United States Patent Office 2,719,170 Patented Sept. 27, 1955

2,719,170

ALKYL OMEGA-CARBOXYALKYL DISULFIDES AND THEIR LOWER ALKYL ESTERS

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No Drawing. Application July 28, 1954, Serial No. 446,417

7 Claims. (Cl. 260—481)

This invention relates to a new class of organic disulfides and to their preparation. More particularly, this invention relates to a new class of organic disulfides which are biologically active as pesticides.

There is considerable interest in compounds which possess biological activity, particularly as inhibitors for the growth of such pests as bacteria, fungi and insects. Although the mechanism by which various pesticides operate to prevent the growth of such organisms is not precisely known, in the case of organic disulfides it may be that it can be correlated with the antagonism these compounds exhibit to lipoic acid activity. The vitamin-like activity of alpha-lipoic acid as a growth factor in cell metabolism is known in the art ("Present Knowledge of Lipoic Acid," Nutrition Reviews 11, 59 (1953)).

It is an object of this invention to provide a new class of organic disulfides and methods for their preparation. A further object is to provide a new class of organic disulfides which are biologically active as pesticides. A still further object is to provide a new class of organic disulfides which are antagonists to alpha-lipoic acid activity. Other objects will appear hereinafter.

These and other objects of this invention are accomplished by providing a new class of compounds, the alkyl omega-carboxyalkyl disulfides and their lower alkyl esters represented by the formula

R—S—S—R′—COOR″

wherein R is an alkyl radical of 1 to 3 carbon atoms, R′ is an alkylene radical of from 2 to 7 carbon atoms, and R″ is hydrogen or lower alkyl of 1 to 4 carbon atoms. These disulfide compounds in which R and R′ are straight-chain saturated aliphatic hydrocarbon radicals are more active in biological applications, e. g., as pesticides and antagonists for lipoic acid than those in which the alkyl and alkylene structures are branched. These preferred straight-chain alkyl omega-carboxyalkyl disulfides and their lower alkyl esters can be represented by the formula

R—S—S—$(CH_2)_n$—COOR″

wherein R is a straight-chain alkyl radical of 1 to 3 carbons, n is an integer of from 2 to 7, and R″ is hydrogen or lower alkyl of 1 to 4 carbon atoms.

The compounds of this invention can be obtained by irradiating with ultraviolet light a mixture of a dialkyldisulfide and a bis-(carboxyalkyl) disulfide or bis-(carboalkoxyalkyl) disulfide or by reaction of a carboxylic or carboalkoxy containing sulfenyl halide with an alkyl mercaptan or by reaction of a carboxylic or carboalkoxy mercaptan with an alkyl sulfenyl halide.

The following examples in which the parts are by weight show the preparation of representative compounds of this invention.

EXAMPLE I

Methyl 5-carboxypentyl disulfide
[CH_3—S—S—$(CH_2)_5COOH$]

Twenty-two parts of bis-(5-carboxypentyl(sisulfide [$HOOC(CH_2)_5$—S—S—$(CH_2)_5COOH$] and 85 parts of methyl disulfide [CH_3—S—S—CH_3] were charged into a glass reaction tube fitted with a cooling jacket. The mixture was irradiated with ultraviolet light for a period of 23 hours. At the end of this time, the mixture was removed from the tube and diluted with about 120 parts benzene. This solution was shaken with small portions of 0.1 N iodine solution and then with a few drops of sodium bisulfite solution, and finally with aqueous sodium bicarbonate until there was no more evolution of carbon dioxide. The aqueous layer was removed and acidified with concentrated hydrochloric acid. The resulting organic layer was removed by extraction with benzene. After drying the benzene solution over anhydrous magnesium sulfate, the solvent was removed by distillation in vacuo, and the residue was distilled through a short path distilling head. The whole distilling apparatus was wrapped in aluminum foil during the distillation to keep out all light. A total of 17.3 parts of methyl 5-carboxypentyl disulfide was obtained as a colorles, somewhat viscous liquid distilling at 128°/0.12 mm., n_D^{25} 1.5192.

