituents. As a consequence a new synthesis has been sought which would allow the formation of such acids, so that the influence of the β-substituents on the restricted rotation might be determined and compared. Wittig, Oppermann and Faber,[3] have reported recently the synthesis and resolution of the amino ester (III) which had a half-life of forty-three minutes at 20° in methanol. The procedure

(1) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry; Eastman Kodak Fellow, 1942–1943.

(2) Adams and Miller, THIS JOURNAL, **62**, 53 (1940); Adams, Anderson and Miller, *ibid.*, **63**, 1589 (1941); Adams and Binder, *ibid.*, **63**, 2773 (1941); Adams and Gross, *ibid.*, **64**, 1786 (1942); Adams, Binder and McGrew, *ibid.*, **64**, 1791 (1942); Adams, Miller, McGrew and Anderson, *ibid.*, **64**, 1795 (1942).

(3) Wittig, Oppermann and Faber, *J. prakt. Chem.*, **158**, 61 (1941).

employed, however, is of limited value with respect to variation of the β-substituent in the acrylic acid.

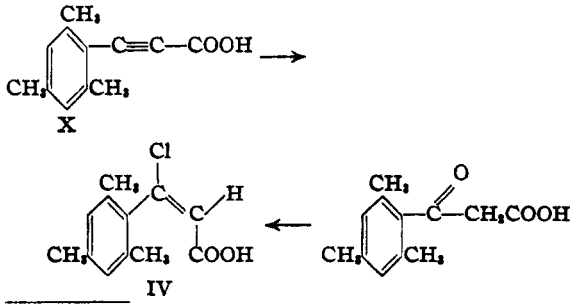


III

Phenylpropiolic acid and its nitrile, amide and ester add readily numerous molecules which lead in most cases to β-substituted-β-phenylacrylic acids. Adaptability of these reactions to di-*ortho*-substituted phenylpropiolic acids has been investigated and the results indicate that a satisfactory and reliable method for obtaining the desired compounds is in hand.

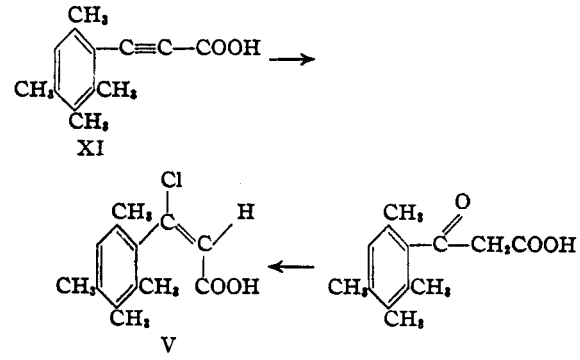
As type molecules, 2,4,6-trimethylphenylpropiolic and 2,3,4,6-tetramethylphenylpropiolic acids were selected for a study of their addition reactions. Aqueous hydrochloric acid and aqueous hydrobromic acids, which serve as reagents for addition of hydrogen chloride[4] and hydrogen bromide[5] to phenylpropiolic acid, did not give satisfactory results with the substituted phenylpropiolic acids. However, anhydrous hydrogen chloride and hydrogen bromide in glacial acetic acid readily caused addition of the halogen acid to yield the β-haloacrylic acids. Aqueous hydriodic acid, on the other hand, resulted in addition of hydrogen iodide. In this way, hydrogen chloride and hydrogen bromide were added to 2,4,6-trimethylphenylpropiolic acid and hydrogen chloride and hydrogen iodide to 2,3,4,6-tetramethylphenylpropiolic acid. By addition of halogen to such propiolic acids, α,β-dihaloacrylic acids should be synthesized and other adducts should give a variety of β-substituted acrylic acids.

The β-chloro-β-(2,4,6-trimethylphenyl)-acrylic acid (IV) and the β-chloro-β-(2,3,4,6-tetramethylphenyl)-acrylic acid (V) obtained by adding hydrogen chloride to 2,4,6-trimethylphenylpropiolic acid and 2,3,4,6-tetramethylphenylpropiolic acid, respectively, were identical with the products formed by the action of phosphorus pentachloride on the corresponding β-keto acids, thus indicating that the geometric configuration of the double-bond substituents is the same.



