1224661

PATENT SPECIFICATION (11) 1224661

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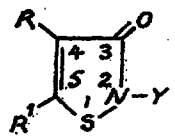
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(54) PREPARATION OF ISOTHIAZOLONE DERIVATIVES

(71) We, ROHM AND HAAS COMPANY, a corporation organized under the laws of the State of Delaware, United States of America, of Independence Mall West, Philadelphia, Pennsylvania 19105, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

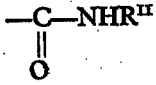
This invention is concerned with a novel process for the preparation of substituted 3-isothiazolones and 3-hydroxyisothiazoles which have biocidal activity as disclosed in copending Applications Nos. 11480/68 and 11481/68 (Serial Nos. 1224662 and 1224663) filed on even date herewith.

More particularly, this invention is concerned with a process for the preparation of compounds of the formula

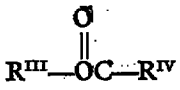


(I)

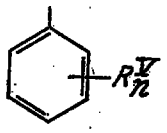
wherein R and R^I are hydrogen, halogen or C_1—C_4 alkyl; and Y is hydrogen, (C_1—C_{18})-alkyl, (C_3—C_8)-cycloalkyl aralkyl of up to 10 carbon atoms, aryl, halogen or (C_1—C_4)-alkyl substituted aryl, dialkylaminoalkyl, in which each alkyl group contains up to 4 carbon atoms, alkylacyl of 2 to 8 carbon atoms, sulfonyl, cyano, or a carbamoyl group having the structure



where R^{II} is (C_1—C_{18})-alkyl, (C_1—C_4)-alkyl sulfonyl, arylsulfonyl, halogen or (C_1—C_4)-alkyl substituted arylsulfonyl, carbalkoxyalkyl of the structure



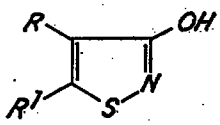
wherein R^{III} is (C_1—C_4)-alkyl and R^{IV} is a (C_1—C_4)-alkylene group; or R^{II} is an aryl group of the formula



wherein R^V is (C_1—C_4)-alkyl, halogen, nitro or (C_1—C_4)-alkoxy and n is a number from 0 to 3.

As regards the various (C_1—C_4)-alkyl containing substituents these are typically methyl, ethyl, propyl, isopropyl or butyl.

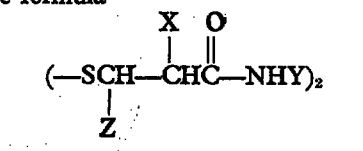
It should be noted that Formula I is a chemically correct designation for all of the compounds prepared by the novel process constituting this invention. However, due to their tautomeric nature, the following formula is somewhat more accurate in those situations where Y represents hydrogen.



(II)

Such compounds, that is, those represented by Formula II are referred to generically as "3-hydroxyisothiazoles", (hereinafter referred to at time as "isothiazoles") whereas all the other compounds encompassed within Formula I are more properly termed "3-isothiazolones" (hereinafter referred to at times as "isothiazolones"). Of course, the latter term may in part be utilized to designate any of the compounds within the scope of Formula I.

In accordance with the invention, the isothiazolones are prepared by the cyclization of a disulfide-amide which may be represented by the formula



(III)

wherein X and Z are hydrogen or (C_1—C_4)-alkyl and Y is as previously defined. Such cyclization is accomplished by reacting the disulfide-amide with a halogenating agent. Typical halogenating agents include chlorine, bromine, sulfuryl chloride, sulfuryl bromide, N-chlorosuccinamide and N - bromosuccinamide. Chlorine and sulfuryl chloride are the preferred halogenating agents.

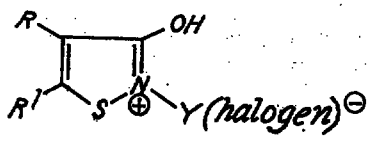
Cyclization is preferably carried out using at least 3 mole equivalents of halogenating agent, or to be more specific halogen. By providing an excess of halogenating agent, the isothiazolone may be halogenated at the 4 and/or 5 positions of Formula I. Where 5 mole equivalents of halogenating agent are available, monohalogenation will take place. For di-halogenation, 7 mole equivalents of halogenating agent are required.

