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3,562,283

1-OXO AND 1,1-DIOXO-3-ISOTHIAZOLONES

Sheldon N. Lewis, Willow Grove, and George A. Miller, Glenside, Pa., assignors to Rohm and Haas Company, Philadelphia, Pa., a corporation of Delaware
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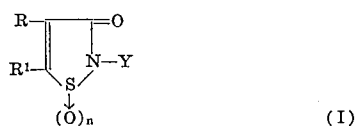
10 Claims

ABSTRACT OF THE DISCLOSURE

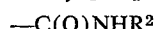
Novel compounds of the 1-oxo- and 1,1-dioxo-3-isothiazolone class of compounds which include 2-alkyl, 2-aryl, 2-carbamoyl and 4- and 5-alkyl and halo derivatives. These compounds are useful as pesticides.

This invention is concerned with 1-oxo-3-isothiazolone, 1,1-dioxo-3-isothiazolone and nuclear substituted derivatives thereof as new compounds and with their method of preparation.

These novel 3-isothiazolones may be represented by the formula



wherein Y is hydrogen, alkyl of 1 to 18 carbon atoms; cycloalkyl of 3 to 8 carbon atoms; aralkyl of up to 10 carbon atoms; halogen, lower alkyl or lower alkoxy substituted aralkyl of up to 10 carbon atoms; aryl, halogen, methyl or nitro substituted aryl; lower hydroxyalkyl, lower haloalkyl, lower carbalkoxyalkyl; lower cyanoalkyl; lower carboxyalkyl; or a carbamoyl group of the structure

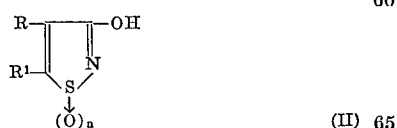


wherein R² is an alkyl group of 1 to 18 carbon atoms, the group $-CH_2COOR^3$ wherein R³ is alkyl of 1 to 18 carbon atoms, aryl or halo-substituted aryl; R and R¹ are individually selected from the group consisting of hydrogen, lower alkyl of 1 to 6 carbon atoms, halogen atoms and phenyl; and metallic, amine and quaternary ammonium salts of those compounds when Y is hydrogen or lower carboxyalkyl; and n is the integer 1 or 2.

Where the expression "lower" is employed in conjunction with terms such as alkyl, alkoxy, and various substituted alkyl's, it is intended to indicate that the alkyl or alkyl portion thereof has a carbon content of 1 to 4 carbon atoms. Typically, the alkyl or alkyl portion may be methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like.

The preferred structures corresponding to Formula I are those in which Y is hydrogen, alkyl of 1 to 18 carbon atoms, aryl, halosubstituted aryl or the carbamoyl group $-C(O)NHR^2$ as defined above.

When Y is hydrogen the compounds may exist in their isomeric form as the 3-hydroxyisothiazoles of the general structure



For the purpose of this invention the compounds shall be referred to as derivatives of 3-isothiazolone.