Anal.—Calcd. for $C_7H_{14}O_2S_2$: C, 43.27; H, 7.20; S, 33.00. Found: C, 42.90; H, 7.50; S, 33.36 33.67

EXAMPLE II

Ethyl 5-carboxypentyl disulfide
[C_2H_5—S—S—$(CH_2)_5COOH$]

Twenty-five parts of bis-(5-carboxypentyl) disulfide [$HOOC(CH_2)_5$—S—S—$(CH_2)_5COOH$] and 104 parts of ethyl disulfide [C_2H_5—S—S—C_2H_5] were mixed in a glass reaction tube fitted with a cooling jacket. The reaction and work-up were carried out as described in Example I except that the period of irradiation was only 8 hours. There was obtained 19.8 parts of ethyl 5-carboxypentyl disulfide as a colorless liquid boiling at 142–145°/0.03 mm., n_D^{24} 1.5139.

Anal.—Calcd. for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74; S, 30.78. Found: C, 46.21; H, 7.81; S, 31.11

EXAMPLE III

Methyl 1-methyl-5-carboxypentyl disulfide

$$[CH_3—S—S—\underset{\displaystyle CH_3}{\underset{|}{CH}}—(CH_2)_4COOH]$$

Twenty-five parts of 6-mercaptoenanthic acid

$$[HS—\underset{\displaystyle CH_3}{\underset{|}{CH}}(CH_2)_4COOH)$$

was dissolved in about 100 parts of anhydrous ether and the solution cooled to −10° C. Then 13.2 parts of methylsulfenyl chloride [CH_3SCl] was added dropwise with stirring from a cooled addition funnel. After the addition was completed, the mixture was refluxed for ¼ hour. The ether solution was extracted with excess aqueous sodium bicarbonate. A few parts of 0.1 N iodine solution was added to the aqueous solution until there was a slight excess of iodine. This excess was destroyed by the addition of aqueous sodium bisulfite. After acidification with conc. hydrochloric acid the mixture was then extracted with two portions of benzene. The benzene solution was dried over anhydrous magnesium sulfate and then the solvent was removed by distillation in vacuo. The residue was distilled as in the previous two examples. There was obtaied 7.8 parts of methyl 1-methyl-5-carboxypentyl disulfide [methyl 2-(6-carboxyhexyl) disulfide] boiling at 120–150° C./0.17 mm., $n_D^{24.5}$ 1.5132. The major portion of this product boiled at 120–125° C./0.17 mm.

Anal.—Calcd. for $C_8H_{16}O_2S_2$: S, 30.79. Found: S, 30.39.

EXAMPLE IV

Methyl 2-carbomethoxyethyl disulfide
[CH_3—S—S—$(CH_2)_2COOCH_3$]

A mixture of 26.9 parts of bis-(2-carbomethoxyethyl) disulfide

[$CH_3OOC(CH_2)_2$—S—S—$(CH_2)_2COOCH_3$]

and 127 parts of methyl disulfide [CH_3—S—S—CH_3] was irradiated in the manner described in Example I for a period of 15½ hours. Upon fractional distillation, there was obtained 22.3 parts of methyl 2-carbomethoxyethyl disulfide boiling at 75°/2.5 mm., 81°/3.5 mm., n_D^{25}=1.5106–1.5110.

Anal.—Calc'd. for $C_5H_{10}O_2S_2$: C, 36.12; H, 6.06. Found: C, 36.15; H, 6.06.

The compounds of this invention are monocarboxylic acids and esters which have a disulfide group, —S—S—, with each of the sulfur atoms being attached to aliphatic carbons and are embraced by the general formula R—S—S—R′—COOR″ wherein R is an alkyl radical of 1–3 carbons, R′ is an alkylene radical of 2–7 carbons, preferably of 3 to 7 carbons, and R″ is hydrogen or lower alkyl of 1 to 4 carbon atoms. Of these compounds, those that contain at least 5 carbons and have the carboxy carbon separated from sulfur by three to seven carbons in a straight chain are most preferred.