Preparation of isothiazolones having the 4 and 5 position substituted with different halogens is achieved by the halogenation of an isothiazolone already halogenated at one of the two positions in question. For example, if a 4 - bromo - 5 - chloro - 3 - isothiazolone is desired, then such can be obtained by bromination of a 5-chloro-3-isothiazolone or the chlorination of a 4-bromo-3-isothiazolone. The starting isothiazolone is, of course, prepared by the cyclization of a disulfide-amide as described herein. Procedures and variations therein for what might be termed "secondary halogenation" would be evident to one skilled in the art.

Temperature is not critical to the reaction process; that is, the cyclization will proceed at any temperature. Generally and preferably, it will be carried out in the range of 0° to 100° C.

The reaction is best carried out in an inert non-aqueous solvent, such as benzene, toluene, xylene, ethyl acetate or ethylene dichloride.

Isothiazonium salts can be formed along with the isothiazolones during the cyclization process when Y in Formula III is hydrogen, alkyl of 1 to 18 carbon atoms or aralkyl of up to 10 carbon atoms. Such salts have the following structure:



(IV)

Where desired or necessary, an acid scavenger can be incorporated in the reaction medium so as to avoid isothiazolium salt formation. Typical scavengers which might be so utilized would include t-amine bases, such as for example, pyridine and triethylamine. It should be noted at this point that the isothiazolium salts can also be transformed or neutralized to free isothiazolones by being contacted with water or weak organic bases.

The disulfide-amides which are cyclized to form the isothiazolones are known and may be prepared in several ways. Typically, an alpha or beta mono-or di-substituted acrylate or acrylic acid is reacted with thiol acetic acid. Upon completion of the reaction, the product is hydrolyzed so as to obtain a beta-mercapto propionic acid, which is, in turn, oxidized to the disulfide acid. This material is then converted to a diacid chloride-disulfide, and in turn, treated with ammonia or substituted ammonia derivatives, such as alkyl amine, aniline, amide, cyanamide, sulfonamide or urea.

The above-described cyclization process is illustrated by the following examples.

Example 1

Preparation of 3-hydroxyisothiazole and 5-chloro-3-hydroxyisothiazole

In a one litre, 3-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel there was mixed 500 ml. of ethylene dichloride and 20.8 g (0.1 mole) of dithiodipropionamide. This mixture was stirred at 10—15° C. and 42.5 g. (0.306 mole) of sulfuryl chloride was added dropwise over 2 hours. On completion of the addition, the reaction slurry was allowed to warm to 25—30° C. and stirred overnight to assure complete reaction. The reaction slurry was then filtered, and the precipitate was digested in 150 ml. of hot water. The aqueous solution was filtered to remove some insoluble material and then cooled in ice to yield after filtration and drying 4.0 g. of 5 - chloro - 3 - hydroxyisothiazole as a tan crystalline solid, m.p. 95—96° C. The aqueous filtrate was then continuously extracted with ether; the ether extract was dried over magnesium sulfate and evaporated to leave 11.1 g. of 3-hydroxyisothiazole which crystallized upon cooling to a white crystalline solid, m.p. 75—76° C. from benzene-hexane.

Example 2

Preparation of 2 - methyl - 3 - isothiazolone and 5 - chloro - 2 - methyl - 3 - isothiazolone

To an ethylene dichloride (1 liter) slurry of dithio - N,N' - dimethyldipropionamide, 70.9 g. (0.3 mole), there was added at 10—15° C. over 1.5 hour 121.5 g. (0.9 mole) of sulfuryl chloride. After addition, the reaction slurry was allowed to warm to 20—25° C. and stirred overnight to assure completion of

the reaction. The slurry was then filtered to give 37.1 g. of 2 - methyl - 3 - isothiazolone hydrochloride, which could be converted to the free 3-isothiazolone by continuous ether extraction from water. The ethylenedichloride filtrate, upon evaporation to approximately one-half volume, yielded an additional quantity (30.5 g.) of less pure hydrochloride. Complete evaporation of the ethylene dichloride filtrate gave 24.7 g. of oily residue which upon sublimation at 0.1 mm. (40—60° C.) gave 11.5 g. of 5 - chloro - 2 - methyl - 3 - isothiazolone, m.p. 44—47° C.