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

1-oxo-3-isothiazolone
1-oxo-2-methyl-3-isothiazolone

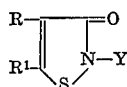
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1-oxo-2-isopropyl-3-isothiazolone
1-oxo-2-sec-butyl-3-isothiazolone
1-oxo-2-t-butyl-3-isothiazolone
1-oxo-2-pentyl-3-isothiazolone
1-oxo-2-hexyl-3-isothiazolone
1-oxo-2-heptyl-3-isothiazolone
1-oxo-2-octyl-3-isothiazolone
1-oxo-2-dodecyl-3-isothiazolone
1-oxo-2-octadecyl-3-isothiazolone
1-oxo-4-methyl-3-isothiazolone
1-oxo-4-ethyl-3-isothiazolone
1-oxo-4-butyl-3-isothiazolone
1-oxo-4-fluoro-3-isothiazolone
1-oxo-4-chloro-3-isothiazolone
1-oxo-4-bromo-3-isothiazolone
1-oxo-5-propyl-3-isothiazolone
1-oxo-4-sec-butyl-3-isothiazolone
1-oxo-4,5-dimethyl-3-isothiazolone
1-oxo-4-methyl-5-ethyl-3-isothiazolone
1-oxo-4-isopropyl-5-chloro-3-isothiazolone
1-oxo-4-chloro-5-ethyl-3-isothiazolone
1-oxo-4-bromo-5-isopropyl-3-isothiazolone
1-oxo-2-t-octyl-4-chloro-5-methyl-3-isothiazolone
1-oxo-2-phenyl-3-isothiazolone
1-oxo-2-(3,4-dichlorophenyl)-4-ethyl-3-isothiazolone
1-oxo-2-(4-chlorophenyl)-4,5-dichloro-3-isothiazolone
1-oxo-2-(propylcarbamoyl)-3-isothiazolone
1-oxo-2-(methylcarbamoyl)-4-chloro-3-isothiazolone
1-oxo-2-(ethylcarbamoyl)-4-chloro-5-methyl-3-isothiazolone
1-oxo-2-(phenylcarbamoyl)-3-isothiazolone
1-oxo-2-(3,4-dichlorophenyl)-5-methyl-3-isothiazolone
1-oxo-2-(N-carbomethoxymethylcarbamoyl)-3-isothiazolone
1-oxo-2-(N-carbethoxymethylcarbamoyl)-4-chloro-3-isothiazolone
1-oxo-2-(N-carbobutoxymethylcarbamoyl)-4-methyl-5-chloro-3-isothiazolone
1-oxo-2-cyclohexyl-3-isothiazolone
1-oxo-2-benzyl-3-isothiazolone
1-oxo-2-(2-hydroxyethyl)-3-isothiazolone
1-oxo-2-(2-chloroethyl)-3-isothiazolone
1-oxo-2-cyanomethyl-3-isothiazolone
1-oxo-2-carboxymethyl-3-isothiazolone
1-oxo-2-(2-carbomethoxyethyl)-3-isothiazolone
1,1-dioxo-3-isothiazolone
1,1-dioxo-2-methyl-3-isothiazolone
1,1-dioxo-2-propyl-3-isothiazolone
1,1-dioxo-2-decyl-3-isothiazolone
1,1-dioxo-2-octadecyl-3-isothiazolone
1,1-dioxo-4-methyl-3-isothiazolone
1,1-dioxo-4-propyl-3-isothiazolone
1,1-dioxo-4-t-butyl-3-isothiazolone
1,1-dioxo-4-chloro-3-isothiazolone
1,1-dioxo-4-bromo-3-isothiazolone
1,1-dioxo-5-chloro-3-isothiazolone
1,1-dioxo-5-ethyl-3-isothiazolone
1,1-dioxo-5-isopropyl-3-isothiazolone
1,1-dioxo-4-methyl-5-chloro-3-isothiazolone
1,1-dioxo-4-methyl-5-chloro-3-isothiazolone
1,1-dioxo-4-chloro-5-methyl-3-isothiazolone
1,1-dioxo-2-t-octyl-4-methyl-3-isothiazolone
1,1-dioxo-2-t-octyl-5-methyl-3-isothiazolone
1,1-dioxo-2-t-octyl-4,5-dimethyl-3-isothiazolone
1,1-dioxo-2-phenyl-3-isothiazolone
1,1-dioxo-2-(4-chlorophenyl)-4-methyl-3-isothiazolone
1,1-dioxo-2-(3,4-dichlorophenyl)-4-methyl-5-chloro-3-isothiazolone
1,1-dioxo-2-(2-chlorophenyl)-4-ethyl-3-isothiazolone
1,1-dioxo-2-(3-chlorophenyl)-5-chloro-3-isothiazolone
1,1-dioxo-2-(isopropoxycarbamoyl)-4-methyl-3-isothiazolone

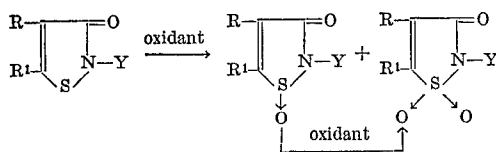
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1,1-dioxo-2-(phenylcarbamoyl)-3-isothiazolone
 1,1-dioxo-2-(3,4-dichlorophenylcarbamoyl)-3-isothiazolone
 1,1-dioxo-2-(N-carbethoxymethylcarbamoyl)-3-isothiazolone
 1,1-dioxo-2-cyclopentyl-3-isothiazolone
 1,1-dioxo-2-(4-chlorobenzyl)-3-isothiazolone
 1,1-dioxo-2-(2-hydroxypropyl)-3-isothiazolone
 1,1-dioxo-2-(3-chloropropyl)-3-isothiazolone
 1,1-dioxo-2-(2-cyanoethyl)-3-isothiazolone
 1,1-dioxo-2-(2-carboxyethyl)-3-isothiazolone
 1,1-dioxo-2-carbethoxymethyl-3-isothiazolone

The compounds of this invention may be prepared by oxidation of the corresponding 3-isothiazolones of the structure



wherein R, R¹ and Y have the meanings previously given. Depending on the reaction conditions for the oxidation either the 1-oxo or the 1,1-dioxo derivative or a mixture of these is produced. The 1-oxo derivative may be directly oxidized to the 1,1-dioxo derivative. The following equation depicts these reactions.



Oxidation of the sulfur atom in a 3-isothiazolone ring was not known in the literature prior to this invention.

