

1224 662

PATENT SPECIFICATION

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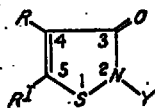


(54) 3-ISOTHIAZOLONES

- (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:—

- 10 This invention is concerned with novel substituted 3-isothiazolones, salts thereof, their preparation, and biocidal compositions containing them.

- 15 The novel 3-isothiazolones (hereinafter referred to at times as "isothiazolones") provided by the invention may be represented by the formula

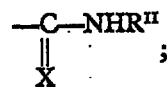


(I)

- 20 wherein Y is C₁-C₁₈ preferably C₃-C₁₈, alkyl; C₃-C₆ cycloalkyl; aralkyl of up to 10 carbon atoms substituted with halogen, C₁-C₄ alkyl, or C₁-C₄ alkoxy; aryl; aryl substituted with
 25 halogen, nitro, C₁-C₄ alkyl, alkylacylamino in which the alkyl group contains up to 4 carbon atoms, carbalkoxy in which the alkyl group contains up to 4 carbon atoms or sulfamoyl; C₁-C₄ hydroxyalkyl; C₁-C₄ haloalkyl; dialkylaminoalkyl in which each alkyl

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group contains up to 4 carbon atoms; or a carbamoyl group of the formula



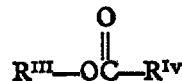
R and R^I each represent hydrogen, halogen or C₁-C₄ alkyl when Y is other than the carbamoyl group provided that both R and R^I are not hydrogen when Y is methyl or ethyl;

R is hydrogen, C₁-C₄ alkyl, halogen or cyano when Y is the carbamoyl group;

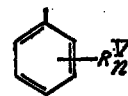
R^I is hydrogen, halogen, C₁-C₄ alkyl or C₂-C₄ haloalkyl when R is hydrogen, C₁-C₄ alkyl or halogen;

R^I is C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl or C₁-C₄ alkylsulfonyl when R is cyano;

X is oxygen or sulfur; and R^{II} is C₁-C₁₈ alkyl, C₁-C₄ alkylsulfonyl, arylsulfonyl, halogen- or C₁-C₄ alkyl-substituted arylsulfonyl, or carbalkoxyalkyl of the formula:



wherein R^{III} is C₁-C₄ alkyl and R^{IV} is an alkylene group of 1 to 4 carbon atoms; or R^{II} is an aryl group of the formula



wherein R^V is C₁-C₄ alkyl, halogen, nitro or C₁-C₄ alkoxy and n is 0, 1, 2 or 3.

As regards the various C_1 — C_4 alkyl-containing substituents mentioned above these are typically methyl, ethyl, propyl, isopropyl, butyl and *t*-butyl.

- 5 Some of the isothiazolones described above can form novel salts which also exhibit biocidal activity. Such salt forming compounds fall within the scope of Formula I wherein Y is alkyl of 1 to 18 carbon atoms; cycloalkyl of 3 to 6 carbon atoms; aralkyl of up to 10 carbon atoms; halogen, C_1 — C_4 alkyl, or C_1 — C_4 alkoxy substituted aralkyl of up to 10 carbon atoms; aryl; halogen, nitro, C_1 — C_4 alkyl, alkylacylamino in which the alkyl group contains up to 4 carbon atoms, carbalkoxy in which the alkoxy group contains up to 4 carbon atoms or sulfamoyl substituted aryl; C_1 — C_4 hydroxyalkyl; C_1 — C_4 haloalkyl; or dialkylaminoalkyl in which each alkyl group contains from 1—4 carbon atoms; and R and R' are selected from the group consisting of hydrogen, C_1 — C_4 alkyl, or halogen.

- 20 Preparation of these biocidally active salts is readily achieved by reacting the above designated 3-isothiazolones with a strong acid. Typical strong acids include hydrochloric, nitric, sulfuric and hydrobromic. Separation of the acid salts from the reaction medium is accomplished by any convenient means known to one skilled in the art.

- 30 Representative Y substituents include methyl, ethyl, propyl, isopropyl, butyl, octyl, decyl, pentadecyl, octadecyl, cyclopropyl, cyclohexyl, benzyl, 3,4-dichlorobenzyl, 4-methoxybenzyl, 3,4-dichlorophenyl, hydroxymethyl, chloromethyl, chloropropyl, diethylaminoethyl, carbamoyl, thiocarbamoyl, methylcarbamoyl, propylcarbamoyl, *t*-octylcarbamoyl, phenylcarbamoyl, ethoxyphenylcarbamoyl, nitrophenylcarbamoyl, carbethoxymethylcarbamoyl, methylthiocarbamoyl and ethylthiocarbamoyl.

- Representative R substituents include bromo, chloro, iodo, cyano, methyl, ethyl, propyl, isopropyl, butyl and *t*-butyl.

- 45 Representative R' substituents are chloro, bromo, iodo, methyl, ethyl, propyl, butyl, chloromethyl, chloropropyl, bromomethyl, bromoethyl, bromopropyl, bromobutyl, methylthio, propylthio, methylsulfinyl, ethylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, and butylsulfonyl.

- Representative R'' substituents are methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, pentyl, isopentyl, hexyl, cyclohexyl, heptyl, octyl, *t*-octyl, nonyl, decyl, dodecyl, octadecyl, phenyl, 2-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 2,4-dimethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3,4-dibromophenyl, 2-bromophenyl, 3,4,5-trichlorophenyl, 4-nitrophenyl, 2,4-dinitrophenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3,5-dimethoxyphenyl, methylsulfonyl, ethylsulfonyl, 4-chlorophenylsulfonyl, 4-methylphenylsul-

fonyl, 3,5-dimethylphenylsulfonyl, carbethoxymethyl and carbethoxyethyl.

Typical compounds within the scope of Formula I include the following:

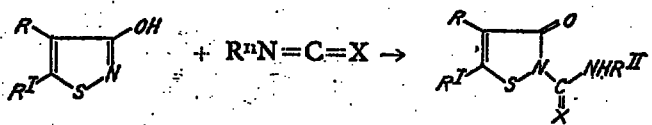
2 - propyl - 3 - isothiazolone,	70	5
2 - butyl - 3 - isothiazolone,		
2 - <i>t</i> - octyl - 3 - isothiazolone,		
2 - decyl - 3 - isothiazolone,		
2 - octyldecyl - 3 - isothiazolone,		
2 - cyclohexyl - 3 - isothiazolone,	75	10
4 - chloro - 2 - methyl - 3 - isothiazolone,		
4 - bromo - 2 - methyl - 3 - isothiazolone,		
5 - chloro - 2 - methyl - 3 - isothiazolone,		
5 - chloro - 2,4 - dimethyl - 3 - isothiazolone,	80	15
4 - bromo - 5 - chloro - 2 - methyl - 3 - isothiazolone,		
4 - bromo - 2 - cyclohexyl - 3 - isothiazolone,		
4,5 - dichloro - 2 - ethyl - 3 - isothiazolone,	85	20
4 - methyl - 2 - octyl - 3 - isothiazolone,		
4,5 - dimethyl - 2 - octyl - 3 - isothiazolone,		
2 - benzyl - 3 - isothiazolone,	90	25
2 - benzyl - 4,5 - dichloro - 3 - isothiazolone,		
2 - benzyl - 5 - chloro - 3 - isothiazolone,		
2 - (2',4' - dichlorobenzyl) - 3 - isothiazolone,	95	30
2 - (4' - methoxybenzyl) - 3 - isothiazolone,		
2 - (4' - ethylbenzyl) - 3 - isothiazolone,		
2 - (3',4' - dichlorophenyl) - 3 - isothiazolone,	100	35
2 - (3',4' - dichlorophenyl) - 4 - methyl - 3 - isothiazolone,		
2 - (4' - methylphenyl) - 3 - isothiazolone,		
2 - hydroxymethyl - 3 - isothiazolone,		
2 - (β - diethylaminoethyl) - 3 - isothiazolone,	105	40
2 - (N - methylcarbamoyl) - 3 - isothiazolone,		
2 - (N - ethylcarbamoyl) - 3 - isothiazolone,		
2 - (N - <i>n</i> - propylcarbamoyl) - 3 - isothiazolone,	110	45
2 - (N - <i>i</i> - propylcarbamoyl) - 3 - isothiazolone,		
2 - (N - butylcarbamoyl) - 3 - isothiazolone,		
2 - (N - hexylcarbamoyl) - 3 - isothiazolone,	115	50
2 - (N - <i>t</i> - octylcarbamoyl) - 3 - isothiazolone,		
2 - (N - decylcarbamoyl) - 3 - isothiazolone,	120	55
2 - (N - dodecylcarbamoyl) - 3 - isothiazolone,		
5 - methyl - 2 - (N - methylcarbamoyl) - 3 - isothiazolone,		
5 - methyl - 2 - (N - ethylcarbamoyl) - 3 - isothiazolone,	125	
5 - propyl - 2 - (N - methylcarbamoyl) - 3 - isothiazolone,		
5 - butyl - 2 - (N - methylcarbamoyl) - 3 - isothiazolone,	130	