Example 3

Preparation of 2 - (3,4 - dichlorophenyl) - 4 - methyl - 3 - isothiazolone

Dithio - (3',4' - dichloro) - diisobutyranilide, 12.8 g. (0.0234 mole), was slurried in 250 ml. of ethylene dichloride and a solution of 9.5 g. (0.0702 mole) of sulfuryl chloride in 25 ml. of ethylene dichloride was added dropwise at 25—30° C. over one hour. The slurry was stirred overnight to ensure completion of the reaction and then filtered to give 8.6 g. of gray 2 - (3,4 - dichlorophenyl) - 4 - methyl - 3 - isothiazolone, m.p. 160—161° C. The product was crystallized from ethyl acetate to give a m.p. of 161—163° C.

Example 4

Preparation of 2 - (N - ethylcarbamoyl) - 3 - isothiazolone

In 2500 ml. of ethylene dichloride there was slurried 210.3 g. (0.60 mole) of dithio - N,N' - bis - (ethylcarbamoyl) - dipropionamide at 10—15° C. Nitrogen was bubbled through the slurry to remove the hydrogen chloride to be formed in the reaction, and 243 g. (1.80 mole) of sulfuryl chloride was added dropwise over two hours. The slurry was then allowed to warm to 25—30° C. and stirred overnight to assure complete reaction. After this time the ethylene dichloride was stripped from the reaction solution to leave a yellow oil residue which was crystallized from benzene/ligroin (90—120° C.) to give 142 g. of cream-coloured 2 - (N - ethylcarbamoyl) - 3 - isothiazolone, m.p. 97—101° C.

Example 5

Preparation of 4 - methyl - 3 - hydroxyisothiazole and 5 - chloro - 4 - methyl - 3 - hydroxyisothiazole

The disulfide-amide, dithiodiisobutyramide, 11.8 g. (0.05 mole), was slurried in 200 ml. of ethylene dichloride. A solution of 21.3 g. (0.15 mole) of sulfuryl chloride in 30 ml. of ethylene dichloride was added slowly at 20—25° C. After addition the slurry was allowed to stir overnight to assure complete reaction. Filtration then gave 9.15 g. of a mixture of solid isothiazolonium chlorides, which are heated in 100 ml. of water, and filtered to yield, after drying, 2.85 g. of 5 - chloro - 4 - methyl - 3 - hydroxyisothiazole, m.p. 122° C. Subsequent cooling of the aqueous solution in ice yielded 2.4 g. of solid 4 - methyl - 3 - hydroxyisothiazole, m.p. 100—105° C.

Example 6

Preparation of 4 - bromo - 5 - chloro - 3 - hydroxyisothiazole

To a solution of 100 ml. of ethyl acetate and 6.8 g. (0.05 mole) of 5 - chloro - 3 - hydroxyisothiazole prepared in accordance with Example 1, there was added at 0° C. a solution of 8 g. (0.05 mole) of bromine in 25 ml. of ethyl acetate. After addition the red reaction solution was allowed to warm to room temperature, and after 1 hour, the solvent was removed under reduced pressure to leave 13.7 g. of dark orange solid. Treatment of this solid with water left, after drying, 8.7 g. of 4 - bromo - 5 - chloro - 3 - hydroxyisothiazole, m.p. 145—147° C. from ethyl acetate.

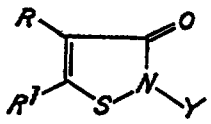
Example 7

Preparation of 4,5 - dichloro - 3 - hydroxyisothiazole

To an ethyl acetate (100 ml.) solution of 5.1 g. (0.050 mole) of 3 - hydroxyisothiazole prepared in accordance with Example 1, there was added 6.75 g. (0.050 mole) of sulfuryl chloride over 20 minutes at 60° C. A white precipitate formed at once. After stirring for 2 hours, the reaction mixture was allowed to warm to room temperature. The reaction mixture was filtered from a small amount of solid material, and the solvent was removed under reduced pressure. In this manner, there was obtained 3.7 g. of gummy solid, which by treatment with water and drying gave 3.2 g. of 4,5 - dichloro - 3 - hydroxy - isothiazole, m.p. 151—154° C. after crystallization from benzene-ethanol.

