

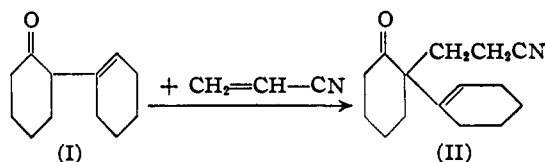
[CONTRIBUTION FROM ROHM AND HAAS CO., INC., AND RESINOUS PRODUCTS AND CHEM. CO.]

The Chemistry of Acrylonitrile. VII. Cyanoethylation of Ketones and Sulfones

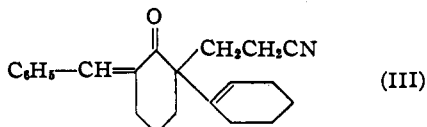
BY HERMAN A. BRUSON AND THOMAS W. RIENER

During the course of an investigation on the reactions of acrylonitrile in the presence of alkalis with various types of active methylene compounds,¹ the behavior of 2-cyclohexenylcyclohexanone (I) toward cyanoethylation was examined.

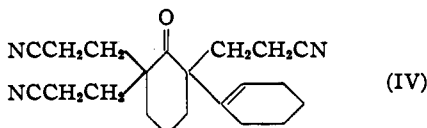
It was found that with one molecular equivalent of acrylonitrile, monocyanoethylation first occurs largely on the methenyl group to give 2-(β -cyanoethyl)-2-cyclohexenylcyclohexanone (II) in about 50% yield, together with unchanged 2-cyclohexenylcyclohexanone and higher cyanoethylation products.



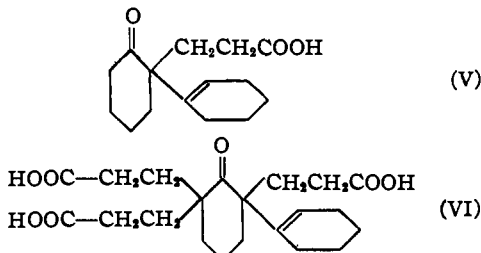
That the methylene group adjacent to the carbonyl in (II) is intact, is shown by the fact that (II) readily yields a crystalline mono-benzylidene derivative (III) with benzaldehyde.



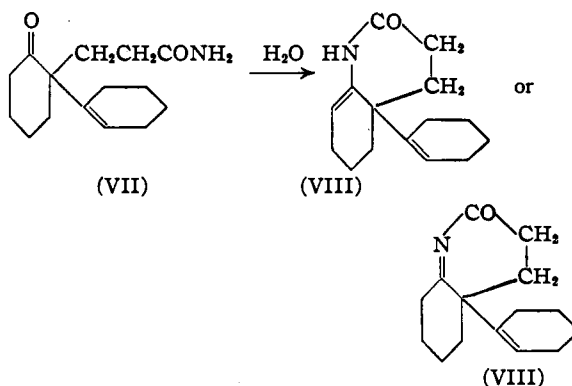
Further cyanoethylation of (II) with two additional molecular equivalents of acrylonitrile yields the *tri*-cyanoethylation product (IV).



Upon alkaline hydrolysis (II) and (IV) yield the respective carboxylic acids (V) and (VI).

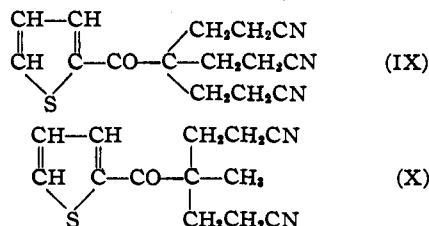


When (II) is treated with aqueous sulfuric acid (1 mole sulfuric acid plus 1 mole water per mole of II) a product is obtained which is not the anticipated amide (VII), but a dehydration product thereof, presumably a cyclohexenyl hexahydroquinolone (VIII)

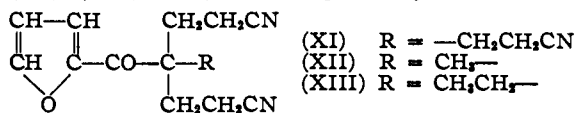


such as would be expected to form when a δ -keto amide (VII) or nitrile (II) reacts with aqueous mineral acids.²

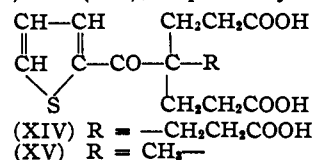
The reaction of acrylonitrile with 2-acetylthiophene and 2-propionylthiophene gave good yields of the corresponding *tri*- and *di*-cyanoethylation products (IX) and (X), respectively.



