United States Patent Office 3,136,689 Patented June 9, 1964

3,136,689

HETEROCYCLIC ESTERS EFFECTIVE AGAINST MICRO-ORGANISMS

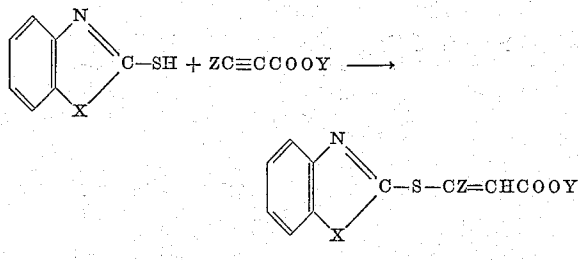
Lee A. Miller, Kirkwood, Mo., assignor to Monsanto Company, St. Louis, Mo., a corporation of Delaware

No Drawing. Original application Dec. 28, 1959, Ser. No. 862,095, now Patent No. 3,068,239, dated Dec. 11, 1962. Divided and this application May 28, 1962, Ser. No. 197,838

7 Claims. (Cl. 167—33)

This invention relates to organic compounds of nitrogen and more particularly provides a class of heterocyclic esters, the method of preparing the same, biological toxicants comprising the new compounds and biological toxicant methods in which the new compounds are employed as the effective ingredients.

According to the invention the valuable heterocyclic compounds are prepared by the reaction of alkyl esters of acetylenic monocarboxylic acids with certain mercapto-substituted polynuclear heterocyclic compounds, substantially according to the scheme:



in which X is selected from the class consisting of —S—, —O—, and —NH—, Y is an alkyl radical of from 1 to 5 carbon atoms, and Z is selected from the class consisting of Y, hydrogen and aryl radicals of from 6 to 10 carbon atoms.

The presently provided compounds are thus alkyl esters of acrylic acid wherein at the 3-position of the acrylic acid there is a substitutent which is a benzothiazolylthio radical, or a benzooxazolylthio radical or a benzimidazolylthio radical and wherein the 3-position may or may not have an alkyl or aryl substituent. Thus when Z of the above formula is hydrogen the compounds are alkyl 3 - (2-benzothiazolylthio)acrylates, or 3-(2-benzoxazolylthio)acrylates or 3 - (2 - benzimidazolylthio)acrylates.

The mercapto-substituted polynuclear heterocyclic compounds which are presently employed are 2-mercaptobenzothiazole, 2-benzoxazolethiol or 2-benzimidazolethiol.

The acetylenic carboxylates which are reacted with the above mercapto-substituted compounds are the alkyl esters of propiolic acid, wherein the alkyl group contains from 1 to 5 carbon atoms and wherein there may be present at the 3-position of the propiolic acid an aliphatic or aromatic substituent. Examples of the presently useful acetylenic esters include the alkyl propiolates such as the methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, amyl, isoamyl, or tert-amyl propiolates; the alkyl tetrolates such as the methyl, ethyl, propyl, butyl or amyl tetrolates; the alkyl 2-pentynoates such as the methyl or butyl 2-pentynoate or the ethyl or isopropyl 4-ethyl 2-pentynoate, the alkyl 2-hexynoates such as methyl or propyl 2-hexynoate; the aryl-propiolates such as ethyl or amyl phenylpropiolate or 2-, 3-, or 4-tolylpropiolate and methyl or butyl α-naphthylpropiolate; the alkyl 2-heptynoates such as ethyl or butyl 2-heptynoate or methyl, ethyl or isobutyl 6-methyl 2-heptynoate; the alkyl 2-octynoates such as methyl or propyl 2-octynoate, etc.

