introduced two cyanoethyl groups on the methylene carbon atom. Cyanoethylation of α-toluenesulfonamide introduced two cyanoethyl groups on the nitrogen atom of the sulfonamido group instead of on the methylene carbon atom.

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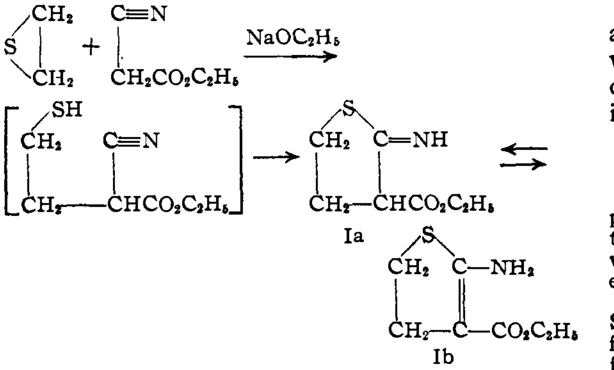
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

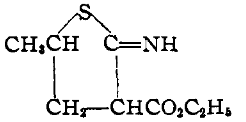
BY H. R. SNYDER AND WYVONA ALEXANDER[1]

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 methods[2] and they appear to be of quite general application.[3]

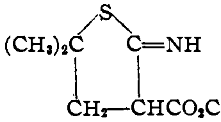
Preliminary tests of reactions between simple olefin sulfides and ethyl malonate, ethyl acetoacetate and ethyl cyanoacetate in the presence of sodium ethoxide indicated that alkylation occurred readily only with the last-named ester. The yield of the condensation product from ethylene sulfide and ethyl 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-thiobutyrolactone[4] by alkaline hydrolysis and decarboxylation, and to γ,γ'-dithio-bisbutyric acid[4] by alkaline hydrolysis, decarboxylation and oxidation.



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



II



III

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

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[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)].

[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).

after evaporation of the ether crystallized very slowly. A solution of this material in about 5 ml. of ethanol was diluted to turbidity with water, chilled and seeded to yield about 4 g. (23%) of 2-imino-3-carbethoxythiophane, melting at 74–78°. Further recrystallization of a sample raised the melting point to 79.5–80°.

Anal. Calcd. for $C_7H_{11}O_2NS$: C, 48.55; H, 6.41. Found: C, 48.59; H, 6.62.

The **hydrochloride** precipitated as a colorless hygroscopic solid when dry hydrogen chloride was passed into an ether solution of the imino ester. The neutralization equivalent of the salt, determined by titration with sodium hydroxide in the presence of phenolphthalein, was 212 (calcd., 210).

The **acetyl derivative** was prepared by heating the imino ester with about 10% excess of acetic anhydride; after recrystallization from ethanol it melted at 73–74°.

Anal. Calcd. for $C_9H_{13}O_3NS$: C, 50.22; H, 6.09. Found: C, 50.58; H, 6.21.

Condensation of Ethyl Cyanoacetate with Propylene Sulfide.—The reaction mixture prepared as described for the ethylene sulfide reaction, except that the propylene sulfide (7.4 g.) was added in one lot, was refluxed one hour and then concentrated to 20 ml. The ethanol solution was decanted from the viscous sirup and poured into ice water. Recrystallization (from aqueous ethanol) of the resulting solid yielded 6 g. (30%) of 2-imino-3-carbethoxy-5-methylthiophane melting at 50–51°.

Anal. Calcd. for $C_8H_{13}O_2NS$: C, 51.31; H, 7.00. Found: C, 51.34; H, 7.06.

From a similar reaction carried out in methanol 2-imino-3-carbomethoxy-5-methylthiophane, m. p. 96–98°, was isolated; the acetyl derivative, m. p. 87–88°, was analyzed.

Anal. Calcd. for $C_9H_{13}O_3NS$: C, 50.22; H, 6.09. Found: C, 50.45; H, 6.28.

Condensation of Ethyl Cyanoacetate with Isobutylene Sulfide.—To a solution prepared from 2.3 g. of sodium and 300 ml. of ethanol was added 15 g. of ethyl cyanoacetate and this mixture was refluxed while 9 g. of isobutylene sulfide was added over a period of one hour. Refluxing was continued for one hour after completion of the addition, and the solution was concentrated to a volume of about 50 ml. The concentrated solution, filtered if not clear, was poured into ice-water to precipitate the product. After recrystallization from aqueous ethanol the 2-imino-3-carbethoxy-5,5-dimethylthiophane, weight 12 g. (60%), melted at 53–54°.

Anal. Calcd. for $C_9H_{15}O_2NS$: C, 53.65; H, 7.51. Found: C, 53.88; H, 7.67.

The **hydrochloride** melted at 122–124° and had a neutralization equivalent of 244 (calcd., 238).

The **acetyl derivative** melted at 69–70°.

Anal. Calcd. for $C_{11}H_{17}O_3NS$: C, 54.30; H, 7.05. Found: C, 54.12; H, 7.26.

2-Imino-3-carbomethoxy-5,5-dimethylthiophane, prepared by the use of methanol instead of ethanol in the above procedure, melted at 137.5–139°.

Anal. Calcd. for $C_8H_{13}O_2NS$: C, 51.31; H, 7.00. Found: C, 51.53; H, 7.19.