In a similar manner, acrylonitrile added to 2-acetylthiophene, 2-propionylthiophene and 2-butyrylthiophene to give the crystalline cyanoethylation products (XI), (XII) and (XIII), respectively.

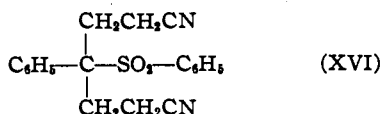


Upon alkaline hydrolysis of the cyano groups, (IX) and (X) gave the corresponding carboxylic acids, (XIV) and (XV), respectively.

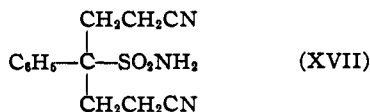


The cyanoethylation reaction was also applied to an active methylene sulfone, namely, benzyl phenyl sulfone C₆H₅CH₂-SO₂-C₆H₅. This reacted smoothly with two equivalents of acrylonitrile in the presence of "Triton B" to give (XVI)

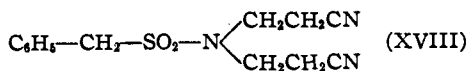
(1) Bruson and Riener, *THIS JOURNAL*, **64**, 2850 (1942).
 (2) Allan and Ball, *ibid.*, **59**, 686 (1937); Kohler, Graustein and Merrill, *ibid.*, **44**, 2536 (1922); Kohler and Souther, *ibid.*, **44**, 2903 (1922); Kohler and Allen, *ibid.*, **46**, 1522 (1924).



In a previous article⁵ it was reported that the cyanoethylation of α -toluene sulfonamide yielded γ -phenyl- γ -(sulfonamido)-pimelonitrile (XVII).



A reinvestigation of this reaction indicates however that the two cyanoethyl groups are attached to the nitrogen atom of the sulfonamido group instead of on the methylene carbon atom, and that the compound is therefore N,N-bis-(2-cyanoethyl)- α -toluenesulfonamide (XVIII).



This was established by the synthesis of (XVIII) from the reaction of benzylsulfonyl chloride with bis-(β -cyanoethyl)-amine, $\text{HN}(\text{CH}_2\text{CH}_2\text{CN})_2$.

Upon alkaline hydrolysis of (XVIII) one of the cyanoethyl groups is eliminated with the formation of benzylsulfonamidopropionic acid $\text{C}_6\text{H}_5\text{-CH}_2\text{SO}_2\text{NHCH}_2\text{CH}_2\text{COOH}$ (XIX).

Experimental

All melting points are uncorrected.

2-(β -Cyanoethyl)-2-cyclohexenylcyclohexanone (II).—To a stirred mixture of 100 g. of *t*-butyl alcohol, 5 g. of aqueous 40% benzyltrimethylammonium hydroxide ("Triton B") and 178 g. of 2-cyclohexenylcyclohexanone⁵ (1 mole), there was added dropwise 53 g. of acrylonitrile (1 mole) during the course of thirty minutes. The exothermic reaction was maintained at 25–30° by cooling. The mixture was stirred for two hours at room temperature after the addition of the acrylonitrile, and was then acidified to congo with dilute hydrochloric acid. The mixture was washed twice with water, dried *in vacuo* to remove moisture and solvent, and the residual oil was distilled under high vacuum (0.2 mm.) to give the following cuts: (a) 25 g., b. p. 110–138°; (b) 44 g., 138–162°; (c) 103 g. 162–172°; (d) 7 g., 172–245°; (e) 16 g., 245–255°; (f) 32 g. residue. Fraction (c) was redistilled to give 91 g. of product which came over as a colorless oil at 152–156° (0.1 mm.), and which solidified to a crystalline solid on standing. Upon recrystallization from petroleum ether it formed white crystals, m. p. 61–62°. An additional 19 g. was obtained by redistilling fraction (b); total yield of product, 110 g. or 47.6%.

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.90; H, 9.18; N, 6.12.

6-Benzylidene-2-(β -cyanoethyl)-2-cyclohexenylcyclohexanone (III).—Freshly distilled benzaldehyde (10.6 g.) was added to a stirred solution of 23.1 g. of II, 50 g. of ethanol and 2 g. of 35% methanolic potassium hydroxide solution. The solution was allowed to stand for forty-eight hours during which time a crystalline deposit formed. The filtered crystals (26 g.) were recrystallized first from methanol and three times from ethanol to give white crystals m. p. 169–170°, which apparently contained a trace of amide.