Oxidations of isothiazole ring structures have been reported by N. R. Hatchard *Journal Organic Chemistry* 29, 667 (1964) and in C. A. 67, 90715 citing A. Bruno et al. *Gazz. chim. ital.* 96, 1009-19 (1966).

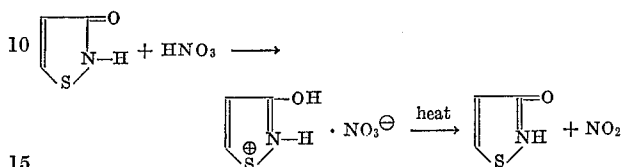
Various types of oxidizing agents may be employed, e.g. peracids such as hydrogen peroxide, performic acid, peracetic acid, perphthalic acid, perbenzoic acid and m-chloroperbenzoic acid; oxides of nitrogen such as dinitrogen tetroxide; nitric acid; and chromic compounds such as chromium trioxide and chromic acid-sulfuric acid (Jones' reagent).

When peracids (R'CO₃H) are employed for the oxidation and the 1-oxo derivative is desired, it is preferred to use no more than one equivalent of the peracid. To prepare the 1,1-dioxo derivative at least two equivalents are theoretically required, but three or more equivalents may be used. Although the oxidations may be run in the absence of a solvent, the use of a solvent is preferred. Any solvent which is not itself oxidized may be used and solvents in the ester, ketone, aliphatic and aromatic hydrocarbon and chlorinated hydrocarbon classes are commonly employed. The chlorinated aliphatic hydrocarbons are preferred. Temperaturewise the reactions may be run in the range of -5° to 60° C. with lower temperatures, e.g. 0° to 15° C., being preferred for the 1-oxo derivatives and higher temperatures, e.g. 5°-25° C., being preferred for the 1,1-dioxo derivatives.

When an oxide of nitrogen such as N₂O₄ is employed at least one equivalent is theoretically required for conversion to the 1-oxo derivative. With this type of oxidizing agent, oxidation to the 1,1-dioxo stage is more difficult and even with excesses of the dinitrogen tetroxide the major product is the 1-oxo derivative. An inert solvent, for example from the ether and chlorinated classes of solvents, is commonly employed although the reaction will proceed in the absence of a solvent. The reaction is usually run in the temperature range of -5° to 35° C. with 0° to 15° C. being preferred. In some instances the nitric acid salt of the 3-isothiazolone forms and this upon mild heating is converted to the 1-oxo derivative.

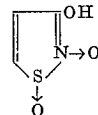
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When nitric acid is used as the oxidizing agent, the acid may have a concentration in the range of 35 to 70% with 65 to 70% being preferred. The reaction temperature may be in the range of -5° to 35° C. with 0° to 15° C. being preferred. The usual product is the 1-oxo derivative, which may be formed from the nitrate salt by mild heating, e.g. in benzene, which is illustrated for 3-isothiazolone as follows:



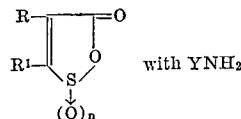
When chromic acid is used as the oxidizing agent it may be employed in from 0.5 to 2 or more equivalents. The 1-oxo derivative is readily formed. The 1,1-dioxo derivative is more difficult to prepare and isolate. An inert solvent, such as a ketonic solvent, is commonly employed although the oxidation will proceed in the absence of a solvent. The reaction is usually run at about room temperature, but will proceed at 0° to 60° C. with 15° to 35° C. being preferred.

Since the possibility existed that oxidation could occur on the N atom of the isothiazolone nucleus, the compounds were examined by spectral and other physical means to distinguish between -NO and -SO or -SO₂ oxidized ring structures. For example structures such as

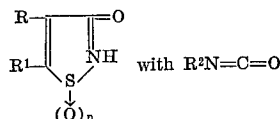


could have been formed. Infrared absorption data showed a strong sulfoxide absorption in the 9.0-9.4μ range for the mono-oxidized products and a strong sulfonyl absorption at 7.55 and 8.4-8.7μ for the dioxidized materials. These data are consistent for the literature values for characteristic sulfoxide and sulfonyl absorptions and not in conformance with N-oxide absorption of related structures. Ultraviolet absorption data, nuclear magnetic resonance data and mass spectra lead to the same conclusion that the products are 1-oxo and 1,1-dioxo-3-isothiazolones.

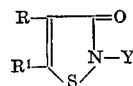
Alternate methods of preparation by which the compounds of this invention may be made include (a) reaction of



wherein R, R¹, Y and n have the meanings given above, and (b) where Y is a -C(O)NHR² group by reaction of



where R, R¹, R² and n have the meanings given above. Because of the availability of the starting 3-isothiazolones, the oxidation of these is the preferred procedure. The 3-isothiazolones of the structure



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are available by methods described in Lewis and Miller patent application U.S. Ser. No. 621,770, filed Mar. 9, 1967 and Lewis, Miller and Law U.S. Ser. No. 672,437, filed Oct. 3, 1967 assigned to a common assignee and which are incorporated herein by reference.