The novel 3-isothiazolones may be prepared by any appropriate method described in the literature such as by conversion of 3-hydroxyisothiazoles, betathio ketoamides, or β -substituted thiocyanocrylamides or thiosulfatoacrylamides. 90

Preparation of the novel 2-carbamoyl and thiocarbamoyl substituted isothiazolones of this invention may be accomplished by reacting a 3-hydroxyisothiazole with an isocyanate or isothiocyanate on a substantially equimolar basis. 96

The unsubstituted 3-hydroxyisothiazole can be synthesized from propiolamide by the method of W. D. Crow and N. J. Leonard, *J. Org. Chem.*, 30, 2660—2665 (1965). Substituted 3-hydroxyisothiazoles are disclosed and can be prepared as shown in copending Application No. 11481/68 (Serial No. 1,224,663) filed on even date herewith and incorporated herein by reference thereto. 100 105

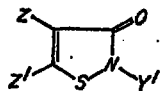
A general reaction for the preparation of carbamoyl substituted 3-isothiazolones from 3-hydroxyisothiazoles and isocyanates or isothiocyanates is shown below: 110



wherein the symbols R, R^I, R^{II} and X are as previously defined.

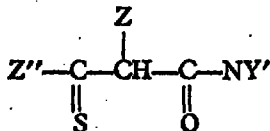
- Although an equimolar ratio of reactants is preferred an excess of up to 2 moles or more of isocyanate or isothiocyanate per mole of 3-hydroxyisothiazole may be employed. In many situations, an inert organic solvent may be utilized in this reaction. Generally, those solvents from the classes of aromatic hydrocarbon, halogenated aromatic hydrocarbon, amide, ester, aliphatic hydrocarbon and ether solvents are preferable. Particularly suitable for the purpose of this invention are those which include benzene, toluene, heptane, ethyl ether, and dioxane. When employing simple isocyanates, the reaction is spontaneous; but with less reactive long chain or aromatic isocyanates, a catalyst or promoter such as a tertiary amine can be profitably utilized. Representative tertiary amines are pyridine and triethylamine. While the reaction temperature is not critical, it is usually conducted in a range of $-20^{\circ}\text{C}.$ to $80^{\circ}\text{C}.$ or more.

In addition, the isothiazolones of the formula

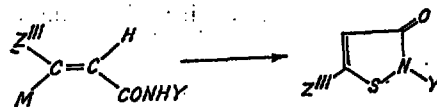


(II)

- may be prepared by the method of Goerdeler and Mittler as described in *Chem. Ber.*, 96, 944-954 (1963). In Formula II, Y' is defined in the same manner as Y in Formula I excepting therefrom only the lower hydroxyalkyl group and,
- Z is hydrogen or lower alkyl and Z' is lower alkyl or lower haloalkyl.
- This preparation involves the halogenation of a substituted betathio keto amide in an inert organic ester solvent, such as ethyl acetate.
- The betathio keto amide referred to may be represented by the formula



- wherein Z and Y' are as defined above and Z'' is lower alkyl.
- Another process for preparing some of the compounds of this invention is that of Crow and Leonard as set forth in the *Journal of Organic Chemistry* reference previously cited. Their method entails the converting of a β -substituted thiocynoacrylamide or thiosulfatoacrylamide to the isothiazolone. This reaction may be represented by the following equation:



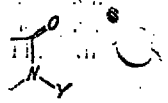
wherein Y is as defined for Formula I, Z''' is hydrogen or lower alkyl and M is $-\text{SCN}$ or $-\text{S}_2\text{O}_3$. Generally and preferably, conversion of the substituted thiocynoacrylamide or thiosulfatoacrylamide to the isothiazolone is achieved by the treating thereof with an acid, such as for example, sulfuric acid. However, when M is SCN , then transition metal salts, such as nickel sulfate, ferrous sulfate, ferric sulfate, copper sulfate and the like, are also readily utilized. In like manner, when M is S_2O_3 , then the conversion can be accomplished with iodine. Preparation of the thiocynoacrylamide and thiosulfatoacrylamide as taught by Crow and Leonard involves the reacting of a substituted propiolamide with thiocyanic acid or thiosulfate.

The 2-hydroxyalkyl-3-isothiazolone derivatives disclosed herein are obtained by reacting formaldehyde or an alkylene oxide, such as ethylene oxide, propylene oxide and the like, with a 3-hydroxyisothiazole. Preparation of the 2-haloalkyl-3-isothiazolones may be accomplished by reacting a 2-hydroxyalkyl-3-isothiazolone with a halogenating agent, such as thionyl chloride, phosphorus tribromide, phosphorus trichloride and the like.

By way of demonstration, the following examples are offered to illustrate this invention and are not to be construed as limitations thereof. In Table I, the compounds prepared by the above-described processes and constituting Examples 1 through 81 are named and their embodiments indicated. Table II lists the elemental analyses and melting points for the examples previously described in Table I. Specific illustrative preparations of Examples 1, 3, 14, 25, 33, 38 and 55 are set forth below.

EXAMPLE 1

A solution of 5.05 parts (0.05 mole) of 3-hydroxyisothiazole in 88 parts of dry benzene was agitated at $25^{\circ}\text{C}.$ There was added to the above solution a 50% benzene solution containing 2.85 parts (0.05 mole) of methylisocyanate. Immediately after addition, a white precipitate began to form which grew progressively thicker upon stirring. This stirring was continued overnight. Filtration of the reaction mixture gave 2.0 parts of white solid 2-(N-methylcarbamoyl)-3-isothiazolone with a melting point of 138°C to $140^{\circ}\text{C}.$ After addition of 35 parts of hexane, the filtrate yielded 3.5 parts of additional pro-



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duct with a melting point of 138° to 139°C. In this manner, a total yield of 5.5 parts (70%) of 2 - (N - methylcarbamoyl) - 3 - isothiazolone was obtained.

to yield 65.0 parts of yellow solid 2 - (N - ethylcarbamoyl) - 3 - isothiazolone. Purification was accomplished by crystallization from a benzene-hexane solution.

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5 EXAMPLE 3

To an agitating solution of 2.9 parts (0.029 mole) of 3-hydroxyisothiazole in 88 parts of benzene, 2.1 parts (0.029 mole) of methylisothiocyanate was added. The reaction was heated at 50° to 60°C. for 10 hours and the reaction medium evaporated to leave 2.5 parts of white solid 2 - (N - methylthiocarbamoyl) - 3 - isothiazolone. The product was recrystallized from ethanol.

EXAMPLE 33

A solution of benzene (66 parts), 3 - hydroxyisothiazole (4.0 parts, 0.04 mole) and 1 part of triethylamine was agitated. Then 8.45 parts (0.04 mole) of n-dodecylisocyanate in 22 parts of benzene was added dropwise at 25°C. After stirring for 12 hours, the reaction solution was evaporated to leave 13.0 parts of 2 - (N - n - dodecylcarbamoyl) - 3 - isothiazolone. The product was crystallized from ethanol.

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15 EXAMPLE 14

To an agitating solution of 3.0 parts (0.025 mole) of 3 - hydroxy - 5 - methyl - isothiazole in 132 parts of dry benzene, 4.0 parts (0.025 mole) of 3-chlorophenylisocyanate was added. The temperature of the exothermic reaction rose from 27° to 48°C. After stirring for two hours, a white solid slurry formed. The solid was filtered off and dried to yield 7.0 parts of 5 - methyl - 2 - (N - 3 - chlorophenylcarbamoyl) - 3 - isothiazolone.

EXAMPLE 38

5 - methyl - 2 - (N - ethylthiocarbamoyl) - 3 - isothiazolone was prepared by reacting 3 - hydroxy - 5 - methylisothiazole and ethylisothiocyanate according to the procedure of Example 3.

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EXAMPLE 55

Aqueous formaldehyde (37 percent), 4.5 g. (0.056 mole) was diluted with 25 ml. of water, and then 3.8 g. (0.028 mole) of potassium carbonate was added. Thereafter, 5.5 g. (0.055 mole) of 3-hydroxyisothiazole was added to the formaldehyde solution in one portion. A solid precipitate soon formed, and after 2 hours stirring, was filtered off to yield 1.8 g. of white solid 2 - hydroxymethyl - 3 - isothiazolone.