(3) Hückel, Neunhoeffer, Gerche and Frank, *Ann.*, **477**, 119 (1930).

Anal. Calcd. for $\text{C}_{22}\text{H}_{25}\text{NO}$: N, 4.39. Found: N, 4.04.

2-Cyclohexenyl-2,6,6-tri-(β -cyanoethyl)-cyclohexanone (IV).—A mixture of 57.8 g. of II, 100 g. of *t*-butyl alcohol and 3 g. of "Triton B" was stirred, and 29 g. of acrylonitrile was added dropwise thereto during the course of thirty minutes at 40–45°. The mixture was stirred thereafter for ten hours at room temperature, and then made faintly acid to congo with dilute hydrochloric acid. The product was washed with water, taken up in ethylene dichloride, washed with water several more times and the ethylene dichloride layer was evaporated to dryness *in vacuo* on the steam-bath.

The residual thick oil was mixed with about three times its volume of methanol and set aside in the refrigerator at 4° to crystallize. After a few hours the light tan crystalline deposit was filtered off; yield was 48.5 g. Upon recrystallization from methanol with a little Norite, the sample for analysis was obtained in white crystals, m. p. 111°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}$: C, 74.78; H, 8.01; N, 12.46. Found: C, 74.73; H, 8.12; N, 12.34.

2-(β -Carboxyethyl)-2-cyclohexenylcyclohexanone (V).—A mixture of 11.5 g. of II, 11.5 g. of potassium hydroxide and 90 g. of water was boiled under reflux until an almost clear solution was formed. This required about twenty hours. The filtered solution was acidified with hydrochloric acid and the taffy-like mass which precipitated was taken up in benzene. The benzene solution was evaporated to dryness *in vacuo* and the residual oil was distilled under high vacuum to give 9 g. of colorless, very viscous oil boiling at 175–180° (0.2 mm.) which crystallized upon rubbing with petroleum ether in the cold. Upon recrystallization from petroleum ether it formed white crystals, m. p. 60–61°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 72.00; H, 8.80. Found: C, 71.78; H, 8.81

2-Cyclohexenyl-2,6,6-tri-(β -carboxyethyl)-cyclohexanone (VI).—A mixture of 6 g. of IV, 72 g. of water and 8 g. of sodium hydroxide was boiled under reflux for ten hours, until practically all the oily material had dissolved. The solution was filtered and acidified with hydrochloric acid to precipitate the crude tricarboxylic acid as a dough-like mass which hardened on standing. It was dried in the air and crystallized twice from nitroethane to form white crystals, m. p. 158–159°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{30}\text{O}_7$: C, 63.96; H, 7.61. Found: C, 63.50; H, 7.76.

Cyclohexenylhexahydroquinolone (VIII).—To a stirred solution of 23.1 g. of II and 50 g. of ethylene dichloride there was added dropwise with cooling, a solution of 10 g. of 98% sulfuric acid and 1.8 g. of water during the course of ten minutes. The reaction temperature was between 30 and 40°. After all had been added the mixture was stirred for fifteen minutes at room temperature and then heated for five hours at 45–50° with constant stirring, and allowed to stand overnight. Water (200 cc.) was then added and the mixture stirred. The white solid which separated was filtered off, washed and dried. Yield was 5 g. Upon crystallization from nitromethane it formed white needles m. p. 213–214°. The analytical sample was dried at 100° in high vacuum.

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.70; H, 9.10; N, 6.13.

From the ethylene dichloride layer there was obtained upon evaporation an additional 10 g. of product, m. p. 212–214° after crystallization from nitromethane. Total yield was 15 g. or 64.9%.

1,1,1-Tri-(β -cyanoethyl)-methyl 2-Thienyl Ketone (IX).—Acrylonitrile (31.8 g.) was added dropwise to a stirred solution of 25.2 g. of 2-acetylthiophene, 25 g. of *t*-butyl alcohol and 2 g. of "Triton B" while maintaining the reaction mixture at 25–30° by cooling. The addition required about thirty minutes during which time crystals began to separate and clog the stirrer so that 50 cc. of additional *t*-butyl alcohol had to be added to form a thinner

suspension. After the addition, the mixture was stirred for two hours, then acidified with dilute hydrochloric acid and the crystalline product filtered off. Yield was 50 g. of a tan-colored, air-dried product or 87.7%. Upon recrystallization from ethanol the sample for analysis formed white, feathery crystals, m. p. 146–147°.