The compounds of this invention accordingly include methyl 3-carboxypropyl disulfide, methyl 4-carboxybutyl disulfide, ethyl 7-carboxyheptyl disulfide, ethyl 5-carboxy-3-ethylpentyl disulfide, propyl 3-carboxypropyl disulfide, and the butyl ester of ethyl 5-carboxypentyl disulfide.

As shown in Examples I, II and IV, the alkyl omega-carboxyalkyl disulfides and alkyl omega-carboalkoxyalkyl disulfides can be obtained by the light catalyzed reaction of an alkyl disulfide of the formula R—S—S—R where R is an alkyl of 1 to 3 carbons, and preferably a straight-chain alkyl radical of 1 to 3 carbons, with a bis-carboxyalkyl disulfide or bis-carboalkoxyalkyl disulfide of the formula R″OOC—R′—S—S—R′—COOR″ wherein R′ is an alkylene radical of 2 to 7 carbons and R″ is hydrogen or a lower alkyl radical of 1 to 4 carbons. The preferred bis-carboxyalkyl disulfides are those of the formula HOOC—$(CH_2)_n$—S—S—$(CH_2)_n$COOH wherein n is an integer from 3 to 7. The following illustrates the products obtained when alkyl disulfides are reacted with carboxyalkylene disulfides: methyl 3-carboxypropyl disulfide results from the reaction of methyl disulfide with bis-(3-carboxypropyl)disulfide; methyl 4-carboxybutyl disulfide from methyl disulfide and bis-(3-carboxybutyl)disulfide; propyl 3-carboxypropyl disulfide from propyl disulfide and bis-(3-carboxypropyl)disulfide.

The reaction is preferably carried out at 0 to 100° C. in the presence of light, particularly ultraviolet light. The apparatus is generally selected such that the effective irradiation is not absorbed by the walls of the reaction vessel if the light source is external. The light source can be within the reaction vessel, however. Inert solvents can be employed. It is preferred to use as solvents compounds that are substantially transparent to the light employed and inert under the reaction conditions. Suitable solvents are hydrocarbons and aliphatic ethers. The time of irradiation depends upon the intensity. In general, times of from 1 to 50 hours are used.

The alkyl omega-carboxyalkyl disulfides can be purified through formation of their alkali metal salts or through distillation of the acid under reduced pressure or by both of these methods.

In addition to this method of preparation, the compounds of this invention can also be prepared by the reaction of a carboxylic or carboalkoxy containing sulfenyl halide, wherein the halogen is of atomic number 17 to 35, i. e., chlorine or bromine, with an alkyl mercaptan or by reaction of a carboxylic or carboalkoxy mercaptan with an alkyl sulfenyl halide, wherein the halogen is of atomic

number of 17 to 35, as illustrated by the following equations:

$$RSH+XSR'COOR''\rightarrow RSSR'COOR''+HX$$

$$RSX+HSR'COOR''\rightarrow RSSR'COOR''+HX$$

wherein X is chlorine or bromine, R is an alkyl radical, preferably straight-chain, of 1 to 3 carbons, R′ is an alkylene radical, preferably straight-chain, of 2 to 7 carbons, and R″ is hydrogen or lower alkyl of 1 to 4 carbons. For example, a mercaptan such as methyl mercaptan or propyl mercaptan can be reacted with 3-carboxypropylsulfenyl chloride to obtain respectively methyl 3-carboxypropyl disulfide and propyl 3-carboxypropyl disulfide. The latter disulfide can also be obtained by reaction of propylsulfenyl chloride with 3-carboxypropyl mercaptan. Propyl mercaptan can be reacted with 7-carboxyheptylsulfenyl chloride to obtain propyl 7-carboxyheptyl disulfide. This general procedure is illustrated by Example III. The reaction is generally carried out by mixing substantially molar amounts of the two reactants at a temperature within the range of —20 to 50° C. The time required for this reaction is generally less than that required for the light catalyzed reaction.