By way of demonstration the following examples are offered to illustrate this invention and are not to be construed as limitations thereof. Table I lists Examples 1-14 of the 1-oxo derivatives and Table II lists Examples 15-19 of the 1,1-dioxo derivatives. Table III lists the method of preparation, yields and melting points for these examples. Table IV gives analytical data for these examples. Specific illustrative preparations of Examples 1, 2 and 15 are set forth below.

EXAMPLE 1.—PREPARATION OF 1-OXO-3-ISOTHIAZOLONE

Method A.—Oxidation of a 3-isothiazolone with a peracid

To a solution of 10.1 g. (0.1 mole) of 3-isothiazolone in 100 ml. of methylene chloride was added dropwise at 0°-10° C. a solution of 21.3 g. (0.1 mole) of m-chloroperbenzoic acid (81% by iodide-thiosulfate titration) in 200 ml. of methylene chloride. The reaction mixture was stirred 0.5 hour and then evaporated to dryness. The residue, after trituration with ether, was 7.1 g. of solid which after recrystallization from benzene melted at 95°-96° C. This is a 60% yield of 1-oxo-3-isothiazolone.

Method B.—Oxidation of a 3-isothiazolone with dinitrogen tetroxide

To a solution of 20.2 g. (0.2 mole) of 3-isothiazolone in 150 ml. of ether at 0°-10° C. was added a solution of 18.4 g. (0.2 mole) of N₂O₄ in 25 ml. of hexane over a period of 5 minutes. The reaction slurry was stirred 10 minutes then filtered to give 21 g. of solid melting at 81°-85° C., which is considered to be 3-hydroxyisothiazole nitrate salt. This salt when crystallized from hot benzene gave off brown fumes of an oxide of nitrogen. The benzene solution upon cooling yielded 14 g. of solid melting at 93°-95° C. This is a 60% yield of 1-oxo-3-isothiazolone.

When the above reaction was carried out at 10°-20° C. there was directly obtained a 70% yield of 1-oxo-3-isothiazolone without the intermediate isolation of 3-hydroxyisothiazole nitrate salt.

Method C.—Oxidation of 3-isothiazolone with nitric acid

A solution of 5 g. (0.05 mole) of 3-isothiazolone in 30 ml. of water was added to 50 g. of concentrated (70%)

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nitric acid at 0° C. A solid formed and after stirring 15 minutes at 0° C. was filtered off and dried to give 6.2 g. of a solid melting at 93°-95° C. from ethanol. The solid was found by analysis to contain 21.92% C, 2.03% H, 16.18% N and 19.21% S; calculated for C₃H₄N₂O₄S is 22.1% C, 1.84% H, 17.1% N and 19.6% S. The solid is a 76% yield of 3-hydroxyisothiazole nitrate salt. Two grams of this salt when crystallized from hot benzene gave evolution of nitrogen dioxide and yielded 0.5 g., a 35% yield, of 1-oxo-3-isothiazolone, melting at 92°-94° C.

EXAMPLE 2.—PREPARATION OF 1-OXO-5-METHYL-3-ISOTHIAZOLONE

Method D.—Oxidation of a 3-isothiazolone with chromic acid

A solution of 11.5 g. (0.1 mole) of 5-methyl-3-isothiazolone in 750 ml. of acetone (purified by distillation from solid potassium permanganate) was treated dropwise at 25° C., under a continuous stream of nitrogen, with 50 ml. of Jones' Reagent (0.2 mole of oxidant) made by dissolving 26.7 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid and then diluting with water to 100 ml. over a period of 1.5 hour. After stirring at room temperature for 18 hours, the reaction was concentrated to 25 g. of green, liquid residue. The residue was diluted with 100 ml. of water and continuously extracted 24 hours to give, after drying and evaporation of the ether, 9.5 g. of light yellow oil. This is a 65% yield of 1-oxo-5-methyl-3-isothiazolone.

EXAMPLE 15.—PREPARATION OF 1,1-DIOXO-3-ISOTHIAZOLONE

Method E.—Oxidation of a 3-isothiazolone

A solution of 10.1 g. (0.1 mole) of 3-isothiazolone in 200 ml. of methylene chloride was treated in portions with 47.3 g. (0.22 mole) of 81% pure m-chloroperbenzoic acid. A slurry resulted and was stirred at room temperature for 2 days. The residue was filtered off and extracted with hot chloroform to give 6.65 g. of insoluble solid melting at 118°-120° C. This is a 49% yield of 1,1-dioxo-3-isothiazolone.