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30 EXAMPLE 25

To an agitating solution of 4 parts (0.04 mole) of 3-hydroxyisothiazole in 88 parts of dry benzene, 2.84 parts (0.04 mole) of ethylisocyanate was added dropwise at 25°C. The solution was stirred at 25°C. for 12 hours; then the solvent was evaporated under vacuum

TABLE I

3-Isothiazolone Examples



Example No.	R	R ¹	Y	Name
1	H	H	—CONHCH ₃	2-(N-methylcarbamoyl)-3-isothiazolone
2	H	CH ₃	—CONHCH ₃	5-methyl-2-(N-methylcarbamoyl)-3-isothiazolone
3	H	H	—CSNHCH ₃	2-(N-methylthiocarbamoyl)-3-isothiazolone
4	Br	CH ₃	—CONHCH ₃	4-bromo-5-methyl-2-(N-methylcarbamoyl)-3-isothiazolone
5	CN	SCH ₃	—CONHCH ₃	4-cyano-5-methylthio-2-(N-methylcarbamoyl)-3-isothiazolone
6	CN	SOCH ₃	—CONHCH ₃	4-cyano-5-methylsulfinyl-2-(N-methylcarbamoyl)-3-isothiazolone
7	CN	SO ₂ CH ₃	—CONHCH ₃	4-cyano-5-methylsulfonyl-2-(N-methylcarbamoyl)-3-isothiazolone
8	H	H	—CONHC ₄ H ₉ ⁿ	2-(N-n-butylcarbamoyl)-3-isothiazolone
9	H	H	—CONHC ₈ H ₁₇ ⁿ	2-(N-octylcarbamoyl)-3-isothiazolone
10	H	CH ₃	—CONHC ₆ H ₅	5-methyl-2-(N-phenylcarbamoyl)-3-isothiazolone
11	CN	SCH ₃	—CONHC ₆ H ₅	4-cyano-5-methylthio-2-(N-phenylcarbamoyl)-3-isothiazolone
12	Br	CH ₃	—CONHC ₆ H ₄ Cl—3	4-bromo-5-methyl-2-(N-3-chlorophenylcarbamoyl)-3-isothiazolone

(14)

TABLE I (Continued)

Example No.	R	R ¹	Y	Name
13	H	CH ₂ Br	—CONHC ₆ H ₄ Cl—3	5-bromoethyl-2-(N-3-chlorophenylcarbamoyl)-3-isothiazolone
14	H	CH ₃	—CONHC ₆ H ₄ Cl—3	5-methyl-2-(N-3-chlorophenylcarbamoyl)-3-isothiazolone
15	CN	SCH ₃	—CONHC ₆ H ₄ Cl—3	4-cyano-5-methylthio-2-(N-3-chlorophenylcarbamoyl)-3-isothiazolone
16	H	H	—CONHC ₆ H ₄ Cl—3	2-(N-3-chlorophenylcarbamoyl)-3-isothiazolone
17	H	CH ₃	—CONHC ₆ H ₄ Cl—2	5-methyl-2-(N-2-chlorophenylcarbamoyl)-3-isothiazolone
18	H	CH ₂ Br	—CONHC ₆ H ₄ Cl—2	5-bromomethyl-2-(N-2-chlorophenylcarbamoyl)-3-isothiazolone
19	Br	CH ₃	—CONHC ₆ H ₃ Cl ₂ —3,4	4-bromo-5-methyl-2-(N-3,4-dichlorophenylcarbamoyl)-3-isothiazolone
20	H	CH ₃	—CONHC ₆ H ₃ Cl ₂ —3,4	5-methyl-2-(N-3,4-dichlorophenylcarbamoyl)-3-isothiazolone
21	CN	SCH ₃	—CONHC ₆ H ₃ Cl ₂ —3,4	4-cyano-5-methylthio-2-(N-3,4-dichlorophenylcarbamoyl)-3-isothiazolone
22	H	CH ₃	—CONHSO ₂ C ₆ H ₄ CH ₃ —4	5-methyl-2-(N-4-tosylcarbamoyl)-3-isothiazolone
23	CN	SCH ₃	—CONHSO ₂ C ₆ H ₄ CH ₃ —4	4-cyano-5-methylthio-2-(N-4-tosylcarbamoyl)-3-isothiazolone
24	Br	CH ₃	—CONHSO ₂ C ₆ H ₄ CH ₃ —4	4-bromo-5-methyl-2-(N-4-tosylcarbamoyl)-3-isothiazolone
25	H	H	—CONHC ₂ H ₅	2-(N-ethylcarbamoyl)-3-isothiazolone
26	H	H	—CONHC ₃ H ₇ - <i>n</i>	2-(N- <i>n</i> -propylcarbamoyl)-3-isothiazolone
27	H	H	—CONHC ₃ H ₇ - <i>i</i>	2-(N- <i>i</i> -propylcarbamoyl)-3-isothiazolone
28	Br	H	—CONHCH ₃	4-bromo-2-(N-methylcarbamoyl)-3-isothiazolone
29	H	H	—CONHC ₆ H ₄ —OCH ₃ —4	2-(N-4-methoxyphenylcarbamoyl)-3-isothiazolone

TABLE I (Continued)

Example No.	R	R'	Y	Name
30	H	H	—CONHC ₆ H ₄ —OCH ₃ —2	2-(N-2-methoxyphenylcarbamoyl)-3-isothiazolone
31	H	H	—CONHC ₆ H ₄ —NO ₂ —3	2-(N-3-nitrophenylcarbamoyl)-3-isothiazolone
32	H	H	—CONHC ₆ H ₃ —Cl ₂ —3,4	2-(N-3,4-dichlorophenylcarbamoyl)-3-isothiazolone
33	H	H	—CONHC ₁₂ H ₂₅	2-(N-n-dodecylcarbamoyl)-3-isothiazolone
34	H	H	—CONHC ₆ H ₃ Cl ₂ —2,5	2-(N-2,5-dichlorophenylcarbamoyl)-3-isothiazolone
35	H	H	—CONHCH ₂ CO ₂ C ₂ H ₅	2-(N-carbethoxymethylcarbamoyl)-3-isothiazolone
36	H	H	—CONHC ₆ H ₄ NO ₂ —4	2-(N-4-nitrophenylcarbamoyl)-3-isothiazolone
37	H	CH ₃	—CONHC ₆ H ₅	5-methyl-2-(N-ethylcarbamoyl)-3-isothiazolone
38	H	CH ₃	—CSNHC ₂ H ₅	5-methyl-2-(N-ethylthiocarbamoyl)-3-isothiazolone
39	H	Cl	—CONHC ₆ H ₅	5-chloro-2-(N-ethylcarbamoyl)-3-isothiazolone
40	H	H	—C ₃ H ₇	2-n-propyl-3-isothiazolone
41	H	H	—C ₄ H ₉ -i	2-i-butyl-3-isothiazolone
42	H	H	—C ₄ H ₉ -n	2-n-butyl-3-isothiazolone
43	H	H	—C ₆ H ₁₁	2-cyclohexyl-3-isothiazolone
44	H	H	—C ₈ H ₁₇ -i	2-i-octyl-3-isothiazolone
45	H	H	—CH ₂ C ₆ H ₄	2-benzyl-3-isothiazolone
46	H	Cl	—CH ₃	5-chloro-2-methyl-3-isothiazolone

TABLE I. (Continued)