Derivatives of the carboxylic group, such as salts, esters and amides, can be prepared from the acids and used. Alkali metal salts, such as the potassium and sodium salts, are generally more soluble than the corresponding acid and are of utility in aqueous solutions for pesticidal applications.

The biological activity of the disulfides of this invention may be related to the fact that they are antagonists for alpha-lipoic acid. In certain biological work, it is highly desirable to be able to examine the exact results of a deficiency of such a factor as alpha-lipoic acid in a system of metabolism in which it is known to be involved. This can sometimes be done by the elaborate process of synthesizing a nutrient medium which differs from a known medium only in the absence of the factor under study. Such a process is not only cumbersome and expensive but may be impossible to achieve due to incomplete knowledge of some details of the original medium.

It is greatly preferred to have available a specific antagonist for the factor being examined so that a deficiency of this factor can be induced directly in a system of metabolism by the simple addition of the antagonist. However, such a situation is very rarely achieved due to the disproportionately large biological effects associated with minute and often subtle alterations in chemical constitution, with the resulting increased difficulty of obtaining a compound whose structure is associated with a specific biological function. In the case of alpha-lipoic acid, antagonistic activity can readily be shown by the pyruvate assay test for lipoic acid as described by Gunsalus, Dolin and Struglia (J. Biol. Chem. 194, 849–857 (1952)).

The disulfides of this invention are antagonists to lipoic acid activity. Particularly effective are the straight-chain disulfide compounds included within this invention.

The disulfides of this invention are useful in pesticidal applications. As fungicides, they are effective against early tomato blight. At concentrations of 0.2%, in an inert medium, methyl 5-carboxypentyl disulfide and ethyl 5-carboxypentyl disulfide protected tomato plant foliage to an extent of 98% against the blight as compared with untreated foliage. These compounds were similarly, 88–93%, effective at a concentration of only 0.04% in an inert medium. When a commercial copper fungicide was employed under the same conditions, it offered 83% and 73% protection at 0.2% and 0.04% concentration, respectively.

The disulfides are useful as insecticides. For example, a 2% solution of ethyl 5-carboxypentyl disulfide in acetone is effective in the control of German roach, flour beetle, spotted mite and bean aphid. At a concentration

of 1% in cottonseed oil, methyl and ethyl 5-carboxypentyl disulfide prevented the oxidation of cottonseed oil in the presence of air at 65° C. for a period exceeding 75 days whereas a control became rancid in 8 days. They can also be used as photoinitiation catalysts for the polymerization of polymerizable ethylenically unsaturated monomers.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that this invention is not limited to the specific embodiments thereof except as defined in the appended claims.

I claim:

1. A disulfide selected from the class consisting of alkyl omega-carboxyalkyl disulfides and their lower alkyl esters represented by the formula

$$R—S—S—R'—COOR''$$

wherein R is an alkyl radical of 1 to 3 carbon atoms, R' is an alkylene radical of 2 to 7 carbon atoms, and R'' is selected from the class consisting of hydrogen and lower alkyl radicals of 1 to 4 carbons.

2. An alkyl omega-carboxyalkyl disulfide represented by the formula

$$R—S—S—(CH_2)_n—COOH$$

wherein R is a straight-chain alkyl radical of 1 to 3 carbons and n is an integer from 2 to 7.

3. An alkyl omega-carboalkoxyalkyl disulfied represented by the formula

$$R—S—S—(CH_2)_n—COOR''$$

wherein R is a straight-chain alkyl radical of 1 to 3 carbons, n is an integer from 2 to 7 and R'' is a lower alkyl radical of 1 to 4 carbons.

4. Methyl 5-carboxypentyl disulfide.

5. Ethyl 5-carboxypentyl disulfide.

6. Methyl 2-carbomethoxyethyl disulfide.

7. Methyl 1-methyl-5-carboxypentyl disulfide.

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