Method F.—Oxidation of 1-oxo-3-isothiazolone

A solution of 2.85 g. (0.024 mole) of 1-oxo-3-isothiazolone in 100 ml. of methylene chloride was treated in portions at 25° C. with 5.17 g. (0.024 mole) of 81% pure m-chloroperbenzoic acid. The resulting slurry was stirred 2 days at room temperature. The reaction mixture was evaporated to dryness and the residue trituated twice with benzene. There was obtained 1.7 g. of insoluble residue melting at 113°-118° C. This is a 53% yield of 1,1-dioxo-3-isothiazolone.

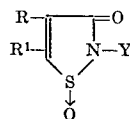


TABLE I.—1-OXO-3-ISOTHIAZOLONE EXAMPLES

Example No.:	R	R ¹	Y	Name
1.....	H	H	H	1-oxo-3-isothiazolone.
2.....	H	CH ₃	H	1-oxo-5-methyl-3-isothiazolone.
3.....	Br	CH ₃	H	1-oxo-4-bromo-5-methyl-3-isothiazolone.
4.....	Cl	Cl	H	1-oxo-4,5-dichloro-3-isothiazolone.
5.....	H	H	-C ₈ H ₁₇ -t	1-oxo-2-t-octyl-3-isothiazolone.
6.....	CH ₃	H	-C ₆ H ₅ Cl-3,4	1-oxo-2-(3,4-dichlorophenyl)-4-methyl-3-isothiazolone.
7.....	H	H	-C(O)NHC ₆ H ₅	1-oxo-2-(N-methylcarbamoyl)-3-isothiazolone.
8.....	H	H	-C(O)NHC ₆ H ₅	1-oxo-2-(N-ethylcarbamoyl)-3-isothiazolone.
9.....	H	H	-C(O)NHC ₆ H ₅ COOC ₂ H ₅	1-oxo-2-(N-carbethoxymethylcarbamoyl)-3-isothiazolone.
10.....	H	CH ₃	-C(O)NHC ₆ H ₅	1-oxo-2-(N-phenylcarbamoyl)-3-isothiazolone.
11.....	H	H	-C(O)NHC ₆ H ₄ Cl-3	1-oxo-2-(N-3-chlorophenylcarbamoyl)-3-isothiazolone.
12.....	H	H	-C(O)NHC ₆ H ₃ Cl ₂ -2,5	1-oxo-2-(N-2,4-dichlorophenylcarbamoyl)-3-isothiazolone.
13.....	H	H	-C(O)NHC ₆ H ₃ Cl ₃ -3,4	1-oxo-2-(N-3,4-dichlorophenylcarbamoyl)-3-isothiazolone.
14.....	H	CH ₃	-C(O)NHC ₆ H ₃ Cl ₃ -3,4	1-oxo-2-(N-3,4-dichlorophenylcarbamoyl)-5-methyl-3-isothiazolone.

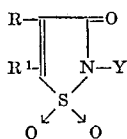


TABLE II.—1,1-DIOXO-3-ISOTHIAZOLONE EXAMPLES

Example No.	R	R1	Y	Name
15.....	H	H	H	1,1-dioxo-3-isothiazolone.
16.....	H	CH ₃	H	1,1-dioxo-5-methyl-3-isothiazolone.
17.....	H	H	—C ₈ H ₁₇ -t	1,1-dioxo-2-t-octyl-3-isothiazolone.
18.....	CH ₃	H	—C ₆ H ₃ Cl ₂ -3,4	1,1-dioxo-2-(3,4-dichlorophenyl)-4-methyl-3-isothiazolone.
19.....	H	H	—C(O)NHC ₂ H ₅	1,1-dioxo-2-(N-ethylcarbamoyl)-3-isothiazolone.

TABLE III.—PREPARATIVE DATA

	Method of preparation	Melting point (° C.)	Yield (percent)
Example:			
1.....	A	93-95	60
	B		60
	C		35
2.....	D	(¹)	65
3.....	A	130-132	46
	B		100
	D		56
4.....	B	142-145	50
5.....	A	75-76	100
6.....	A	108-111	89
7.....	A	160-163	80
8.....	A	100-103	70
9.....	A	(¹)	61
10.....	A	170-173	67
11.....	A	148-151	87
12.....	A	153-154	72
13.....	A	189-192	81
14.....	A	172-175	72
15.....	E	118-120	49
	F		53
16.....	E	105-110	20
17.....	E	63-65	82
18.....	E	167-170	51
19.....	E	125-128	44

¹ Oil.² Decomposition.

mites, insects, phytopathogenic fungi, and various micro-organisms such as bacteria, fungi and algae.