Example No.	R	R ¹	Y	Name
47	H	Cl	-CH ₂ C ₆ H ₄	5-chloro-2-benzyl-3-isothiazolone
48	Cl	Cl	-CH ₃	4,5-dichloro-2-methyl-3-isothiazolone
49	CH ₃	H	-CH ₃	2,4-dimethyl-3-isothiazolone
50	CH ₃	H	-C ₆ H ₄ Cl ₂ -3,4	4-methyl-2-(3,4-dichlorophenyl)-3-isothiazolone
51	H	H	-C ₆ H ₄ Cl ₂ -3,4	2-(3,4-dichlorophenyl)-3-isothiazolone
52	Cl	Cl	-CH ₂ C ₆ H ₅	4,5-dichloro-2-benzyl-3-isothiazolone
53	Br	Cl	-CH ₃	4-bromo-5-chloro-2-methyl-3-isothiazolone
54	Br	H	-CH ₃	4-bromo-2-methyl-3-isothiazolone
55	H	H	-CH ₂ OH	2-hydroxymethyl-3-isothiazolone
56	H	H	-CH ₂ CH ₂ N(CH ₂ CH ₃) ₂	2-(β-diethylaminoethyl)-3-isothiazolone
57	H	H	-C ₃ H ₇ .HCl	2-n-propyl-3-isothiazolone hydrochloride
58	H	Cl	-CH ₃ .HCl	5-chloro-2-methyl-3-isothiazolone hydrochloride
59	H	H	-C ₂ H ₅ .HCl	2-ethyl-3-isothiazolone hydrochloride
60	H	H	-CH ₃ .HCl	2-methyl-3-isothiazolone hydrochloride
61	H	H	-CH ₂ C ₆ H ₅ .HCl	2-benzyl-3-isothiazolone hydrochloride
62	H	H	-C ₁₂ H ₂₅ -n	2-n-dodecyl-3-isothiazolone
63	H	H	-C ₁₄ H ₂₉ -n	2-n-tetradecyl-3-isothiazolone

TABLE I (Continued)

Example No.	R	R'	Y	Name
64	H	H	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}-4$	2-(4-chlorobenzyl)-3-isothiazolone
65	H	H	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}-2$	2-(2-chlorobenzyl)-3-isothiazolone
66	H	H	$-\text{CH}_2-\text{C}_6\text{H}_3-\text{Cl}_2-2,4$	2-(2,4-dichlorobenzyl)-3-isothiazolone
67	H	H	$-\text{CH}_2-\text{C}_6\text{H}_3-\text{Cl}_2-3,4$	2-(3,4-dichlorobenzyl)-3-isothiazolone
68	H	H	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3-4$	2-(4-methoxybenzyl)-3-isothiazolone
69	H	H	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_3-4$	2-(4-methylbenzyl)-3-isothiazolone
70	H	H	$-\text{CH}_2-\text{CH}(-\text{C}_6\text{H}_5)\text{C}_6\text{H}_5$	2-(2-ethylhexyl)-3-isothiazolone
71	H	H	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$	2-(2-phenylethyl)-3-isothiazolone
72	H	Cl	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$	2-(2-phenylethyl)-5-chloro-3-isothiazolone
73	H	H	$-\text{CH}(\text{CH}_3)\text{C}_6\text{H}_5$	2-(1-phenylethyl)-3-isothiazolone
74	H	H	$-\text{C}_{10}\text{H}_{21}-n$	2-n-decyl-3-isothiazolone
75	H	H	$-\text{C}_8\text{H}_{17}-n$	2-n-octyl-3-isothiazolone
76	Cl	H	$-\text{C}_8\text{H}_{17}-i$	2- <i>i</i> -octyl-4-chloro-3-isothiazolone
77	Br	H	$-\text{C}_8\text{H}_{17}-i$	2- <i>i</i> -octyl-4-bromo-3-isothiazolone
78	H	H	$-\text{C}_9\text{H}_{19}-n$	2-n-nonyl-3-isothiazolone
79	H	Cl	$-\text{C}_9\text{H}_{17}-n$	2-n-octyl-5-chloro-3-isothiazolone
80	H	H	$-\text{C}_6\text{H}_4\text{NO}_2-4$	2-(4-nitrophenyl)-3-isothiazolone
81	H	H	$-\text{C}_6\text{H}_4\text{COOC}_2\text{H}_5-4$	2-(4-carboxyphenyl)-3-isothiazolone

TABLE II

- 80 H H $-\text{C}_6\text{H}_4\text{NO}_2-4$ 2-(4-nitrophenyl)-3-isothiazolone
- 81 H H $-\text{C}_6\text{H}_4\text{COOC}_2\text{H}_5-4$ 2-(4-carboethoxyphenyl)-3-isothiazolone

TABLE II

Characterization of Examples

Example No	Melting Point in °C.	Analysis*				
		C	H	N	S	Cl
1	138—140	38.16(37.9)	4.04(3.8)	17.45(17.1)	20.24(20.2)	
2	138—145	41.55(41.8)	4.63(4.7)	15.60(16.3)	18.23(18.6)	
3	155—158	34.62(34.5)	3.66(3.5)	15.76(16.1)	35.52(36.7)	
4	191—195	28.74(28.7)	2.98(2.8)	10.90(11.2)		**31.68(31.8)
5	207—210	35.96(36.7)	3.24(3.1)	17.91(18.3)	28.23(27.9)	
6	158—160	34.10(34.3)	2.95(2.9)	16.95(17.1)	23.38(26.1)	
7	146—150	31.90(32.2)	3.07(2.7)	15.23(16.1)	23.48(24.5)	
8	oil	47.91(47.8)	6.01(6.0)	13.92(14.0)	16.03(16.0)	
9	oil			11.41(10.9)		
10	142—146	56.52(54.2)	4.29(4.5)	12.10(12.6)	14.39(14.3)	
11	183—186	49.00(49.5)	3.16(3.1)	14.51(14.4)		
12	200—202	38.32(38.1)	2.37(2.3)	7.86(8.1)		
13	178—180	38.02(38.1)	2.56(2.3)	7.65(8.1)	9.59(9.2)	
14	142—144	49.38(49.2)	3.36(3.4)	10.11(10.4)	12.02(11.9)	
15	192—194	43.29(44.3)	2.57(2.5)	12.78(12.9)	19.94(19.7)	

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TABLE II (Continued)

Example No.	Melting Point in °C.	Analysis*			
		C	H	N	S
16	120—123	47.90(47.1)	3.16(2.8)	10.98(11.0)	12.24(12.6)
17	162—164	49.78(49.3)	3.58(3.4)	10.78(10.4)	11.72(11.9)
18	199—201	38.28(38.1)	2.45(2.3)	8.19(8.1)	9.38(9.2)
19	235—237	34.42(34.6)	1.84(1.9)	7.20(7.3)	
20	195—207	44.42(43.4)	2.89(2.6)	8.56(9.2)	10.87(10.6)
21	118—120	39.96(40.0)	2.10(2.0)	11.52(11.7)	18.22(17.8)
22	170—173	46.18(46.2)	4.03(3.9)	9.01(9.0)	20.92(20.5)
23	163—168	39.50(42.2)	3.46(3.0)	11.65(11.1)	26.01(26.1)
24	199—203	38.79(38.4)	2.98(2.9)	6.95(7.5)	16.66(17.1)
25	103—105	41.91(41.8)	4.71(4.7)	16.10(16.3)	18.22(18.6)
26	84—88	45.06(44.9)	5.67(5.4)	14.66(15.0)	16.90(17.1)
27	53—56	44.86(44.9)	5.45(5.4)	14.89(15.0)	17.05(17.1)
28	194—197	25.80(25.3)	2.58(2.1)	11.60(11.9)	12.75(13.6)
29	134—137	52.88(52.8)	4.19(4.0)	11.23(11.2)	12.68(12.8)
30	140—145	52.16(52.8)	4.40(4.1)	11.13(11.2)	12.20(12.8)
31	195—198	45.97(45.3)	2.68(2.7)	15.79(15.9)	11.87(12.1)
32	172—174	41.51(41.6)	2.10(2.1)	9.67(9.7)	

TABLE II (Continued)

Example	Melting	Analysis*
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TABLE II (Continued)

Example No.	Melting Point in °C.	Analysis*			
		C	H	N	Cl
33	60—62	61.41(61.5)	8.84(9.0)	8.90(9.0)	10.12(10.3)
34	179—180	41.41(41.6)	2.27(2.1)	9.77(9.7)	10.89(11.1)
35	80—83	42.02(41.7)	4.64(4.3)	11.41(12.2)	
36	225—230	45.59(45.3)	2.79(2.7)	15.75(15.9)	11.98(12.1)
37	53—56	44.77(45.2)	5.46(5.4)	14.41(15.1)	16.50(17.2)
38	73—103	41.44(41.7)	4.86(5.0)	13.79(13.9)	31.60(31.7)
39	53—55	35.12(34.87)	3.42(3.39)	13.47(13.56)	15.33(15.50) 17.31(17.19)
40	65—68	50.28(50.3)	6.17(6.33)	9.83(9.78)	22.30(22.3)
41	75—79	46.76(53.5)	6.76(7.06)	8.42(8.92)	16.43(20.4)
42	99	52.10(53.5)	7.11(7.06)	8.54(8.92)	19.35(20.4)
43	109—111	58.96(59.0)	7.20(7.10)	7.59(7.65)	17.41(17.5)
44	97—100	61.91(62.0)	9.03(9.0)	6.55(6.57)	14.89(15.03)
45	78—80	62.82(62.8)	4.84(4.7)	7.22(7.3)	16.97(16.75)
46	44—47	32.80(32.1)	2.64(2.7)	9.55(9.5)	20.79(21.4) 23.48(23.7)
47	57—59	53.19(53.2)	3.46(3.6)	6.18(6.2)	13.80(14.2) 15.01(15.74)
48	114—117	27.31(26.1)	1.43(1.6)	7.22(7.6)	17.42(17.4) 37.89(38.6)
49	58—68	45.99(46.4)	5.77(5.4)	11.38(10.8)	24.39(24.8)