Anal. Calcd. for $C_{16}H_{16}N_2OS$: C, 63.15; H, 5.26; N, 14.73; S, 11.22. Found: C, 63.04; H, 5.20; N, 14.77; S, 11.28.

γ -Methyl- γ -thienoyl-pimelonitrile (X).—To a stirred solution of 55 g. of 2-propionylthiophene, 50 g. of *t*-butyl alcohol and 3 g. of "Triton B," there was added dropwise 42.4 g. of acrylonitrile while cooling the mixture to 25–30°. After the addition the mixture was stirred for twenty-four hours during which time the product separated in crystalline form. The mixture was neutralized with dilute hydrochloric acid and the crystals filtered off. Yield was 94 g. of air dried product or 98%. Upon crystallization from ethanol the sample for analysis formed white flaky crystals, m. p. 81–82°.

Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 63.41; H, 5.69; N, 11.38; S, 13.00. Found: C, 63.34; H, 5.65; N, 11.31; S, 13.27.

Tri-(β -cyanoethyl)-2-acetylfuran (XI).—To a stirred mixture of 6 g. of "Triton B," 200 g. of *t*-butyl alcohol and 99 g. of 2-acetylfuran⁴ there was added dropwise 143 g. of acrylonitrile during the course of an hour while cooling the mixture to 22–28°. During the addition a heavy crystalline mush formed. To assist the stirring, 150 g. more of *t*-butyl alcohol was added, and the mixture was stirred for eighteen hours at room temperature. The catalyst was then neutralized with dilute hydrochloric acid and the crystalline product filtered off sharply by suction. Yield was 216 g. After recrystallization from ethanol it formed white crystals, m. p. 121–122°.

Anal. Calcd. for $C_{16}H_{18}N_6O_2$: C, 66.91; H, 5.57; N, 15.61. Found: C, 66.77; H, 5.68; N, 15.52.

γ -Furoyl- γ -methylpimelonitrile (XII).—The 2-propionylfuran used was prepared from furan, propionic anhydride and hydrogen iodide by the method of Hartough and Kosak.⁴ It was thoroughly freed from traces of acidity (which poison the catalyst), by several washings with soda solutions and two distillations.

Acrylonitrile (32.4 g.) was added dropwise to a stirred solution of 38 g. of 2-propionylfuran, 50 g. of *t*-butyl alcohol and 3 g. of "Triton B" at 24–28°. The mixture was stirred for twenty-four hours thereafter at room temperature, then neutralized with dilute hydrochloric acid and washed with water. The oil layer was separated and dried *in vacuo* at 90°. The product formed a thick oil (69 g.) which crystallized slowly on scratching and standing eventually forming a solid, waxy mass. After several recrystallizations from ethanol, the sample for analysis formed white crystals, m. p. 49°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 67.83; H, 6.09; N, 12.17. Found: C, 67.89; H, 6.11; N, 12.06.

γ -Furoyl- γ -ethylpimelonitrile (XIII).—The 2-butyrylfuran used was prepared from furan, hydrogen iodide and butyric anhydride.⁴ It boiled at 83–84° (10 mm.). It must be freed from traces of acidity which poison the catalyst.

A mixture of 30 g. of 2-butyrylfuran, 30 g. of *t*-butyl alcohol and 2 g. of "Triton B" was treated with 23 g. of acrylonitrile as described above. The dark resinous sirup obtained gradually crystallized to yield 36 g. of white crystalline product after washing with a little *t*-butyl alcohol. The sample for analysis was recrystallized twice from ethanol to give large prisms, m. p. 102°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.47. Found: C, 68.70; H, 6.58; N, 11.39.

1,1,1-Tri-(β -carboxyethyl)-methyl 2-Thienyl Ketone (XIV).—A mixture of 14.3 g. of IX, 100 g. of water and 12 g. of sodium hydroxide was boiled under reflux for

twelve hours. The filtered solution was acidified with hydrochloric acid. A heavy oil separated which solidified to a crystalline mass. Yield was 14 g. of air-dried product. Upon crystallization from nitromethane it formed white crystals, m. p. 183–184°. The sample for analysis was dried in high vacuum at 100°.

Anal. Calcd. for $C_{18}H_{18}O_7S$: C, 52.63; H, 5.26; S, 9.35. Found: C, 52.65; H, 5.34; S, 9.23.