One method of evaluation used was by a procedure known as a streak test. In this test the compounds to be examined were dissolved in an appropriate solvent and added to two sterile Petri plates in an amount necessary to provide 1000 p.p.m. of the compound in one plate and 100 p.p.m. in the other plate when diluted with 20 ml. of the appropriate nutrient agar. The compound and the agar were thoroughly mixed and allowed to harden. The agar surface was streaked with agar-grown cultures of representative bacterial, fungal or algal cultures. The plates were then incubated at the appropriate time and temperature for the given culture and then observed for inhibition of growth. The following system was employed to rate the activity of the compounds:

0=complete inhibition
 1+=slight growth
 2+=moderate inhibition
 3+=slight inhibition
 4+=no inhibition

Table V gives the results using three bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*); three

TABLE IV.—ANALYTICAL DATA

TABLE IV. ANALYTICAL DATA									
Examp- le	Empirical formula	Analysis (percent of the element found; calculated values in parentheses)							
		C	H	N	S	Halogen or Oxygen			
1.....	C ₃ H ₃ NO ₃ S	30.63	(30.8)	2.62	(2.6)	11.53	(11.9)	26.18	(27.4)
2.....	C ₄ H ₅ NO ₃ S	34.61	(36.6)	4.30	(3.8)	9.62	(10.7)	20.66	(24.4)
3.....	C ₄ H ₅ BrNO ₃ S	22.75	(22.9)	1.96	(1.9)	6.48	(6.7)	14.86	(15.3)
4.....	C ₃ H ₃ Cl ₂ NO ₃ S	20.60	(19.4)	1.10	(0.5)	7.39	(7.5)	17.07	(17.2)
5.....	C ₁₁ H ₁₀ NO ₃ S	57.75	(57.7)	8.48	(8.4)	6.18	(6.1)	13.75	(14.0)
6.....	C ₁₀ H ₉ Cl ₂ NO ₃ S	44.96	(45.1)	2.86	(2.7)	5.15	(5.3)	11.80	(12.0)
7.....	C ₃ H ₃ N ₂ O ₃ S	34.52	(34.4)	3.48	(3.4)	16.00	(16.1)	-----	Oxygen, 27.79 (27.5).
8.....	C ₃ H ₃ N ₂ O ₃ S	38.47	(38.3)	4.33	(4.3)	14.28	(14.9)	-----	Oxygen, 25.75 (25.5).
9.....	C ₃ H ₃ N ₂ O ₃ S	40.06	(39.0)	4.09	(4.1)	11.65	(11.4)	-----	Oxygen, 31.93 (32.5).
10.....	C ₁₁ H ₁₀ N ₂ O ₃ S	61.41	(61.5)	8.84	(9.0)	8.90	(9.0)	10.12	(10.3)
11.....	C ₁₀ H ₇ ClN ₂ O ₃ S	44.26	(44.4)	2.80	(2.6)	10.34	(10.4)	12.08	(11.8)
12.....	C ₁₀ H ₇ Cl ₂ N ₂ O ₃ S	39.49	(39.4)	2.04	(2.0)	9.24	(9.2)	10.82	(10.5)
13.....	C ₁₀ H ₇ Cl ₂ N ₂ O ₃ S	39.49	(39.4)	1.93	(2.0)	9.24	(9.2)	10.09	(10.5)
14.....	C ₁₁ H ₈ Cl ₂ N ₂ O ₃ S	40.60	(41.2)	2.60	(2.5)	8.90	(8.8)	9.83	(10.0)
15.....	C ₃ H ₃ NO ₃ S	27.23	(27.1)	2.61	(2.3)	10.36	(10.5)	23.98	(24.1)
16.....	C ₄ H ₅ NO ₃ S	32.83	(32.7)	3.47	(3.4)	9.21	(9.5)	-----	-----
17.....	C ₁₁ H ₁₀ NO ₃ S	53.77	(53.9)	7.74	(7.8)	5.73	(5.7)	12.82	(13.0)
18.....	C ₁₀ H ₇ Cl ₂ NO ₃ S	41.11	(41.1)	2.55	(2.4)	4.82	(4.8)	10.90	(11.0)
19.....	C ₃ H ₃ NO ₄ S	35.33	(35.3)	4.26	(3.9)	13.20	(13.7)	15.50	(15.7)

The novel 1-oxo and 1,1-dioxo-3-isothiazolones of this invention are biologically active. Representative compounds have effective control of various types of weeds, 75

fungi *Aspergillus niger* (*A. niger*), *Rhizopus* spp. (*Rhiz.*) and *Rhodotorula* spp. (*Rhod.*) and three algae *Chlorella pyrenoidosa* (*Chlorella*), *Scenedesmus obliquus* (*Scene.*) and *Phormidium* spp. (*Square D*).