②

(32)

TABLE II (Continued)

Example No.	Melting Point in °C.	Analysis*			
		C	H	N	S
50	161—163	45.92(45.8)	2.88(2.7)	5.59(5.35)	11.91(12.2)
51	131—133	43.95(43.9)	1.95(2.05)	5.66(5.69)	13.09(13.0)
52	62—64	47.10(46.1)	2.86(2.7)	5.35(5.4)	12.48(12.3)
53	86—87	22.24(21.0)	1.81(1.3)	5.82(6.1)	13.83(14.0)
54	94—97	25.68(24.7)	1.75(2.0)	7.22(7.2)	
55	124—126	36.43(36.5)	3.75(3.7)	10.44(10.7)	24.30(24.4)
56	oil	52.70(54.1)	6.35(8.06)	14.17(14.0)	13.70(16.0)
57	87—90	38.64(40.2)	5.88(5.61)*	7.50(7.79)	16.85(17.83)
58	—	25.78(25.8)	3.17(2.7)	7.07(7.5)	14.9(17.2)
59	144—146	36.44(36.3)	4.80(4.8)	8.30(8.5)	19.20(19.3)
60	162—166	30.76(31.8)	4.27(4.0)	8.89(9.3)	20.79(21.2)
61	147—153	52.78(52.8)	4.60(4.39)	6.33(6.51)	14.21(14.1)
62	46—49	66.98(66.9)	9.90(10.0)	5.25(5.2)	11.72(11.90)
63	53—55	68.86(68.7)	10.61(10.5)	4.68(4.7)	10.88(10.8)
64	87—88	52.78(53.2)	3.54(3.6)	6.02(6.3)	14.59(14.2)
65	99—100	53.39(53.2)	3.69(3.6)	6.18(6.3)	13.95(14.2)
					15.75(15.7)
					15.96(15.7)

TABLE II (Continued)

Example No.	Melting Point in °C.	Analysis*			
		C	H	N	S

TABLE II (Continued)

Example No.	Melting Point in °C.	Analysis*			
		C	H	N	Cl
66	122-124	46.18(46.2)	2.80(2.7)	5.25(5.4)	26.85(27.3)
67	87-89	45.87(46.2)	2.62(2.7)	5.15(5.4)	27.33(27.3)
68	80-82	59.74(59.7)	4.96(5.0)	6.25(6.3)	14.58(14.5)
69	76-77	64.60(64.4)	5.32(5.4)	6.60(6.8)	15.60(15.6)
70	119-120 (.005 mm) ^b	60.81(62.0)	8.88(8.9)	6.46(6.6)	14.70(15.0)
71	76-78	64.35(64.5)	5.49(5.4)	6.75(6.8)	15.40(15.6)
72	55-59	55.22(55.2)	3.95(4.2)	5.62(5.9)	13.16(13.4)
73	138-140 (.003mm) ^b	62.52(64.5)	5.27(5.4)	6.45(6.8)	14.10(15.6)
74	41-42	64.80(64.7)	9.31(9.6)	5.46(5.8)	13.49(13.2)
75	120(0.01mm) ^b	62.00(62.0)	8.81(8.9)	6.48(6.6)	14.89(15.0)
76	137-140	52.38(53.5)	7.81(7.3)	5.62(5.7)	12.19(14.5)
77	138-142	44.76(45.2)	6.48(6.2)	4.58(4.8)	**25.8(27.4)
78	30-31	63.34(63.45)	9.40(9.29)	6.08(6.17)	13.97(14.10)
79	oil	55.05(53.4)	7.76(7.3)	5.76(5.7)	11.13(14.35)
80	170-175 dec.	48.62(48.7)	2.78(2.72)	12.77(12.60)	—
81	141-142	58.12(57.8)	4.46(4.44)	5.70(5.62)	12.79(12.85)

*The number parenthesized represents the theoretical value, as calculated, using the empirical formula of each compound.

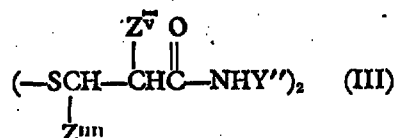
**Analysis for bromine.

^aNeutralization equivalent.

^bBoiling Point in °C.

23

The new 3-isothiazolones can also be prepared by a new process involving the cyclization of a disulfide-amide of the formula



wherein Z^{III} and Z^{IV} are hydrogen or C_1-C_4 alkyl and Y'' is as previously defined for Y except that it is other than hydroxyalkyl, carbamoyl or thiocarbamoyl. Such cyclization is preferably accomplished by reacting the disulfide-amide with a halogenating agent. Typical halogenating agents include chlorine, bromine, sulfonyl chloride, sulfonyl bromide, N-chlorosuccinamide, N-bromosuccinamide and the like. Chlorine and sulfonyl chloride are the preferred halogenating agents.

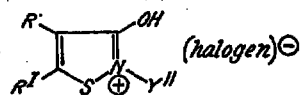
Cyclization of the disulfide-amide will take place when 3 mole equivalents of halogenating agent, or to be more specific halogen, are employed in the reaction. By providing an excess of halogenating agent, the isothiazolone may be halogenated at the 4 and/or 5 positions of Formula I. Where 5 mole equivalents 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 carried out in an inert non-aqueous solvent, such as benzene, toluene, xylene, ethyl acetate, ethylene dichloride and the like.

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



(IV)

wherein Y'' , R, and R' are as hitherto defined. Where desired or necessary, an acid scavenger can be incorporated in the reaction medium so as to avoid isothiazolonium 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 isothiazolonium 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 further examples.

EXAMPLE 82

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

To an ethylene dichloride (1 litre) slurry of dithio-N,N'-dimethyldipropionamide, 70.9 g. (0.3 mole), there was added at $10-15^\circ\text{C}$. over 1.5 hour 121.5 g. (0.9 mole) of sulfonyl chloride. After addition, the reaction slurry was allowed to warm to $20-25^\circ\text{C}$. 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. ($40-60^\circ\text{C}$.) gave 11.5 g. of 5-chloro-2-methyl-3-isothiazolone, m.p. $44-47^\circ\text{C}$.

EXAMPLE 83

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 sulfonyl chloride in 25 ml. of ethylene dichloride was added dropwise at 25—30°C. over one hour. The slurry was stirred overnight to insure 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.

- 10 The novel isothiazolones and salts of this invention are biocidally active compounds, and as such, are suitable for treating vendible products to render them less susceptible to deterioration due to infestation with living organisms including fungi, bacteria, algae, nematodes, mites and insects. Furthermore, these novel compounds possess the unexpected property of being resistant to inhibition by common additives or contaminants, such as lecithin, normal horse serum, alkylbenzene sulfonates, water-soluble lanolin, sodium chromate, sodium nitrite, glycerol and propylene glycol.
- 20 It was also determined that other isothiazolones, namely, 2 - methyl - 3 - isothiazolone and 2 - ethyl - 3 - isothiazolone are likewise effective for the control of living organisms. These compounds were described by Leonard

and Crow in the *Journal of Organic Chemistry* article previously cited. However, Leonard and Crow did not attribute any biocidal properties to the compounds in question. Such characteristics were unknown until the present discovery.

Fungicidal evaluation of the isothiazolones of this invention along with the Leonard and Crow compounds was carried out by the standard slide spore germination test (cf. *Phytopathology*, 33, 627 (1943), utilizing spores of *Alternaria solani* (Alt.), *Sclerotinia fructicola* (Scl.) and *Stemphylium sarcinaeforme* (Stem.) or *Botrytis Cinerea* (Bot.). The values obtained for the concentration in parts per million (ppm) which effectively controlled 50% of the spores (ED₅₀) are given in Table III.

Antibacterial activity was evaluated by the Serial Dilution Test (Broth Titer Test) wherein a series of broths containing varying dilutions of a test compound and an organism are halved starting with 1:1000. The values obtained, which are also shown in Table III, represent the maximum dilution at which the compound under evaluation renders complete control of the organism. *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) were the bacterial organisms employed in this test.