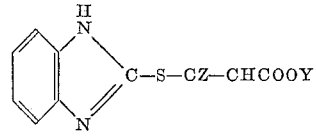
Examples of compounds prepared according to the presently provided process include, methyl, ethyl, or amyl 3-(2-benzothiazolylthio)acrylate; ethyl, propyl or butyl (2-benzoxazolylthio)acrylate; butyl, isoamyl, or methyl 3-(2-benzimidazolylthio)acrylate; methyl or ethyl 3 - (2-benzothiazolylthio)-2-butenoate; methyl or butyl 3 - (2-benzoxazolylthio)-2-butenoate; butyl or amyl 3-(2-benzimidazolylthio)-2-butenoate; methyl or ethyl 3-(2-benzothiazolylthio)-2-pentenoate, butyl or methyl 3-(2-benzoxazolylthio)-2-butenoate, amyl or butyl 3-(2-benzimidazolylthio)-2-pentenoate, methyl or ethyl 3-(2-benzoxazolylthio)2-pentenoate, amyl or isopropyl 3-(2-benzothiazolylthio)-2-hexenoate, ethyl or methyl 3-(2-benzoxazolylthio)2 - hexenoate, amyl or methyl 3-(2-benzimidazolylthio) - 2-hexenoate, methyl or ethyl 3-(2-benzothiazolylthio)-heptenoate, butyl or isopropyl 3-(2-benzoxazolylthio)-2-heptenoate, butyl or propyl 3-(2-benzothiazolylthio)-2-octenoate, methyl or ethyl 3-(2-benzoxazolylthio)-2-octenoate, methyl or ethyl 3-(2-benzothiazolylthio)-3-phenylacrylate, ethyl or isopropyl 3 - (2 - benzoxazolylthio)-3-phenylacrylate, methyl or butyl 3 - (2 - benzothiazolylthio)-3-(2-tolyl)acrylate, ethyl or propyl 3 - (2-benzothiazolylthio)-3-(4-ethylphenyl)acrylate, methyl or ethyl 3-(2-benzothiazolylthio) - 3 - (β-naphthyl) acrylate, ethyl or propyl 3-(2-benzoxazolylthio)-3 - (α - naphthyl)acrylate, butyl or methyl 3 - (2-benzimidazolylthio-3-(β-naphthyl)acrylate, etc.

Reaction of the present mercapto-substituted polynuclear heterocyclic compounds with the acetylenic esters takes place in the presence of basic or acidic catalysts. Basic catalysts useful in the process include organic bases such as pyridine, the quaternary ammonium salts or bases such as trimethylbenzylammonium hydroxide, the alkali and alkali metal hydroxides or basically reacting salts thereof such as sodium, potassium, lithium, calcium, or magnesium hydroxide, carbonate or acetate; alkali or alkali metal alcoholates such as sodium methylate, etc. Examples of useful acidic catalysts are acid reacting metallic salts, such as cuprous or cupric, stannous or stannic, ferrous or ferric acetates, sulfates or chlorides, organic or inorganic acids such as acetic, sulfuric, phosphoric or oxalic acid, etc. While I prefer to use as a catalyst a material which is soluble in the mixture of the two reactants such solubility of the catalyst in the reactants is not a necessary property of the catalyst.

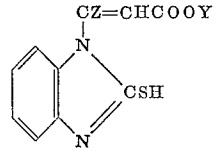
According to the invention the presently provided heterocyclic thioalkenoates are readily prepared by simply mixing the mercapto compound with the acetylenic ester in the presence of either the acidic or basic catalyst, and in the presence of an inert diluent or solvent if desired, and allowing the resulting reaction mixture to stand at ordinary or increased temperatures until formation of the substituted olefinic ester has occurred. Useful solvents or diluents include benzene, xylene, dioxane, dichlorobenzene or hexane. Depending on the nature of the individual reactants and of the catalyst employed, the reaction may occur under varying conditions of temperature and pressure. For optimum yields, it is advantageous to heat the reaction mixture at temperatures of, say, from approximately 60° C. to the refluxing temperature of the reaction mixture.

Inasmuch as molecular equivalents of the mercapto compound and the acetylenic ester are involved in the formation of the presently provided substituted olefinic esters, it is advantageous to employ stoichiometric proportions of the two reactants. If desired, however, any excess of either reactant may be employed since any unreacted material is readily separated from the product.

It has been observed that in the reactions with the 2-benzimidazolethiol, the product is generally a mixture of the isomeric alkyl 3-(2-benzimidazolylthio)alkenoates.

(I) 

and the alkyl 3-[1-(2-mercaptobenzimidazole)]acrylates

(II) 

It will be noted that (II) is formed by addition of the acetylenic ester at the imino radical of the thiol rather than at the mercapto radical. There is a preferential tendency for (I); so that (II) is present in minor amounts. While (II) may be removed from the reaction mixture by customary isolating procedures, e.g. fractional distillation, extraction or fractional crystallization, for most purposes it is unnecessary to provide (I) in a pure form. That it is because the crude (I), i.e., the reaction product which consists essentially of (I), is useful directly for a wide variety of industrial and agricultural purposes.