TABLE V.—CONTROL OF MICROORGANISMS (RANK IN STREAK TEST)

	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>A. niger</i>	Rhiz.	Rhod.	Chlorella	Scene.	Square D
Example:									
2.....	0	0	0	3+	4+	2+	3+	4+	2+
3.....	0	0	0	4+	4+	4+	2+	4+	3+
5.....	0	0	0	0	0	0	1	4+	4+
6.....	0	0	0	1+	2+	3+	0	0	0
7.....	0	0	0	0	0	0	1+	0	4+
8.....	0	0	0	4+	4+	4+	4+	4+	3+
9.....	0	0	0	4+	4+	4+	4+	4+	4+
10.....	0	0	0	4+	0	1+	4+	4+	1+
11.....	0	0	0						
12.....	0	0	1+	1+	0	1+	0	0	0
13.....	0	0	1+	2+	0	1+	3+	3+	2+
14.....	0	0	0	4+	4+	4+	0	0	0
15.....	0	0	0	4+	4+	4+	4+	4+	4+
16.....	0	2+	0						
17.....	4+	0	4+	4+	4+	4+	4+	4+	4+
18.....	4+	4+	2+	4+	4+	2+	3+	4+	4+
19.....	0	1+	0	4+	4+	4+	4+	4+	4+

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 represent the maximum dilution at which the compound under evaluation renders complete control of the organism. Table VI gives this value for the organisms *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*).

TABLE VI.—SERIAL DILUTION TEST

	<i>S. aureus</i>	<i>E. coli</i>
Example:		
1.....	1:2,000	1:4,000
2.....	1:2,000	1:2,000
3.....	1:2,000	1:2,000
5.....	1:1,000	1:1,000
6.....	1:32,000	1:1,000
7.....	<1:1,000	1:1,000
8.....	1:1,000	1:1,000
9.....	1:1,000	1:1,000
10.....	1:1,000	1:2,000
11.....	1:2,000	1:1,000
12.....	1:4,000	1:1,000
13.....	1:32,000	1:1,000
15.....	1:1,000	1:1,000
16.....	<1:1,000	1:1,000
17.....	1:8,000	1:1,000
18.....	<1:1,000	1:1,000
19.....	<1:1,000	<1:1,000

Representative compounds of this invention were evaluated as fungicides in standard greenhouse tests. The compound of Example 3 when used to treat corn seed at a rate of 1 oz. per bushel gave good protection of the seed when planted in soil infested with *Pythium* sp. The compound of Example 6 gave good protection of rice by a foliar spray containing 1200 p.p.m. against *Helminthosporium oryzae* and of beans by a foliar spray containing 150 p.p.m. against *Erysiphe polygoni*. Tomato foliage was protected against the bacterial canker disease, *Corynebacterium michiganense* by an aqueous spray containing 1200 p.p.m. of the compound of Example 8. The compound of Example 13 as a spray containing 1200 p.p.m. protected tomato plants from late blight, *Phytophthora infestans*. The compound of Example 18 at 1200 p.p.m. gave excellent protection against *Corynebacterium michiganense*, *Phytophthora infestans*, the rice blast disease *Piricularia oryzae* and downy mildew of grapes *Plasmopara viticola*.

In standard greenhouse tests on the various stages of the two-spotted mite, *Tetranychus urticae*, using sprays containing 1% of the active ingredient the compound of Example 6 gave a 50% control of the mite eggs and 100% control of the adult mites, the compounds of Examples 8 and 9 gave 100% control as mite ovicides, and the compound of Example 13 gave 90% control of the mite larvae. As a 1% spray the compound of Example 2 gave a 60% control of the cabbage looper, *Trichoplusia ni*, and the compound of Example 3 gave excellent control of the root knot nematode, *Meloidogyne hapla*.

Representative compounds of this invention were evaluated in a standard postemergence type herbicide test.

In this test two-week old plants were sprayed with the test compound at a rate of 10 lbs. per acre. Four monocotyledonous species including millet (*Setaria italica*), rye grass (*Lolium multiflorum*), sorghum (*Sorghum vulgare*) and wildoats (*Avena fatua*) and four dicotyledonous plants curly dock (*Rumex crispus*), flax (*Linum usitatissimum*), tomatoes (*Lycopersicon esculentum*) and velvet-leaf (*Abutilon theophrasti*) were used. The percent injury was measured two weeks after application. The data are presented in Table VII as the average percent injury for the monocotyledonous species (Monocots) and for the dicotyledonous species (Dicots).