TABLE III

Microbiological Activity

Example No.	Fungicidal Evaluation			Bacteriostatic Evaluation	
	Alt.	Scl.	Stem.(Bot.)	<i>S. aureus</i>	<i>E. coli</i>
1	<1	<1	<1	1: 64,000	1: 32,000
2	1—10	<1	1—10	1: 64,000	1: 16,000
3	—	—	—	1: 32,000	1: 8,000
4	<1	<1	<1	1: 2,000	1: 1,000
5	1—10	<1	<1	<1: 1,000	1: 1,000
6	10—50	10—50	10—50	1: 2,000	1: 1,000
7	10—50	10—50	10—50	1: 1,000	1: 1,000
8	<1	<1	1—10	1: 32,000	1: 4,000
9	10—50	10—50	50—200	1: 32,000	1: 8,000
10	10—50	10—50	10—50	1: 1,000	1: 1,000
11	50—200	50—200	10—50	—	—
12	10—50	10—50	10—50	1: 1,000	1: 1,000
13	50—200	50—200	10—50	1: 1,000	1: 1,000

TABLE III (Continued)

Example No.	Fungicidal Evaluation			Bacteriostatic Evaluation	
	Alt.	Scl.	Stem.(Bot.)	S. aureus	E. coli
14	10-50	<1	10-50	1: 1,000	1: 1,000
15	200-1000	>1000	50-200	1: 1,000	1: 2,000
16	1-10	1-10	10-50	1: 8,000	1: 8,000
17	50-200	10-50	10-50	1: 1,000	1: 1,000
18	200-1000	200-1000	50-200	1: 4,000	1: 1,000
19	>1000	>1000	>1000	<1: 1,000	<1: 1,000
20	>1000	>1000	>1000	—	—
21	>1000	>1000	>1000	—	—
22	50-200	50-200	50-200	1: 1,000	1: 1,000
23	200-1000	200-1000	200-1000	1: 1,000	1: 1,000
24	200-1000	50-200	50-200	1: 1,000	1: 4,000
25	10-50	10-50	10-50	1: 25,600	1: 16,000
26	10-50	10-50	10-50	1: 64,000	1: 8,000
27	10-50	50-200	10-50	1: 64,000	1: 4,000
28	1-10	<1	10-50	1: 4,000	1: 2,000
29	—	—	—	1: 8,000	1: 8,000
30	—	—	—	1: 8,000	1: 8,000
31	—	—	—	1: 2,000	1: 2,000
32	1-10	50-200	10-50	1: 512,000	1: 8,000
33	>1000	>1000	>1000	1: 2,000	1: 1,000
34	10-50	10-50	50-200	1: 8,000	1: 2,000
35	<1	10-50	10-50 ^a	1: 8,000	1: 2,000
36	10-50	50-200	10-50 ^a	1: 4,000	1: 2,000
37	50-200	<1	10-50 ^a	1: 8,000	1: 16,000
38	10-50	50-200	<1	1: 32,000	1: 4,000
39	—	—	—	1: 16,000	1: 32,000
40	<1	<1	<1	1: 8,000	1: 32,000
41	10-50	1-10	1-10	1: 4,000	1: 8,000
42	<1	10-50	10-50	1: 8,000	1: 32,000

TABLE III (Continued)

Example No.	Fungicidal Evaluation			Bacteriostatic Evaluation	
	Alt.	Scl.	Stem.(Bot.)	S. aureus	E. coli
43	<1	<1	<1	1: 32,000	1: 8,000
44	—	—	—	1: 8,000	1: 1,000
45	—	—	—	1: 32,000	1: 64,000
46	—	—	—	1:128,000	1:256,000
47	—	—	—	1: 64,000	1: 64,000
48	—	—	—	1: 32,000	1: 64,000
49	—	—	—	1: 2,000	1: 4,000
50	<1	<1	<1	1:256,000	1: 1,000
51	<1	<1	<1	1,512,000	1: 2,000
52	—	—	—	1:128,000	1: 64,000
53	—	—	—	1:128,000	1: 64,000
54	—	—	—	—	—
55	—	—	—	1: 8,000	1: 32,000
56	—	—	—	1: 8,000	1: 4,000
57	1—10	10—50	10—50	1: 32,000	1: 8,000
58	—	—	—	1:256,000	1:128,000
59	10—50	50—200	50—200	1: 16,000	1: 8,000
60	<1	<1	<1	1: 32,000	1: 32,000
61	1—10	1—10	10—50	1: 32,000	1: 32,000
62	—	—	—	1:1,000,000	1: 1,000
63	—	—	—	1: 1,000	<1: 1,000
64	—	—	—	1: 64,000	1: 16,000
65	—	—	—	1: 64,000	1: 16,000
66	—	—	—	1:256,000	1: 4,000
67	—	—	—	1:256,000	1: 16,000
68	—	—	—	1: 16,000	1: 8,000
69	—	—	—	1: 32,000	1: 8,000
70	—	—	—	1: 64,000	1: 2,000
71	—	—	—	1: 16,000	1: 8,000

TABLE III (Continued)

Example No.	Fungicidal Evaluation			Bacteriostatic Evaluation	
	Alt.	Scl.	Stem.(Bot.)	S. aureus	E. coli
72	—	—	—	1: 64,000	1: 64,000
73	—	—	—	1: 32,000	1: 8,000
74	—	—	—	1:2,000,000	1: 16,000
75	—	—	—	1:128,000	1: 8,000
76	—	—	—	1: 8,000	<1: 1,000
77	—	—	—	1: 8,000	<1: 1,000
78	—	—	—	1:512,000	1: 8,000
79	—	—	—	1: 8,000	1: 16,000
2-methyl-3-isothiazolone	<1	<1	<1	1: 16,000	1: 32,000
2-ethyl-3-isothiazolone	<1	<1	—	1: 8,000	1: 16,000

5 Selected isothiazolones were also evaluated as algacides by the Fitzgerald Test (Applied Microbiology, 7, 205—211, No. 4, 1959) and found to be exceptionally effective.

10 Further fungicidal activity on the part of the isothiazolones was demonstrated by their utilization in seed treatment applications. By seed treatment is meant the disseminating of a biocidally active material over a seed subject to the attack of microorganisms, and particularly fungi, in an amount which is effective to control such microorganisms without deleteriously effecting such seed. In most circumstances, the biocidally active material, in this case, the isothiazolones or compositions thereof will be applied to the surface area of the seeds to be treated. This may be accomplished by varying means common to the art, such as slurring, soaking, dusting and spraying.

25 The amount of isothiazolone required so as to be effective in a seed treatment application will vary depending upon conditions, such as the type of seed, the method of application, soil and atmospheric conditions and the like. Generally, an application in the range of about

0.25 to 20 ounces of active ingredient, namely, the isothiazolone per 100 pounds of seed will be effective to control any undesirable microorganisms and so provide protection to the seed. An application of active agent in the range of about 1.0 to 10 ounces per 100 pounds of seed is preferred.

35 An experimental technique was employed to demonstrate the effectiveness of these compounds for seed treatment. This involved slurring two lots of 100 corn seeds each with the iso-thiazolone under evaluation at a level of 1 to 2 ounces per bushel of seed. For purposes of comparison, an untreated control was also included. After drying, the seeds were planted in a muck soil infested with *Pythium* and having a high moisture content. The corn seeds were maintained in this soil for a week at about 10°C. so as to permit infection. Upon completion of this period of time, the temperature was elevated and maintained at about 21° to 27°C. so as to permit germination of the non-infected seed. The number of seeds germinating were counted after emergence of the plant and such data is set forth in Table IV.