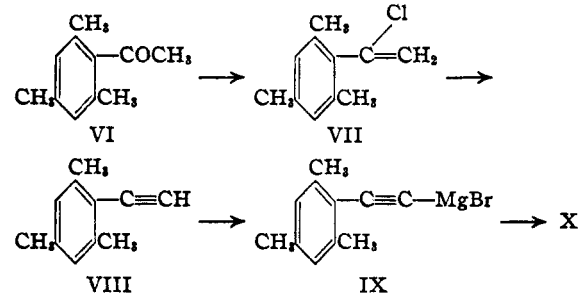
IV

(4) Mulliken, Dissertation, Leipzig, 1890.
(5) Michael and Browne, *Ber.*, **19**, 1378 (1886).



V

The preparation of the propiolic acids (X and XI) was carried out by the scheme illustrated for 2,4,6-trimethylphenylpropiolic acid (VI–X).



VI VII VIII IX

Experimental

α - Chloro - α - (2,4,6 - trimethylphenyl) - ethylene.—This substance was prepared according to the directions of Vaughn and Nieuwland.[6] A mixture of 165 g. of acetomesitylene and 240 g. of phosphorus pentachloride was heated to 60° for three hours, then at 100° for forty-five minutes. The reaction mixture was cooled, poured into a slush of ice and water, and the product removed by extraction with ether. Distillation of the washed and dried ether extracts gave 90 g. (50%) of α-chloro-α-(2,4,6-trimethylphenyl)-ethylene; b. p. 122–124° (25 mm.). The residue, after distillation of the main product, solidified and was treated with Norite in petroleum ether (b. p. 90–110°). A second crystallization from aqueous ethanol gave white crystals of ω-chloroacetomesitylene; m. p. 62–63° (cor.)[7]; yield 37 g. (19%).

Acidification of the alkaline washings of the initial reaction mixture yielded an oil which solidified partially upon standing. The oily material was removed by extraction with boiling carbon tetrachloride and the residue was recrystallized from water; m. p. 229–232° (cor.). This compound analyzes for the phosphoric acid ester of α-hydroxy-α-(2,4,6-trimethylphenyl)-ethylene.

Anal. Calcd. for $C_{11}H_{15}O_4P$: C, 54.56; H, 6.22. Found: C, 54.42; H, 6.39.

2,4,6-Trimethylphenylpropiolic Acid.—A solution of 25 g. of 2,4,6-trimethylphenylacetylene[6] in 50 cc. of dry ether was added dropwise to a stirred solution of ethylmagnesium bromide prepared from 27 g. of ethyl bromide in 65 cc. of dry ether and 6 g. of magnesium. The reaction mixture was refluxed and stirred for one and one-half hours, then transferred to a catalytic hydrogenation apparatus, cooled in an ice–salt bath, and carbon dioxide passed in at a pressure of 3 atmospheres. The ice-bath was retained for thirty minutes while the mixture was shaken by hand. Automatic shaking was continued for twelve hours at room temperature while the pressure was maintained at 2.5–3 atmospheres.

(6) Vaughn and Nieuwland, THIS JOURNAL, **56**, 1207 (1934).
(7) Collett, *Bull. soc. chim.*, [3] **17**, 506 (1897).

The reaction mixture was cooled in an ice-bath and poured and rinsed into iced dilute hydrochloric acid. The ether layer was extracted several times with small portions of 10% aqueous sodium hydroxide, and the combined alkaline layers extracted once with ether. The propiolic acid was obtained by acidification of the ice-cold alkaline solution with iced dilute hydrochloric acid. After recrystallization from benzene and petroleum ether (b. p. 90–110°) there was obtained 9.5 g. of long white needles; m. p. 165–167° (cor.) with decomposition.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.55; H, 6.43 Found: C, 76.44; H, 6.68.

Evaporation of the ether solution after the alkaline extraction and distillation of the residue yielded 8 g. of 2,4,6-trimethylphenylacetylene. The yield of pure acid on the basis of the recovered starting material was 43%.

β - Chloro - β - (2,4,6 - trimethylphenyl) - acrylic Acid.—Dry hydrogen chloride was bubbled for five hours through a solution of 1 g. of 2,4,6-trimethylphenylpropiolic acid in 25 cc. of glacial acetic acid maintained at 80–90°.[8] The reaction mixture was poured into 200 cc. of ice water and 0.80 g. (67%) of chloroacrylic acid was obtained. The product was purified by recrystallization from petroleum ether (b. p. 90–110°) and from dilute ethanol; white crystals, m. p. 145–146° (cor.).