TABLE VII.—HERBICIDAL DATA

	Percent injury	
	Monocots	Dicots
Example:		
1.....	68	83
2.....	100	100
3.....	95	85
5.....	52	95
6.....	52	88
7.....	58	82
8.....	35	48
9.....	32	42
10.....	52	80
11.....	8	25
12.....	5	25
13.....	48	50
14.....	100	100
16.....	15	22
17.....	75	100
18.....	65	92
19.....	82	100

In general, loci subject to attack by microorganisms may be protected in accordance with this invention by incorporating into said loci one or more of the 1-oxo and 1,1-dioxo-3-isothiazolones in an amount which is effective to control said microorganisms. The exact amount of the 3-isothiazolone will, of course, vary with the medium being protected, the microorganisms being controlled, the particular compound or composition being employed and the like. Commonly this is the range of from 0.1 to 10,000 p.p.m.

For use as pesticides the compounds of this invention may be used as solutions in organic solvents or formulations. For example they may be formulated as wettable powders, emulsifiable concentrates, dusts, granular formulations or flowable emulsifiable concentrates. In such formulations the 1-oxo and 1,1-dioxo-3-isothiazolones are extended with an agronomically acceptable liquid or solid carrier and, when desired, suitable surfactants are likewise incorporated. Surfactants commonly used in the art may be found in the John W. McCutcheon, Inc. publication "Detergents and Emulsifiers 1967 Annual."

The isothiazolones may be taken up on or mixed with a finely particled solid carrier, as for example, clays, in organic 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%. For ultimate applications, these concentrates

are normally extended with additional solid from about 1 to 20%.

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 surfactants in from 0.5 to 10% by weight.

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 of 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. The concentration of the active ingredients may vary from 10 to 80%, preferably in the range of 25 to 50%.

For use as phytopathogenic agents, these compounds should be applied in an effective 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.

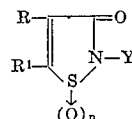
For use as miticides, insecticides, agricultural bactericides and fungicides, dilute sprays may be applied at concentrations of 0.05 to 20 pounds of the active isothiazolone ingredient per 100 gallons of spray. They are usually applied at 0.1 to 10 pounds per 100 gallons and preferably at 0.125 to 5 pounds per 100 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.

For use as herbicides the compounds may be applied at a rate of 0.25 to 50 pounds of the active ingredient per acre and preferably in the range of 1 to 15 pounds per acre.

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

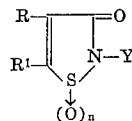
We claim:

1. A compound of the formula



wherein Y is hydrogen, alkyl of 1 to 18 carbon atoms; cycloalkyl of 3 to 8 carbon atoms; benzyl of up to 10 carbon atoms; halogen, lower alkyl or lower alkoxy substituted aralkyl of up to 10 carbon atoms; phenyl; halogen, methyl or nitro substituted phenyl; lower hydroxyalkyl, lower haloalkyl, lower carbalkoxyalkyl; lower cyanoalkyl; lower carboxyalkyl; or a carbamoyl group of the structure $-\text{C}(\text{O})\text{NHR}^2$ wherein R^2 is an alkyl group of 1 to 18 carbon atoms, the group $-\text{CH}_2\text{COOR}^3$ wherein R^3 is alkyl of 1 to 18 carbon atoms, phenyl or halo-substituted phenyl; R and R^1 are individually selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, halogen atoms and phenyl; and n is the integer 1 or 2.

2. A compound of the formula



wherein Y is hydrogen, alkyl of 1 to 18 carbon atoms, phenyl, halo-substituted phenyl or a carbamoyl group of the structure $-\text{C}(\text{O})\text{NHR}^2$ wherein R^2 is an alkyl group of 1 to 18 carbon atoms, the group $-\text{CH}_2\text{COOR}^3$ wherein R^3 is alkyl of 1 to 18 carbon atoms, phenyl or halo-substituted phenyl; R and R^1 are individually selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms and halogen atoms; and n is the integer 1 or 2.

3. The compounds of claim 1 wherein n of the formula is 1.

4. The compounds of claim 1 wherein n of the formula is 2.

5. The compound of claim 1 which is 1-oxo-3-isothiazolone.

6. The compound of claim 1 which is 1,1-dioxo-3-isothiazolone.

7. The compound of claim 1 which is 1-oxo-4-bromo-5-methyl-3-isothiazolone.

8. The compound of claim 1 which is 1-oxo-2-(3,4-dichlorophenyl)-4-methyl-3-isothiazolone.

9. The compound of claim 1 which is 1-oxo-2-(N-ethylcarbamoyl)-3-isothiazolone.

10. The compound of claim 1 which is 1,1-dioxo-2-(3,4-dichlorophenyl)-4-methyl-3-isothiazolone.

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ALEX MAZEL, Primary Examiner

R. J. GALLAGHER, Assistant Examiner

U.S. Cl. X.R.

260—302, 327; 424—270