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TABLE IV
Seed Treatment

Test Compound	Number of Plants Germinating/200 seeds
Untreated	10
2- <i>t</i> -butyl-3-isothiazolone	100
2- <i>n</i> -octyl-3-isothiazolone	144
2- <i>t</i> -octyl-3-isothiazolone	184
2- <i>n</i> -nonyl-3-isothiazolone	164
2-methyl-5-chloro-3-isothiazolone	150
2-methyl-4,5-dichloro-3-isothiazolone	140
2- <i>n</i> -octyl-5-chloro-3-isothiazolone	150
2- <i>t</i> -octyl-4-chloro-3-isothiazolone	160
2- <i>t</i> -octyl-4-bromo-3-isothiazolone	148
2-(2,4-dichlorobenzyl)-3-isothiazolone	80
2-(2-ethylhexyl)-3-isothiazolone	182
2-(1-phenylethyl)-3-isothiazolone	176
2-(2-phenylethyl)-3-isothiazolone	160

- 5 Evaluation of the isothiazolones with regard to pesticidal activity demonstrated their exceptional control of numerous nematodes, mites, insects, such as beetles and aphids. Some typical nematodes, insects and mites which we controlled when contacted with the compounds of this invention included the following:
- 10 Northern root knot nematode (*Meloidogyne hapla*), Mexican bean beetle (*Epilachna varivesta*), black carpet beetle (*Attagenus piceus*), confused flour beetle (*Tribolium confusum*), granary weevil (*Sitophilus granarius*), two spotted mite (*Tetranychus urticae*), house fly
- 15 (*Musca domestica*), Southern armyworm (*Prodenia eridania*), German cockroach (*Blattella germanica*), and green peach aphid (*Myzus persicae*).
- 20 Generally, control of a living organism is achieved in accordance with this invention by contacting the organism with an isothiazolone in an amount which is effective to control said organism. Any of the techniques known in the art may be employed to disseminate the
- 25 isothiazolones in a manner so as to achieve the desired contact with the organism to be con-

trolled. Spraying and fumigating are typical of such techniques.

The compounds of this invention may be readily utilized as slimicides, algacides, bactericides, fungicides or combinations thereof in any loci and particularly in aqueous media, such as for example, water-cooling systems, swimming pools, paper pulp processes, etc. In addition, these compounds and/or compositions thereof may serve functions, such as for example, preservatives, especially fabric preservatives, soap additives, sanitizing agents, and preservatives for metal working compounds and aqueous film-forming compositions.

In general, a loci subject to attack by microorganisms may be protected in accordance with this invention by incorporating into said loci an isothiazolone or salt thereof in an amount which is effective to control said microorganisms. The exact amount of isothiazolone required will, of course, vary with the medium being protected, the microorganisms being controlled, the particular isothiazolones or compositions thereof being em-

played and the like. Typically, in a liquid medium, excellent control is obtained when the isothiazolones are incorporated in the range of 0.1 to 10,000 parts per million (ppm) or 0.00001 to 1% based on the weight of the medium. A range of 1 to 2000 ppm is preferred.

The term "control", as employed in this specification, is to be construed as any means which adversely affects the existence or growth of any living organism or microorganism. Such means may comprise a complete killing action, eradication, arresting in growth, inhibition, reduction in number or any combination thereof.

Outstanding fungistatic activity by the isothiazolones was exhibited when they were employed as paint preservatives and paint fungistats. Microbial activity in acrylic based paint emulsions is effectively inhibited when these compounds are incorporated at the rate of about 2—20 pounds or more per 100 gallons of paint.

The biocidal compositions provided by the invention may be in the form of concentrates for dilution by the end-user or ready-for-use compositions. Most usually the compositions, whether they be concentrates or ready-for-use compositions, will contain one or more active compounds provided by the invention and one or more of the following, namely a solid diluent which may or may not be herbicidally inert and which is usually finely divided, a liquid diluent which may or may not be herbicidally inert and which may or may not be a common organic solvent, a surfactant, an adhesive agent, and a pesticide such as another fungicide, an acaricide, molluscicide, or an insecticide. Surfactants of some sort, e.g. emulsifying or dispersing agents, are practically always present.

Ready-for-use biocidal compositions usually contain an agronomically acceptable carrier. By "agronomically acceptable carrier" is meant any substance which can be utilized to dissolve, disperse or diffuse the chemical incorporated therein without impairing the effectiveness of the toxic agent and which does no permanent damage to such environment as soil, equipment and agronomic crops.

For use as biocides, the compounds of this invention are usually formulated so as to render them suitable for subsequent dissemination. For example, the isothiazolones may be formulated as wettable powders, emulsion concentrates, dusts, granular formulations, aerosols or flowable emulsifiable concentrates. In such formulations, the isothiazolones are extended with a liquid or solid carrier and, when desired, suitable surfactants are likewise incorporated.

Compounds provided by this invention may be dissolved in a water-miscible liquid, such as ethanol, isopropanol or acetone. Such solutions are easily extended with water.

The isothiazolones may be taken up on or mixed with a finely particled solid carrier, as for example, clays, inorganic silicates, carbonates, and silicas. Organic carriers may also be employed. Dust concentrates are commonly made wherein isothiazolones are present in the range of 20 to 80% by weight. For ultimate applications, these concentrates are normally extended with additional solid from about 1 to 20% by weight.

Wettable powder formulations are made by incorporating the compounds of this invention in an inert, finely divided solid carrier along with a surfactant which may be one or more emulsifying, wetting, dispersing or spreading agents or blend of these. The isothiazolones are usually present in the range of 10 to 80% by weight, and the surfactants in from 0.5 to 10% by weight. Commonly used emulsifying and wetting agents include polyoxyethylated derivatives of alkylphenols, fatty alcohols, fatty acids, and alkylamines; alkylarene sulfonates and dialkyl sulfosuccinates. Spreading agents include such materials as glycerol mannitan laurate and a condensate of polyglycerol and oleic acid modified with phthalic anhydride. Dispersing agents include such materials as the sodium salt of the copolymer of maleic anhydride and an olefin such as diisobutylene, sodium lignin sulfonate and sodium formaldehydenaphthalene sulfonates.

One convenient method for preparing a solid formulation is to impregnate the isothiazolone toxicant onto the solid carrier by means of a volatile solvent, such as acetone. In this manner, adjuvants, such as activators, adhesives, plant nutrients, synergists and various surfactants, may also be incorporated.

Emulsifiable concentrate formulations may be prepared by dissolving the isothiazolones provided by this invention in an agronomically acceptable organic solvent and adding a solvent-soluble emulsifying agent. Suitable solvents are usually water-immiscible and may be found in the hydrocarbon, chlorinated hydrocarbon, ketone, ester, alcohol and amide classes of organic solvents. Mixtures of solvents are commonly employed. The surfactants useful as emulsifying agents may constitute about 0.5 to 10% by weight of the emulsifiable concentrate and may be anionic, cationic, or non-ionic in character. Anionic surfactants include alcohol sulfates or sulfonates, alkylarene sulfonates and sulfosuccinates. Cationic surfactants include fatty acid alkylamine salts and fatty acid alkyl quaternary compounds. Non-ionic emulsifying agents include ethylene oxide adducts of alkylphenols, fatty alcohols, mercaptans and fatty acids. The concentration of the active ingredients may vary from 10 to 80% by weight, preferably in the range of 25 to 50% by weight.

For use as phytopathogenic agents, the isothiazolones should be applied in an effective

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amount sufficient to exert the desired biocidal activity by techniques well known in the art. Usually, this will involve the application of the isothiazolones to the loci to be protected in an effective amount when incorporated in an agronomically acceptable carrier. However, in certain situations it may be desirable and advantageous to apply the compounds directly onto the loci to be protected without the benefit of any substantial amount of carrier. This is a particularly effective method when the physical nature of the isothiazolones is such as to permit what is known as "low-volume" application, that is, when the compounds are in liquid form or substantially soluble in higher boiling solvents.

The application rate will, of course, vary depending upon the purpose for such application, the isothiazolones being utilized, the frequency of dissemination and the like.

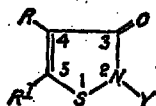
For use as agricultural bactericides and fungicides, dilute sprays may be applied at concentrations of 0.05 to 20 pounds of the active isothiazolone ingredient per 100 U.S. gallons of spray. They are usually applied at 0.1 to 10 pounds per 100 U.S. gallons and preferably at 0.125 to 5 pounds per 100 U.S. gallons. In more concentrated sprays, the active ingredient is increased by a factor of 2 to 12. With dilute sprays, applications are usually made to the plants until run-off is achieved, whereas with more concentrated or low-volume sprays the materials are applied as mists.

The compounds of this invention may be utilized as the sole biocidal agents or they may be employed in conjunction with other fungicides, insecticides, miticides and comparable pesticides.

In field tests, the isothiazolones described above were effective in controlling fungi which cause broccoli downy mildew (*Peronospora parasitica*), bean powdery mildew (*Erysiphe polygoni*), wheat powdery mildew (*Erysiphe graminis*), rice blast (*Piricularia oryzae*), and tomato blights (*Phytophthora infestans*) and (*Alternaria solani*).