The presently provided alkyl 3-(2-benzothiazolylthio)-alkenoates or 3-(2-benzoxazolylthio)alkenoates or the 3-2-benzimidazolythio)alkenoates and mixtures of the latter with the isomeric alkyl 3-[1-(2-mercaptobenzimidazole)] acrylates are stable, rather high-boiling viscous liquids or waxy to crystalline solids which are useful as lubricant additives, as vulcanization accelerators for rubbers, as copolymerizing monomers with vinyl compounds in synthetic resin and plastics manufacture, and as biological toxicants, e.g., as herbicides, bacteriostats, fungistats and insecticides. They are particularly valuable as pre-emergent herbicides in that they possess a specificity of effect so that they can be used as de-weeders without adversely affecting the crop. The benzothiazolylthio compounds are noteworthy in that they serve as crab grass eradicants without killing or substantially injuring the lawn grasses.

The invention is further illustrated by, but not limited to, the following examples:

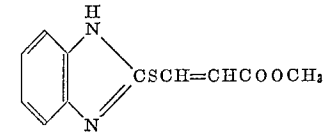
Example 1

A mixture consisting of 8.4 g. (0.1 mole) of methyl propiolate and 50 ml. of benzene was added continuously to a mixture consisting of 16.7 g. (0.1 mole) of 2-mercaptobenzothiazole, 100 ml. of benzene and 1 ml. of 40% methanolic trimethylbenzylammonium methoxide. The reaction mixture, which darkened immediately, was heated at reflux for 12 hours. It was then dissolved in 100 ml. of ether and washed with two 50 ml. portions of saturated aqueous ammonium chloride. Evaporation of the organic solvents gave as residue a brown slurry. This was distilled through a small Vigreux column to give the substantially pure methyl 3-(2-benzothiazolylthio)acrylate, B.P. 171–172° C./0.5 mm., M.P. 68–70° C., which analyzed 52.51% carbon and 3.60% hydrogen as against 52.56% and 3.61%, the respective calculated values.

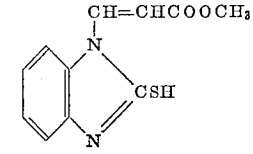
Example 2

To a reaction vessel there was charged 15.0 g. (0.1 mole) of 2-benzimidazolethiol, 9.2 g. (0.11 mole) of methyl propiolate and 100 ml. of benzene. Upon addition of 1 ml. of trimethylbenzylammonium hydroxide catalyst to the mixture, darkening was noted and the temperature of the reaction mixture rose exothermally to about 45° C. In order to assure complete reaction the whole was then refluxed for 12 hours. At the end of that time the black reaction mixture was evaporated to give a dark brown, pasty solid which could not be recrystallized from methanol. Difficulty in crystallization

was due to the presence in the product of the following two isomers:

(I) 

and

(II) 

Analysis of the pasty solid after washing it with three 50 ml. portions of hexane gave 56.62% carbon and 4.36% hydrogen, compared with 56.39% and 4.30%, the respectively calculated value for either isomer, i.e.

$C_{11}H_{10}N_2O_2S$

Infrared analysis showed it to consist essentially of (I), i.e., methyl 3-(2-benzimidazolylthio)acrylate and a minor amount of (II), i.e., methyl 3-[1-(2-mercaptobenzimidazole)]acrylate.

Example 3

When a catalytic quantity (1 ml.) of trimethylbenzylammonium hydroxide was added to a mixture consisting of 15.1 g. (0.1 mole) of 2-benzoxazolethiol, 9.2 g. (0.11 mole) of methyl propiolate and 100 ml. of benzene, the mixture blackened and spontaneously warmed to 45° C. The whole was then heated at reflux for 12 hours. Upon evaporation of the solvent there was obtained a black oil which solidified upon standing. Repeated recrystallization from methanol gave the substantially pure methyl 3-(2-benzoxazolylthio)acrylate, buff needles, M.P. 93.5–95.0° C., which analyzed 56.14% carbon and 4.10% hydrogen compared with 56.16% and 3.86% the respective calculated values for $C_{11}H_9NO_3S$. Infrared analysis showed the presence of the —C=N structure at 1590 cm.$^{-1}$, the presence of C—O— ester structure at 1230 and 1220 cm.$^{-1}$, and the presence of 4 adjacent protons at 755 and 750 cm.$^{-1}$.