Anal. Calcd. for $C_{12}H_{13}O_2Cl$: C, 64.13; H, 5.83. Found: C, 63.85; H, 5.83.

An acid of the same *cis–trans* configuration was obtained from 2,4,6-trimethylbenzoylacetic acid[9] by the procedure described by Adams and Miller.[2a] From 6.5 g. of 2,4,6-trimethylbenzoylacetic acid and 25 g. of phosphorus pentachloride in 50 cc. of ice-cold phosphorus oxychloride there was obtained 5.0 g. (71%) of chloro acid. Recrystallization from petroleum ether (b. p. 90–110°) resulted in a melting point of 145–146° (cor.). A mixed melting point with the chloroacrylic acid prepared from the propiolic acid showed no depression.

β-Bromo-β-(2,4,6-trimethylphenyl)-acrylic Acid.—Dry hydrogen bromide was bubbled through a solution of 0.6 g. of 2,4,6-trimethylphenylpropiolic acid in 25 cc. of glacial acetic acid for twenty-four hours at room temperature. The acetic acid solution was diluted with 250 cc. of ice water and an oil separated which solidified when triturated with water; yield 0.68 g. (79%). Repeated recrystallization from petroleum ether (b. p. 90–110°) resulted in white crystals, m. p. 135–135.5° (cor.).

Anal. Calcd. for $C_{12}H_{13}O_2Br$: C, 53.53; H, 4.86. Found: C, 53.51; H, 4.94.

Examination of the ligroin mother liquors gave no indication of another form of the bromo acid but a very small quantity of material melting with decomposition was probably mesitylpropiolic acid.

The acid could be made also by using the following aqueous procedure which, however, gave lower yields. To 50 cc. of constant-boiling hydrobromic acid saturated at 0° with hydrogen bromide gas, 0.5 g. of 2,4,6-trimethylphenylpropiolic acid was added and the mixture was gently refluxed for two hours. Upon cooling, 0.2 g. of long brown needles separated in clusters, m. p. 133–135°. A mixed melting point with the acid prepared in glacial acetic acid showed no depression.

α - Chloro - α - (2,3,4,6 - tetramethylphenyl) - ethylene.—A solution of 135 g. (0.77 mole) of acetoisodurene in 125 cc. of phosphorus oxychloride and 25 cc. of phosphorus trichloride was cooled in an ice-bath and 160 g. (0.77 mole) of phosphorus pentachloride was added. The cold solution was allowed to warm spontaneously to room temperature then heated in a water-bath to 55°, where the temperature was maintained for eight hours. The bath temperature was raised to 65–70° and maintained there for fifteen hours.

The excess phosphorus halides were hydrolyzed by pouring onto ice with vigorous stirring and the aqueous layer decanted and extracted with ether. The combined organic layers were washed with water, 10% aqueous sodium carbonate, and water, then dried over "Drierite." Removal of the ether and distillation of the residue gave the following fractions; (1) b. p. 140–145° (28 mm.) (mainly 140–141°), weight 109 g.; (2) b. p. 145–175° (28 mm.) solidified in the receiver m. p. 77–85°; weight 35 g.; (3) residue not distilling 15 g.

The main portion was distilled twice more; b. p. 225° (745 mm.), $n^{20}D$ 1.5335; d^{20} 1.0247.

Anal. Calcd. for $C_{12}H_{15}Cl$: C, 74.02; H, 7.77 Found: C, 74.18; H, 7.80.

The solid material in the second fraction was purified by recrystallization from petroleum ether (b. p. 90–110°), m. p. 88–88.5° (cor.) or by distillation; b. p. 144° (6 mm.). It was undoubtedly ω-chloro-2,3,4,6-tetramethylacetophenone.

Anal. Calcd. for $C_{12}H_{15}OCl$: C, 68.38; H, 7.20. Found: C, 68.46; H, 7.18.

Acidification of the alkaline extract gave an oil which solidified and was purified by extraction with boiling carbon tetrachloride and crystallization from aqueous methanol; white plates, m. p. 184–184.5° (cor.). Presumably this is the phosphoric acid ester of α-hydroxy-α-(2,3,4,6-tetramethylphenyl)-ethylene. The analyses were not entirely consistent owing to difficulty in burning.