WHAT WE CLAIM IS:—

1. A process for preparing a compound of Formula I below, or a tautomer thereof,



(I)

wherein Y is hydrogen, (C_1—C_{18})-alkyl, (C_3—C_6) - cycloalkyl, aralkyl of up to 10 carbon atoms, aryl, halogen or (C_1—C_4)-alkyl substituted aryl, dialkylaminoalkyl in which each alkyl group contains up to 4 carbon atoms, (C_2—C_8)-alkylacyl, sulfonyl, cyano, or a carbamoyl group of the formula



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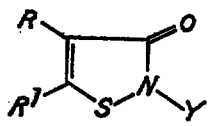
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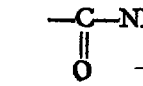
WHAT WE CLAIM IS:—

1. A process for preparing a compound of Formula I below, or a tautomer thereof,

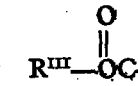


(I)

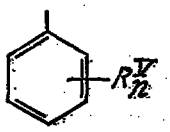
wherein Y is hydrogen, (C_1—C_{18})-alkyl, (C_3—C_6) - cycloalkyl, aralkyl of up to 10 carbon atoms, aryl, halogen or (C_1—C_4)-alkyl substituted aryl, dialkylaminoalkyl in which each alkyl group contains up to 4 carbon atoms, (C_2—C_8)-alkylacyl, sulfonyl, cyano, or a carbamoyl group of the formula



wherein R^{II} is (C_1—C_{18})-alkyl, (C_1—C_4)-alkylsulfonyl, arylsulfonyl, halogen or (C_1—C_4)-alkyl substituted arylsulfonyl, carbalkoxyalkyl of the formula

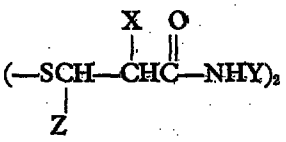


wherein R^{III} is (C_1—C_4)-alkyl and R^{IV} is a (C_1—C_4)-alkylene group; or R^{II} is an aryl group of the formula



wherein R^V is (C_1—C_4)-alkyl, halogen, nitro or (C_1—C_4)-alkoxy and n is a number from 0 to 3; and

R and R^I are hydrogen, halogen or (C_1—C_4)-alkyl; said process comprising cyclizing a disulfide-amide by reacting it with a halogenating agent, said disulfide-amide being of the formula



wherein X and Z are hydrogen or (C_1—C_4)-alkyl, and Y is as defined above.

2. A process according to Claim 1 wherein Y is a (C_1—C_{18})-alkyl, (C_3—C_6) - cycloalkyl, aralkyl of up to 10 carbon atoms, aryl, halogen or (C_1—C_4) - alkyl substituted aryl, dialkyl-aminoalkyl in which each alkyl group contains up to 4 carbon atoms, (C_2—C_8)-alkylacyl, sulfonyl or cyano.

3. A process according to Claim 1 wherein Y is a carbamoyl group as defined in Claim 1.

4. A process according to Claim 1 wherein Y is (C_1—C_{18})-alkyl.

5. A process according to Claim 1 wherein the halogenating agent is present to the extent of at least 3 mole equivalents.

6. A process according to Claim 1, wherein the halogenating agent is present to the extent of at least 5 mole equivalents.

7. A process according to Claim 6 wherein the compound resultant therefrom is subsequently halogenated with a different halogen than that utilized in preparing said compound.

8. A proces according to Claim 1 wherein the halogenating agent is present to the extent of at least 7 mole equivalents.

9. A process according to any one of the preceding claims wherein the cyclization reaction is carried out in an inert non-aqueous solvent.

10. A process according to any one of the preceding claims wherein the halogenating agent in the cyclization reaction is chlorine, bromine, sulfuryl chloride, sulfuryl bromide, N-chloro-succinamide or N-bromo-succinamide.

11. A process according to any one of the preceding claims wherein the cyclization reaction is carried out in the presence of an acid scavenger.

12. A process according to Claim 1 carried out substantially as hereinbefore described with reference to any one of the foregoing Examples.

13. A substituted 3-isothiazolone whenever prepared by a process according to any of the preceding claims.

For the Applicants,
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