γ -Methyl- γ -thienoylpimelic Acid (XV).—A mixture of 12.3 g. of (X), 100 g. of water and 12 g. of sodium hydroxide was boiled under reflux for eight hours. The filtered solution was acidified with hydrochloric acid. An oil precipitated which gradually solidified to a crystalline mass. Yield of air-dried product was 12 g. Upon crystallization from nitromethane, the product formed white crystals, m. p. 137–138°.

Anal. Calcd. for $C_{13}H_{16}O_5S$: C, 54.92; H, 5.63; S, 11.26. Found: C, 54.44; H, 5.83; S, 11.23.

γ -Phenyl- γ -phenylsulfonylpimelonitrile (XVI).—To a stirred solution of 5.8 g. of benzyl phenyl sulfone, 40 g. of acetonitrile and 0.5 g. of "Triton B" there was added dropwise 2.7 g. of acrylonitrile while the reaction mixture was maintained at 32–38° by occasional cooling. The mixture was then stirred for eighteen hours at room temperature, neutralized with dilute hydrochloric acid and the product washed with water and dried *in vacuo*. The residual oil (5 g.) crystallized when rubbed with ethanol. After recrystallization from ethanol the product formed white crystals, m. p. 180°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.45; H, 5.32; N, 8.29; S, 9.47. Found: C, 67.80; H, 5.53; N, 8.26; S, 9.25.

***N,N*-bis-(2-Cyanoethyl)- α -toluenesulfonamide (XVIII).**—To a solution of 6.2 g. of bis- β -cyanoethylamine in 50 g. of benzene, there was added 8.5 g. of benzylsulfonyl chloride (obtained from Eastman Kodak Co.). The clear solution gradually deposited a slimy precipitate. After standing two hours, the mixture was filtered free from this material and the filtrate allowed to stand overnight. The white crystalline deposit which separated therefrom was filtered off and recrystallized from ethanol. It melted at 103° and was identical with the product obtained from the cyanoethylation of α -toluenesulfonamide.⁵

A mixed melting point of the two products showed no depression.

β -(Benzylsulfonylamido)-propionic Acid (XIX).—A mixture of 10 g. of (XVIII), 12 g. of sodium hydroxide and 80 cc. of water was boiled under reflux for six hours. The clear solution obtained was acidified with hydrochloric acid and the crystalline precipitate filtered off and dried. Yield was 9 g. After recrystallization from hot water the product formed white flaky crystals, m. p. 151–152°, having an acid no. 230 (calcd., 230).

Anal. Calcd. for $C_{10}H_{12}NO_4S$: C, 49.38; H, 5.35; N, 5.76; S, 13.16. Found: C, 49.13; H, 5.64; N, 5.68; S, 13.26.

Acknowledgment.—To Mr. Clyde W. Nash for all analyses and to Mr. Raymond Luckenbaugh for preparing several of the intermediates.

Summary

1. Acrylonitrile reacts with 2-cyclohexenylcyclohexanone to yield a *mono*- and a *tri*-cyanoethylation product from which the corresponding carboxylic acids were prepared.

2. Mono-cyanoethylcyclohexenylcyclohexanone yields a cyclohexenylhexahydroquinolone upon treatment with sulfuric acid.

3. Cyanoethylation products of 2-acylthiophenes and 2-acylfurans were prepared.

4. Cyanoethylation of benzyl phenyl sulfone

(4) Hartough and Kosak, *THIS JOURNAL*, **68**, 2641 (1946). The product should be free from traces of acidity.

(5) Bruson and Riener, *ibid.*, **66**, 25 (1943).

introduced two cyanoethyl groups on the methylene carbon atom. Cyanoethylation of α -toluene-sulfonamide introduced two cyanoethyl groups on

the nitrogen atom of the sulfonamido group instead of on the methylene carbon atom.