WHAT WE CLAIM IS:—

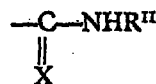
1. A compound of the general formula



(I)

wherein Y is 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, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, dialkylaminoalkyl in which each alkyl group con-

tains up to 4 carbon atoms or a carbamoyl group of the formula



in which R and R^I are hydrogen, halogen or C_1-C_4 alkyl when Y is other than the carbamoyl group provided that both R and R^I are not hydrogen when Y is methyl or ethyl;

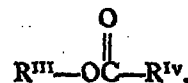
R is hydrogen, C_1-C_4 alkyl, halogen or cyano when Y is the carbamoyl group;

R^I is C_1-C_4 alkyl or C_1-C_4 haloalkyl when R is hydrogen, C_1-C_4 alkyl or halogen;

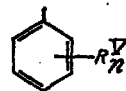
R^I is a C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl or C_1-C_4 alkylsulfonyl when R is cyano;

X is oxygen or sulfur; and

R^{II} is C_1-C_{18} alkyl, C_1-C_4 alkylsulphonyl, arylsulfonyl, halogen- or (C_1-C_4) -alkyl-substituted arylsulfonyl, or 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 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 0, 1, 2 or 3.

2. A compound according to Claim 1 wherein Y is 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, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl or dialkylamino-alkyl in which each alkyl group contains up to 4 carbon atoms.

3. A compound according to Claim 1 wherein Y is the carbamoyl group as defined in Claim 1.

4. A compound according to Claim 3 wherein X is oxygen.

5. A compound according to Claim 4 wherein R^{II} is C_1-C_{18} alkyl.

6. A compound according to Claim 2 wherein Y is C_3-C_{18} alkyl and the acid salts thereof.

7. A compound according to Claim 1 wherein R is halogen.

8. A compound according to Claim 1 or 2 wherein R^I is halogen.

9. A compound according to Claim 8 wherein R^I is chloro.

10. A compound as defined in Claim 1 except that Y may also represent aralkyl of up to 10 carbon atoms substituted with halo-

amount sufficient to exert the desired biocidal activity by techniques well known in the art. Usually, this will involve the application of the isothiazolones to the loci to be protected in an effective amount when incorporated in an agronomically acceptable carrier. However, in certain situations it may be desirable and advantageous to apply the compounds directly onto the loci to be protected without the benefit of any substantial amount of carrier. This is a particularly effective method when the physical nature of the isothiazolones is such as to permit what is known as "low-volume" application, that is, when the compounds are in liquid form or substantially soluble in higher boiling solvents.

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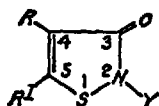
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WHAT WE CLAIM IS:—

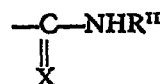
1. A compound of the general formula



(I)

wherein Y is 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, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, dialkylaminoalkyl in which each alkyl group con-

tains up to 4 carbon atoms or a carbamoyl group of the formula



in which R and R^I are hydrogen, halogen or C_1-C_4 alkyl when Y is other than the carbamoyl group provided that both R and R^I are not hydrogen when Y is methyl or ethyl;

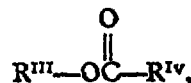
R is hydrogen, C_1-C_4 alkyl, halogen or cyano when Y is the carbamoyl group;

R^I is C_1-C_4 alkyl or C_1-C_4 haloalkyl when R is hydrogen, C_1-C_4 alkyl or halogen;

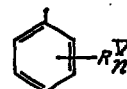
R^I is a C_1-C_4 alkylthio, C_1-C_4 alkylsulfanyl or C_1-C_4 alkylsulfonyl when R is cyano;

X is oxygen or sulfur; and

R^{II} is C_1-C_{18} alkyl, C_1-C_4 alkylsulphonyl, arylsulfonyl, halogen- or (C_1-C_4) -alkyl-substituted arylsulfonyl, or 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 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 0, 1, 2 or 3.

2. A compound according to Claim 1 wherein Y is 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, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl or dialkylamino-alkyl in which each alkyl group contains up to 4 carbon atoms.

3. A compound according to Claim 1 wherein Y is the carbamoyl group as defined in Claim 1.

4. A compound according to Claim 3 wherein X is oxygen.

5. A compound according to Claim 4 wherein R^{II} is C_1-C_{18} alkyl.

6. A compound according to Claim 2 wherein Y is C_3-C_{18} alkyl and the acid salts thereof.

7. A compound according to Claim 1 wherein R is halogen.

8. A compound according to Claim 1 or 2 wherein R^I is halogen.

9. A compound according to Claim 8 wherein R^I is chloro.

10. A compound as defined in Claim 1 except that Y may also represent aralkyl of up to 10 carbon atoms substituted with halo-





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gen, C_1-C_4 alkyl or C_1-C_4 alkoxy or aryl substituted with nitro, alkylacylamino or carbalkoxy in each of which the alkyl group contains up to 4 carbon atoms, or sulfamoyl and except that R^1 may also represent hydrogen or halogen when R is hydrogen, C_1-C_4 alkyl or halogen with the proviso that both R and R^1 are not hydrogen when Y is methyl or ethyl.

11. 2 - (3,4 - Dichlorophenyl) - 3 - isothiazolone.

12. 2 - Benzyl - 3 - isothiazolone.

13. 2 - n - Propyl - 3 - isothiazolone.

14. 2 - Cyclohexyl - 3 - isothiazolone.

15. 5 - Chloro - 2 - methyl - 3 - isothiazolone.

16. 2 - (N - Methylcarbamoyl) - 3 - isothiazolone.

17. 4 - Bromo - 5 - methyl - 2 - (N - methylcarbamoyl) - 3 - isothiazolone.

18. 2 - (N - n - Butylcarbamoyl) - 3 - isothiazolone.

19. A salt of a compound according to Claim 1 in which Y is other than carbamoyl.

20. A salt of a compound according to Claim 10 in which Y is other than carbamoyl.

21. A compound according to Claim 10 being any of those individual compounds (or salts thereof) disclosed in the foregoing specification with the exception of the compounds claimed in Claims 11-18.

22. A biocidal composition containing (I) at least one compound according to Claim 10, 2 - methyl - 3 - isothiazolone, 2 - ethyl - 3 - isothiazolone or a salt of any of such compounds and (II) a surfactant, adhesive agent, another pesticide or a solid diluent.

23. A composition according to Claim 22 containing a compound according to any one of Claims 11-18.

24. Seeds treated, as hereinbefore defined, with a compound according to Claim 10 or a salt thereof.

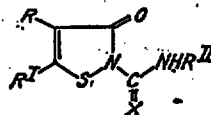
25. Seeds treated, as hereinbefore defined, with any of the compounds listed in foregoing Table IV with the exception of 2 - n - octyl - 3 - isothiazolone.

26. A substrate containing a biocide in an amount sufficient to render it less susceptible to deterioration due to the attack of micro-organisms, wherein the biocide is a compound according to Claim 10, 2 - methyl - 3 - isothiazolone, 2 - ethyl - 3 - isothiazolone or a salt of any of such compounds and wherein said substrate is a fabric, a soap, a sanitizing agent, a metal working compound, an aqueous film-forming composition, paint, paper pulp, swimming pool water or water in use in a cooling tower.

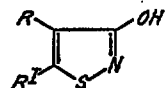
27. A substrate according to Claim 26 which is a liquid medium in which the biocidal compound is incorporated in an amount

from 0.1 to 10,000 parts per million based on the weight of the medium.

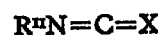
28. A process for preparing a compound of the formula



which comprises reacting a compound of the formula

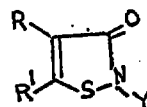


with a compound of the formula

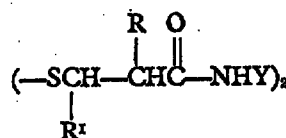


wherein R, R^1 , R^u and X are as defined in Claim 1.

29. A process for the preparation of a compound of the formula:



where Y is as defined in Claim 1 or 10 with the proviso that it is other than hydroxyalkyl, carbamoyl or thiocarbamoyl and R and R^1 are hydrogen or C_1-C_4 alkyl with the proviso that at least one of R and R^1 is other than hydrogen when Y is methyl or ethyl, which process comprises cyclizing a disulfide-amide of the formula



where R, R^1 and Y are as above defined, the cyclization being carried out by reacting the disulfide-amide with a halogenating agent.

30. A compound according to Claim 10 whenever prepared by a process according to Claim 28 or 29.

31. A method in which a vendible product is treated with a biocide to render it less susceptible to deterioration due to infestation by fungi, bacteria, algae, nematodes, mites or insects wherein the biocide is any compound as listed under (I) in Claim 22.

32. Seeds treated, as hereinbefore defined, with 2 - n - octyl - 3 - isothiazolone.

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