2,3,4,6-Tetramethylphenylacetylene.—A solution of 0.81 mole of sodium ethylate was prepared by adding 18.6 g. of sodium to 300 cc. of absolute ethanol. This solution was refluxed in an oil-bath (bath temperature 110°) and stirred with a Hershberg wire stirrer while 76 g. (0.39 mole) of α-chloro-α-(2,3,4,6-tetramethylphenyl)-ethylene was dropped into the reaction mixture during the course of thirty minutes. Stirring and refluxing were continued for ten hours, then 175 cc. of ethanol was removed by distillation over a period of two hours. The residue was poured into ice water and acidified with hydrochloric acid. The product was removed by extraction with ether and washed with water, 10% aqueous sodium carbonate, again with water, and dried over "Drierite."

Evaporation of the ether left a residue which was distilled and separated into the following fractions: (1) b. p. to 123° (21 mm.), weight 1 g. (discarded); (2) b. p. 123–128° (21 mm.), weight 23 g.; (3) b. p. 132–137° (23 mm.), weight 17 g.; (4) b. p. 137–145° (23 mm.), weight 24 g.; (5) residue 8 g. The yield of fractions 2 and 3 was 40 g. (65%) of slightly impure isodurylacetylene.

Fractions 2 and 3 which had about the same index of refraction, were combined and distilled twice more; b. p. 86° (1 mm.); $n^{20}D$ 1.5561; d^{20} 0.9463; Beilstein halogen test negative.

Anal. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.42; H, 9.27.

2,3,4,6-Tetramethylphenylpropiolic Acid.—The carbonation of the acetylene Grignard was carried out as previously described. From 15.8 g. of 2,3,4,6-tetramethylphenylacetylene was obtained 13.5 g. (67%) of acid. Two recrystallizations from petroleum ether (b. p. 90–110°) and one from chloroform gave long white needles from petroleum ether, flat white plates from chloroform; m. p. 164–164.5° (cor.) with decomposition.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.43; H, 7.13.

2,3,4,6-Tetramethylbenzoylacetic Acid.—This acid was prepared by carbonation of the bromomagnesium enolate of acetoisodurene.[8] From 17.6 g. of acetoisodurene in 50 cc. of dry ether and the Grignard reagent from 16.4 g. of ethyl bromide and 3.6 g. of magnesium in 50 cc. of dry ether, carbonated and worked up in the usual manner was obtained 15.5 g. (71%) of β-keto acid. The product was purified by dissolving in a large volume of warm benzene and concentrating this solution under a gentle air stream until crystallization occurred; m. p. 113–114° (cor.) with decomposition.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32 Found: C, 70.72; H, 7.31.

(8) James, *J. Chem. Soc.*, **99**, 1620 (1911).

(9) Fuson, Fugate and Fisher, THIS JOURNAL, **61**, 2362 (1939).

β - Chloro - β - (2,3,4,6 - tetramethylphenyl) - acrylic Acid.—Hydrogen chloride was added to 2,3,4,6-tetramethylphenylpropiolic acid under the conditions used in the preparation of β-chloro-β-(2,4,6-trimethylphenyl)-acrylic acid. From 1 g. of isodurylpropiolic acid was obtained 1.03 g. (90%) of the hydrogen chloride adduct. Recrystallization from petroleum ether gave large white needles, m. p. 185° (cor.).

Anal. Calcd. for $C_{13}H_{15}O_2Cl$: C, 65.41; H, 6.33. Found: C, 65.46; H, 6.46.

This same acid was obtained in 46% yield by treatment of 2,3,4,6-tetramethylbenzoylacetic acid with phosphorus oxychloride and phosphorus pentachloride.[2a] A mixed melting point of the two samples showed no depression.

β - Iodo - β - (2,3,4,6 - tetramethylphenyl) - acrylic Acid.—The general procedure used has been described by Michael.[10] From 7 g. of 2,3,4,6-tetramethylphenylpropiolic acid suspended in 10 cc. of constant boiling hydriodic acid for nine days at room temperature was obtained 1.24 g. of air-dried material. The acid was purified by recrystallization from carbon tetrachloride; white crystals m. p. 183–184° (cor.); yield 1.0 g. (90%).

Anal. Calcd. for $C_{13}H_{15}O_2I$: C, 47.29; H, 4.58. Found: C, 47.16; H, 4.53.

(10) Michael, *Ber.*, **34**, 3640 (1901).