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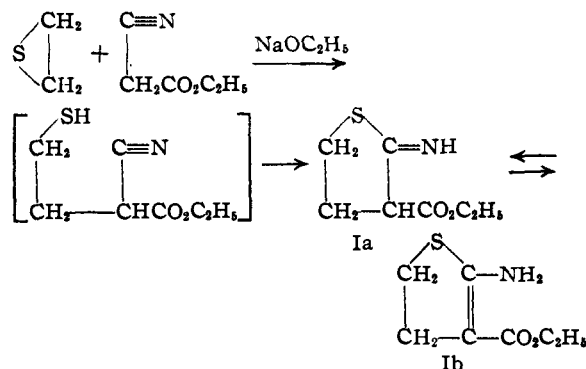
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of 2-Iminothiophanes from Ethyl Cyanoacetate and Alkene Sulfides

By H. R. SNYDER AND WYVONA ALEXANDER¹

The structural similarity of alkene sulfides to alkene oxides suggests that these sulfur compounds may be useful in the alkylation of active methylene compounds. Such alkylations with the alkene oxides have become important synthetic methods² and they appear to be of quite general application.³

Preliminary tests of reactions between simple olefin sulfides and ethyl malonate, ethyl acetate and ethyl cyanoacetate in the presence of sodium ethoxide indicated that alkylation occurred readily only with the last-named ester. The yield of the condensation product from ethylene sulfide and ethyl cyanoacetate was not large (23%), much of the cyclic sulfide being lost through polymerization. As might have been expected, the yields from propylene sulfide and isobutylene sulfide, which have less tendency toward polymerization, were higher (30 and 60%, respectively). The products of the reactions were solid basic esters which could be converted to hydrochlorides and acetyl derivatives. The presence of a basic group and an ester group in the molecule from ethylene sulfide and the cyanoacetate suffices to establish the structure of the substance as I. The structure is confirmed by



the conversion of the product to γ -thiobutyrolactone⁴ by alkaline hydrolysis and decarboxylation, and to γ,γ' -dithio-bisbutyric acid⁴ by alkaline hydrolysis, decarboxylation and oxidation.

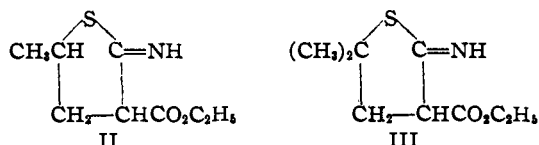
(1) Present address: Calco Chemical Division, American Cyanamid Co., Bound Brook, N. J.

(2) For an application to the synthesis of thiamin see Buchman, *THIS JOURNAL*, **58**, 1803 (1936).

(3) Glickman and Cope, *ibid.*, **67**, 1012 (1945).

(4) Holmberg and Schjånberg, *Arkiv. Kemi, Mineral Geol.*, **14A**, No. 7 (1940) [*C. A.*, **35**, 2113 (1941)].

In the alkylation of ethyl cyanoacetate with propylene oxide and isobutylene oxide the less highly alkylated carbon atom of the oxide becomes attached to the active methylene carbon atom.³ Accordingly, one would expect the products from propylene sulfide and isobutylene sulfide to have the structures II and III. The properties of the



compounds are compatible only with these structures (or their tautomers). Hydrolysis, decarboxylation and oxidation of II gave the known γ,γ' -dithio-bis-valeric acid, and similar treatment of III gave a disulfide which proved identical with γ,γ' -dithio-bis-isocaproic acid synthesized by another method. An independent proof of the orientation of the methyl groups in III resulted from the desulfurization with Raney nickel alloy.^{5,6} The desulfurization was carried out in aqueous alkali under conditions such that hydrolysis first occurred; the product unquestionably was isobutylmalonic acid.

When the condensations of propylene sulfide and isobutylene sulfide with ethyl cyanoacetate were carried out in methanol solution ester interchange occurred and the methyl esters corresponding to II and III were obtained.

Experimental

The Preparation of the Alkene Sulfides.—The ethylene, propylene and isobutylene sulfides used in this investigation were obtained from the oxides through treatment with aqueous potassium thiocyanate as described in an earlier paper.⁷

Condensation of Ethyl Cyanoacetate with Ethylene Sulfide.—No entirely satisfactory procedure was found for this condensation; the best results were obtained by the following method. To a solution prepared by dissolving 2.3 g. of sodium in 250 ml. of absolute ethanol was added 20 g. of ethyl cyanoacetate; this mixture was refluxed while 6 g. of ethylene sulfide was added dropwise over a period of one hour. Refluxing was continued for one hour, after which time the ethanol was distilled. The residue was extracted with ether, leaving large amounts of insoluble, probably polymeric, material. The sirup remaining

(5) Mozingo, Wolf, Harris and Folkers, *THIS JOURNAL*, **65**, 1013 (1943).

(6) Schwenk, Papa, Whitman and Ginsberg, *J. Org. Chem.*, **9**, 1 (1944); **7**, 587 (1942).

(7) Snyder, Stewart and Ziegler, *THIS JOURNAL*, **69**, 2672 (1947).