Hydrolysis of Condensation Products with Strong Alkali.—Hydrolysis by ten per cent. sodium or potassium hydroxide was brought about by refluxing for an hour. The γ-thiolactone of the corresponding dicarboxylic acid was formed. From 2-imino-3-carbethoxythiophane a liquid acid was obtained which was readily decomposed to γ-thiobutyrolactone (n^{20}_D 1.5241) (lit.[4] n^{20}_D 1.5242). Hydrolysis of 2-imino-3-carbethoxy-5,5-dimethylthiophane yielded a solid acid (2-keto-5,5-dimethylthiophane-3-carboxylic acid) which melted with decomposition at 90–91°.

Anal. Calcd. for $C_7H_{10}O_3S$: C, 48.26; H, 5.79; neutralization equivalent, 174. Found: C, 48.31 H, 6.09; neut. equiv., 174.

Hydrolysis and Oxidation of the Condensation Products.—The products of condensation were hydrolyzed by refluxing for about six hours with an excess of 10% sodium carbonate solution. The hydrolysis mixture was cooled, acidified and extracted with ether. Evaporation of the ether left a residue of a liquid mercapto acid which was readily oxidized to the solid disulfide by the addition of aqueous iodine-potassium iodide solution.

Compound I yielded γ,γ′-dithio-bisbutyric acid, melting at 108–109° (lit.[4] 109–110°). Compound II yielded γ,γ′ dithio-bis-valeric acid melting at 117–118° (lit.[8] 118–121°). The neutral equivalent was determined as 132 (calcd. 133). The liquid mercapto acid obtained by the hydrolysis of compound III had the reactions of a tertiary mercaptan; it distilled at 110° (10 mm.).

Anal. Calcd. for $C_6H_{12}O_2S$: C, 48.62; H, 8.16. Found: C, 49.52 H, 8.30.

The solid acid obtained by oxidation melted at 84–85°.

Anal. Calcd. for $C_{12}H_{22}O_4S_2$: C, 48.95; H, 7.53; neut. equiv., 147. Found: C, 49.26; H, 7.79; neut. equiv., 144.

This acid showed no depression in melting point when mixed with a sample of γ,γ′-dithio-bis-isocaproic acid prepared by the method described below.

Preparation of γ,γ′-Dithio-bis-isocaproic Acid.—Fifteen grams of Δ^{β}-isohexenoic acid, prepared according to Goldberg and Linstead,[9] was mixed with about 15 ml. of liquid hydrogen sulfide and 2 g. of flowers of sulfur in a steel bomb and heated at 180° for ten hours. Addition of hydrogen sulfide to olefinic compounds under these conditions has been shown to follow Markownikoff's rule.[10] The residue, after evaporation of the hydrogen sulfide, was dissolved in 100 ml. of ether and washed several times with sodium bicarbonate solution. No γ-mercaptoisocaproic acid was found in the aqueous extract, presumably because of thiolactone formation. The residue from the removal of the ether was refluxed for sixteen hours with 8 g. of sodium carbonate in 100 ml. of water. The mixture was cooled, acidified and extracted with ether. From the ether extract, 7 g. (44%) of γ-mercaptoisocaproic acid, boiling at 107–109° (10 mm.), was obtained. Oxidation by aqueous iodine yielded γ,γ′-dithio-bis-isocaproic acid, melting at 84–85°.

Isocaproic Acid from Compound III.—A Raney nickel-aluminum alloy reduction of 2-imino-3-carbethoxy-5,5-dimethylthiophane by the procedure described by Papa, Schwenk and Whitman[6] gave isobutylmalonic acid which melted at 105–106.5° (lit.[11a] 108°). No depression of melting point was noted when this compound was mixed with an authentic sample. The neutralization equivalent was determined as 80 (calcd. 80). Bromination yielded α-bromoisobutylmalonic acid which decomposed at 134.5–136° (lit.[11b] 139–141°). Isobutylmalonic acid was readily decarboxylated. The resulting isocaproic acid boiled at 198° (lit.[11c] 199.7° at 732 mm.); the anilide melted at 110–111° (lit.[12] 112°), and the *p*-bromophenacyl ester melted at 76–77° (lit.[13] 77°).

Summary

In the presence of sodium ethoxide ethylene sulfide reacts with ethyl cyanoacetate to give 2-imino-3-carbethoxythiophane, the reaction evidently consisting in alkylation followed by cyclization through interaction of the thiol and cyano groups. Propylene sulfide and isobutylene sulfide react similarly to give 2-imino-3-carbethoxy-5-methylthiophane and 2-imino-3-carbethoxy-5,5-dimethylthiophane, respectively.

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[8] Schjanberg, *Ber.*, **74**, 1751 (1941).

[9] Goldberg and Linstead, *J. Chem. Soc.*, 2343 (1928).

[10] Jones and Reid, This Journal, **60**, 2452 (1938).

[11] Beilstein, "Handbuch der organische Chemie," 4th ed., Julius Springer, Berlin, 1920, (a) Vol. II, p. 683; (b) Vol. II, p. 684; (c) Vol. II, p. 328.

[12] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc.. New York, N. Y.. 1940, 2nd ed., p. 181.

[13] Karrer and Geiger, *Helv. Chim. Acta*, **24**, 289 (1941).