Example 4

This example shows evaluation of the methyl 3-(2-benzothiazolylthio)acrylate of Example 1 and the methyl 3-(2-benzoxazolylthio)acrylate of Example 3 against mosquito larvae. The following procedure was employed:

Culture tubes (rimless, 25 x 200 mm.) were respectively filled with 70 cc. of distilled water. Acetone solutions (1.0%) of the test compounds were then respectively pipetted into the culture tubes in a quantity calculated to give a 10 p.p.m. concentration of either the compound of Example 1 or the compound of Example 3 in each of said tubes. Each tube was rubber-stoppered and shaken vigorously to facilitate complete mixing. To each tube of the resulting test solutions there was then added approximately 25 yellow fever mosquito (*Aedes aegypti* Linne) larvae, and the test solutions, with their larvae content, were allowed to stand for 24 hours at room temperature. Observation of the tubes of larvae at the end of that time showed 100% kill of larvae in the tubes containing either the compound of Example 1 or the compound of Example 3.

Example 5

This example describes testing of the methyl 3-(2-benzothiazolylthio)acrylate of Example 1 against *Monilinia fructicola,* the causal agent of brown rot of stone fruits. The following procedure was used:

A spore suspension of the organism was prepared from a 7 day old culture thereof on a slant of an agar culture

medium by removing said spores with a rubber policeman from the slant and suspending them in distilled water. The concentration of spores was adjusted to about 40,000 per ml. of water. The test compound was added to water in a concentration calculated to give 50 parts of the compound per million parts of water. An 0.02 ml. aliquot of each of the resulting solutions was pipetted respectively into duplicate wells of a depressed glass slide and allowed to evaporate to dryness. Then an 0.1 ml. aliquot of the above spore suspension was pipetted into each well. The concentration of the test compound in each well was thus lowered to 10 parts per million parts of diluent. The slides were then incubated in a moist chamber for 18 hours at 25° C. Inspection of the slides at the end of this time showed no germination of spores in the presence of the 10 p.p.m. concentration of the test compound, i.e., on the slides in which said methyl 3-(2-benzothiazolylthio)acrylate had been deposited; whereas there was profuse spore germination on "controls," i.e., on slides in which none of said compound had been deposited.

Example 6

This example shows testing of the methyl 3-(2-benzothiazolylthio)acrylate of Example 1 against the fungus *Aspergillus niger*. The following procedure was used:

An inoculum preparation of *Aspergillus niger* SN–111 was prepared by adding 10 ml. of sterile distilled water to a 7-day old, Sabourard's dextrose agar slant culture thereof and dislodging the spores into the water with a transfer needle.

Culture media was prepared by respectively adding 18 ml. of Sabourard's dextrose agar to 18 x 150 mm. straight side test tubes, capping with metal culture tube caps, and sterilizing in an autoclave for fifteen minutes at 121° C.

A stock solution of the test compound was prepared by respectively dissolving 100 mg. of said test compound in 10 ml. of acetone: a 1% acetone solution of the compound was thus obtained.

Using a sterile 5 ml. pipette, 2 ml. of said 1% solution was transferred to a tube of melted, sterile culture media prepared as described above. A dilution of 1 part of test compound per 1,000 parts of agar resulted. This was further diluted with additional sterile agar to give a 100 p.p.m. concentration of the test compound in the agar. The thus-diluted agar was then poured into sterile Petri dishes and allowed to harden.

The four plates of agar were then respectively inoculated with one drop of the above-described inoculum preparation. Examination of the plates after a five-day incubation period showed no growth of the *Aspergillus niger* at the 100 p.p.m. concentration of the methyl 3-(2-benzothiazolylthio)acrylate.

Example 7

This example describes testing of the methyl 3-(2-benzothiazolylthio)acrylate of Example 1 against the bacteria *Staphylococcus aureus* and *Salmonella typhosa*. The following testing procedure was employed:

A 1.0% acetone solution of the test compound was prepared and added to sterile, melted nutrient agar to give an 0.1% (1,000 p.p.m.) concentration of the test compound in the agar. The 0.1% agar solution of the test compound was then poured into a Petri dish and allowed to harden. This plate was inoculated with both the *Staphylococcus aureus* and the *Salmonella typhosa*, and incubated for two days at 37° C. At the end of that time, inspection of the plate showed no growth of either organism on the plate which contained the 0.1% concentration of the test compound.