Summary

1. Di-*ortho*-substituted phenylpropiolic acids have been shown to undergo similar addition reactions to phenylpropiolic acid though somewhat less readily. A method thus becomes available for preparing arylacrylic acids with restricted rotation in which the β-substituent can be varied.

2. Hydrogen chloride has been added to 2,4,6-trimethylphenylpropiolic acid with formation of β-chloro-β-(2,4,6-trimethylphenyl)-acrylic acid. Hydrogen bromide gives the corresponding brominated acrylic acid.

3. Hydrogen chloride has been added to 2,3,4,-6-tetramethylphenylpropiolic acid to give β-chloro-β-(2,3,4,6-tetramethylphenyl)-acrylic acid. Hydrogen iodide gives the corresponding iodinated acrylic acid.

4. The β-chloroacrylic acids mentioned in 2 and 3 are identical with those obtained by the action of phosphorus pentachloride on 2,4,6-trimethylbenzoylacetic acid and 2,3,4,6-tetramethylbenzoylacetic acid, respectively.

URBANA, ILLINOIS RECEIVED JULY 28, 1943

[CONTRIBUTION FROM NOYES LABORATORY, UNIVERSITY OF ILLINOIS, AND THE RESEARCH LABORATORIES, MERCK AND CO., INC.]

ω,ω'-Bimethionine

BY H. R. SNYDER, E. E. HOWE, GEORGE W. CANNON AND MELVIN A. NYMAN

The *dl*-methionine obtained by adaptation of the procedure of Barger and Weichselbaum[1] to the preparation of larger quantities has been found to be contaminated with a less-soluble material[2] which now has been identified as a mixture of the racemic and meso forms of ω,ω'-bimethionine, $HO_2CCH(NH_2)CH_2CH_2SCH_2CH_2SCH_2CH_2CH(NH_2)CO_2H$. Most of the impurity, originally called "pseudomethionine," could be removed by crystallization from water, but detectable amounts always remained in the methionine. These traces of the contaminant could not be removed by crystallization from acetic acid, aqueous methanol, aqueous ethanol, aqueous acetone or aqueous pyridine. Conversion of the methionine to the copper salt or the formyl derivative, followed by crystallization of the derivative and regeneration of the methionine, likewise failed to remove all the impurity.

The impurity may be detected by the use of a solution of anhydrous copper sulfate in concentrated sulfuric acid. A yellow color is produced when natural methionine or pure *dl*-methionine is added to this solution.[3] A green tint is distinguishable in the yellow solution when the contaminated methionine is tested.[2] A bright green color is produced when the isolated impurity is added to the test solution.

"Pseudomethionine" is a high-melting amphoteric solid. It can be recrystallized from a large volume of hot water and thus freed of methionine. Analyses of the substance and its acetyl and benzoyl derivatives indicated that its empirical formula is $C_5H_{10}O_2NS$. The molecular weight of the acetyl derivative indicated that the molecular formula of "pseudomethionine" is $C_{10}H_{20}O_4N_2S_2$. The neutral equivalent of the acetyl derivative indicated that the molecule contains two free carboxyl groups. A Dumas nitrogen determination and a Van Slyke amino-nitrogen determination indicated that two free amino groups are present. Tests for C-methyl, S-methyl, and disulfide groups were negative.

If the precursor of the substance is formed by alkylation of sodium ethyl phthalimidomalonate, the dichloride which leads to "pseudomethionine" either must be present in or must be formed from the monochloride, $CH_3SCH_2CH_2Cl$. The most likely mode of decomposition of β-chloroethyl methyl sulfide is through autoalkylation to form sulfonium salts. Sulfonium halides are known to decompose to sulfides and alkyl halides.[4]

(1) Barger and Weichselbaum, "Organic Syntheses," Coll. Vol. II, p. 384 (1943); *Biochem. J.*, **25**, 997 (1931).

(2) Sofin, Rosenblum and Schultz, Merck and Co., Inc., private communication.

(3) Sofin, Rosenblum and Schultz, Merck and Co., Inc., *J. Biol. Chem.*, **147**, 557 (1943).

(4) Ray and Levine, *J. Org. Chem.*, **2**, 267 (1937); for other references, see Connor, "Organic Sulfur Compounds," Gilman's "Organic Chemistry," Chapter 10, John Wiley and Sons, Inc., New York, N. Y., 1942, ed. 2, Vol. I, p. 868.