The present compositions are characterized by a high degree of efficacy in that even in very low concentration, e.g., in a concentration of as low as one p.p.m. they may be extremely effective against bacteria and fungi. Biological toxicant compositions containing the present

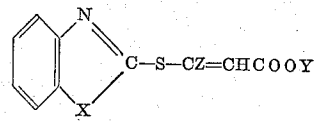
compounds are advantageously obtained by first preparing a solution thereof in an organic solvent and then adding the resulting solution to water containing an emulsifying agent to form an oil-in-water emulsion. Because of their effectiveness, they are present in the toxicant compositions in only very small concentrations, for example in concentrations of from 0.0001 percent to 1.0 percent by weight of the total weight of the emulsion. Emulsifying agents which may be employed are those customarily used in the art for the preparation of oil-in-water emulsions. Examples of emulsifying agents which may be used include alkylbenzenesulfonates, long chained polyalkylene glycols, long chained alkylsulfosuccinates, etc.

While the present compounds are most advantageously employed as biological toxicants by incorporating them into an emulsion as herein described, they may also be incorporated into solid carriers such as clay, talc, pumice or bentonite to give compositions which may be applied either to infested areas or to locale which may be subject to infestation. They may also be dissolved in liquefied gases such as the fluorochloroethanes or methyl chloride and applied from aerosol bombs containing the solution.

This application is a division of my copending application, Serial No. 862,095, filed December 28, 1959, now U.S. Patent No. 3,068,239, December 11, 1962.

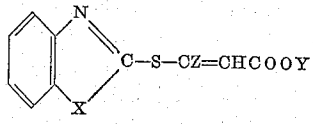
What I claim is:

1. The method of combatting micro-organisms which comprises exposing said micro-organisms to a growth-inhibiting quantity of a compound of the formula



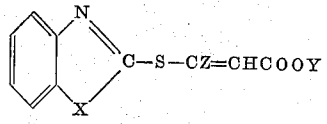
in which X is selected from the class consisting of —S—, —O— and —NH—, in which Y is alkyl of from 1 to 5 carbon atoms, and Z is selected from the class consisting of Y, hydrogen and hydrocarbon aryl of from 6 to 10 carbon atoms.

2. The method of combatting micro-organisms which comprises exposing said micro-organisms to a growth-inhibiting quantity of a compound of the formula



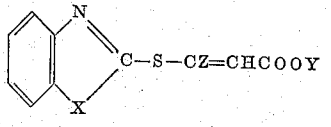
in which Y is alkyl of from 1 to 5 carbon atoms, and Z is selected from the class consisting of Y, hydrogen and hydrocarbon aryl of from 6 to 10 carbon atoms.

3. The method of combatting insect larvae which comprises applying to their habitat a composition containing as the essential larvicidal component a compound of the formula



in which X is selected from the class consisting of —S—, —O— and —NH—, in which Y is alkyl of from 1 to 5 carbon atoms, and Z is selected from the class consisting of Y, hydrogen and hydrocarbon aryl of from 6 to 10 carbon atoms.

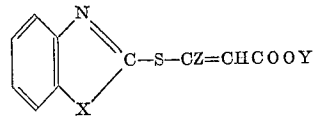
4. The method of inhibiting fungus growth which comprises exposing the fungi to a growth-inhibiting quantity of a compound of the formula



in which X is selected from the class consisting of —S—, —O—, and —NH—, in which Y is alkyl of from 1 to 5 carbon atoms, and Z is selected from the class consisting of Y, hydrogen and hydrocarbon aryl of from 6 to 10 carbon atoms.

5. The method of claim 4 wherein the compound is an alkyl 3-(2-benzothiazolylthio)acrylate having from 1 to 5 carbon atoms in the alkyl group.

6. The method of inhibiting growth of bacteria which comprises exposing the bacteria to a growth-inhibiting quantity of a compound of the formula



in which X is selected from the class consisting of —S—, —O—, and —NH—, in which Y is alkyl of from 1 to 5

carbon atoms, and Z is selected from the class consisting of Y, hydrogen and hydrocarbon aryl of from 6 to 10 carbon atoms.

7. The method of claim 6 wherein the compound is an alkyl 3-(2-benzothiazolylthio)acrylate having from 1 to 5 carbon atoms in the alkyl group.

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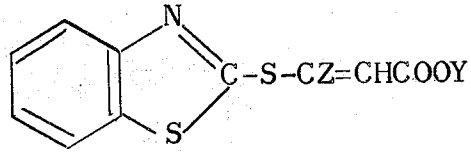
CERTIFICATE OF CORRECTION

Patent No. 3,136,689 June 9, 1964

Lee A. Miller

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 6, lines 44 to 49, the formula should appear as shown below instead of as in the patent:



Signed and sealed this 3rd day of November 1964.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents