AUSTRALIA

PATENTS ACT 1990

655608

PATENT REQUEST : STANDARD PATENT

I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant(s)/Nominated Person(s):

Rohm and Haas Company

of

Independence Mall West, Philadelphia, Pennsylvania, 19105, United States of America

[54] Invention Title:

Antimicrobial compositions comprising iodopropargyl butylcarbamate and 1,2-benzisothiazolone

[72] Name(s) of actual inventor(s):

Samuel Eugene SHERBA
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Basic Convention Application(s) Details:

[31] Application Number	[33] Country	Code	[32] Date of Application
619285	United States of America	US	27 November 1990

DATED this TWENTY SEVENTH day of NOVEMBER 1991

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a member of the firm of DAVIES COLLISON CAVE for and on behalf of the applicant(s)

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NOTICE OF ENTITLEMENT

We, **Rohm and Haas Company**, the applicant named in the accompanying Patent Request state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors.

The Nominated Person is entitled to claim priority from the basic application listed on the patent request because the Nominated Person is the assignee of the applicants in respect of the basic application, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY SEVENTH day of NOVEMBER 1991

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1451564)

AU9188234

(12) PATENT ABRIDGMENT (11) Document No. AU-B-88234/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 655608

(54) Title
ANTIMICROBIAL COMPOSITIONS COMPRISING IODOPROPARGYL BUTYLCARBAMATE AND 1,2-BENZISOTHIAZOLONE

(51)[5] International Patent Classification(s)
A61K 031/22 **A01N 033/02** **A01N 043/80** **A61L 002/18**
C02F 001/50 **D21H 021/36** **A61K 031/425**

(21) Application No. : **88234/91** (22) Application Date : **27.11.91**

(30) Priority Data

(31) Number	(32) Date	(33) Country
619285	**27.11.90**	**US UNITED STATES OF AMERICA**

(43) Publication Date : **28.05.92**

(44) Publication Date of Accepted Application : **05.01.95**

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(56) Prior Art Documents
AU 88236/91 A01N 47/12 43/40

(57) Claim

1. Composition comprising a first component which is 1,2-benzisothiazolone, and a second component which is iodopropargyl butylcarbamate; the ratio of the first component to the second component being from 10000:1 to 1:1000.

7. A method for inhibiting or preventing the growth of bacteria, fungi, or algae in a locus subject or susceptible to contamination thereby, which comprises incorporating onto or into the locus, in an amount effective to adversely affect said growth, a composition according to any preceding claim.

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COMPLETE SPECIFICATION

NAME OF APPLICANT(S):

Rohm and Haas Company

ADDRESS FOR SERVICE:

DAVIES COLLISON CAVE
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

INVENTION TITLE:

Antimicrobial compositions comprising iodopropargyl butylcarbamate and 1,2-benzisothiazolone

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

The present invention concerns microbicidal compositions and methods of controlling microbes.

Japanese Patent 217,907 of May 15, 1986 (Derwent Abstract 86-165153/26) discloses industrial fungicide compositions containing benzimidazole and/or isothiazolone derivatives and 3-iodo-2-propynyl N-butyl carbamate and/or 2,3,3-triiodo allyl alcohol.

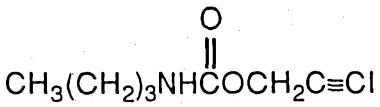
The presence of microbes in various aqueous systems such as latices, paints, coatings, cooling water systems, decorative ponds and the like, can cause deterioration or disfigurement of these systems. For example, painted surfaces may be disfigured by the unsightly buildup of microbes, thus detracting from the overall aesthetics of the painted article; cooling towers may lose efficiency due to the buildup of microbes on surfaces, thus reducing the heat transfer capabilities of the tower. It is conventional to practice methods which inhibit the microbial deterioration of such systems by incorporating a variety of additives or combination of additives that are characterized by having antimicrobial activity.

A wide variety of materials have been used to control microbes in different environments, some of which are: chlorine/bromine compounds, glutaraldehyde, isothiazolones, organotin formulations, copper salts, quaternary ammonium compounds (SD Strauss and PR Puckorius in *J. Power*, S[illegible] 1984), and triazines. Each has deficiencies related to toxicity, pH and temperature sensitivity, limited effectiveness, chemical stability, and/or compatibility.

Based on the aforementioned performance deficiencies of conventional antimicrobial compounds there is a need for more effective antimicrobial agents that can be used at lower dosage rates, thus being more cost effective for the end user, reducing the pollution load on the affected environmental systems, and

reducing the side effects to nearby non-target organisms, such as fish, useful crops, etc.

Among the many antimicrobial compounds which have been proposed, only a relatively small number have become useful in practice. Two examples are iodopropargyl butylcarbamate, which has the formula



and 1,2-benzisothiazolone. However, the use of these two compounds together has not previously been disclosed.

In a first aspect the present invention provides a composition comprising a first component which is 1,2-benzisothiazolone, and a second component which is iodopropargyl butylcarbamate; the ratio of the first component to the second component being from 10000:1 to 1:1000.

In another aspect, the invention provides a method for inhibiting or preventing the growth of bacteria, fungi, or algae in a locus subject or susceptible to contamination thereby, which comprises incorporating onto or into the locus, in an amount effective to adversely affect said growth, a composition as defined above.

Preferably the compositions of the invention further comprise an inert, agronomically acceptable or pharmaceutically acceptable carrier.

An important utility of the invention is in imparting microbial resistance to a coating or an impregnant composition comprising incorporation of the composition of the invention in the coating or impregnant, preferably at a concentration of about 0.1 ppm to about 2 percent, more preferably at a concentration of about 1 ppm to 1 percent, and most preferably at a concentration of about 10 to 4000 ppm.

In a marine antifoulant composition, on the other hand, the antimicrobial composition of the invention comprises about 1 to 10 percent of the antifoulant

composition.

In a therapeutic pharmaceutical formulation, e.g., lotion, cream, ointment or topical treatment; in the treatment of metal working fluids; and in the protection of fabric, leather, paper or wood materials, the microbicidal composition is added at a concentration of from about 0.1 ppm to about 2 percent by weight. In aqueous media, the microbicidal composition comprises from about 0.1 ppm to about 1 percent of the aqueous system depending on the specific end use; for example, in cooling water tower applications and with pulp or paper manufacturing processes, the microbicidal composition is added at a concentration from about 0.1 to about 1000 ppm by weight. In cosmetic formulations, e.g., face or hand creams, toiletries, etc.; and in the treatment of fuel systems, e.g., jet fuel, gasoline, heating oil, etc., the microbicidal composition is added at a concentration of from about 0.1 ppm to about 1 percent by weight.

The microbial resistant compositions can also be used in construction products such as stucco, roof mastics, wall mastics, and masonry coatings for algae protection; in clear finishes and coatings to protect underlying substrates from algae; for algae control in aquaculture, including aquaria, fish hatcheries, shrimp ponds, finfish ponds, mollusc and crustacean cultivation; for algae control in recreational and decorative bodies of water such as swimming pools, lakes, fountains and decorative ponds; for algae control in bodies of water for industrial or municipal use, such as settling or separation ponds, waste treatment ponds, and water reservoirs; for algae control in hydroponic farming; for algae control in processing and manufacture of pulp and paper products; for inclusion in plastics or in coatings for plastics to protect against algae; and in plastics or coatings for plastics for swimming pool liners.

We prefer compositions wherein the weight ratio of (A) to (B) is about 2000:1 to about 1:100. A particularly preferred ratio range is about 200:1 to about 1:100 by weight.

The following examples represent just a few of the many uses of the invention. They are intended to be illustrative but not limiting. Various

modifications, alternatives, and improvements should become apparent to those skilled in the art.

EXAMPLES

A. General Procedure

MIC values represent the Minimum Inhibitory Concentration. This is defined as the lowest level of compound required to completely inhibit (repress) the growth of a given organism.

A synergistic effect is defined as the response of two variables which is greater than the sum of both parts alone. Synergy was determined from combination studies with two compounds by the method of calculation described by F. C. Kull, P. C. Eisman, H. D. Sylwestrowicz and R. K. Mayer, *Applied Microbiology* 9,538 (1961):

$$\frac{Q_a}{Q_A} + \frac{Q_b}{Q_B} = \text{synergism index} \qquad \text{(SI)}$$

where:

Q_A = quantity of compound A, acting alone, producing an end point (MIC)

Q_a = quantity of compound A, in mixture, producing an end point (MIC)

Q_B = quantity of compound B, acting alone, producing an end point (MIC)

Q_b = quantity of compound B, in mixture, producing an end point (MIC)

The following SI values may be attained:

SI > 1 represents antagonistic effect,

SI = 1 represents additive effect,

SI < 1 represents synergy.

Efficacy studies were conducted on a variety of microorganisms with iodopropargyl butylcarbamate and 1,2-benzisothiazolone mixtures. The MIC studies were conducted using microtiter plate assays in trypticase soy broth (TSB) medium. In this method, a wide range of concentrations was tested by preparing two-fold serial dilutions of the compound in 96-well plastic microtiter plates. All liquid media transfers were performed with calibrated single or multichannel digital pipetters. Stock solutions of compounds were prepared in appropriate solvents and dispensed to the growth medium. All subsequent dilutions in plates were made using the desired growth medium; total volume of liquid in each well was 100 µl. Each plate contained a concentration of both compounds made by serially titrating equal volumes of liquids in two directions in the microtiter plate. Each plate contained a control row for each combination (one component only), hence, the individual compound MIC values were also determined.

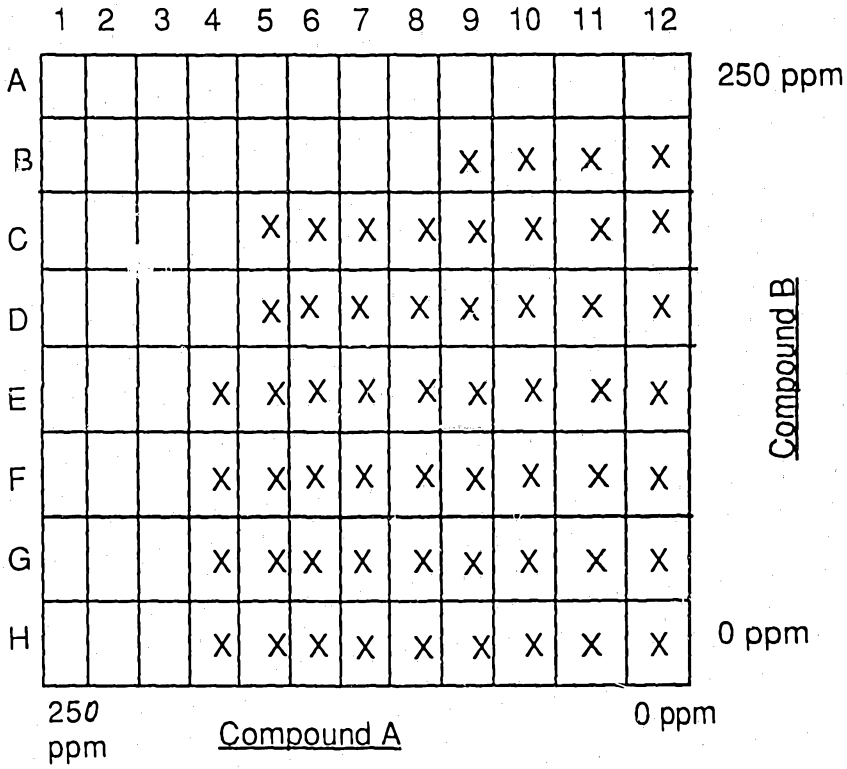
EXAMPLE 1 Pseudomonas aeruginosa

Using a pure culture of *Pseudomonas aeruginosa*, various combinations of 1,2-benzisothiazolone (Compound A) and iodopropargyl butylcarbamate (Compound B, acetone solution) were subjected to MIC determinations (TSB medium).

MIC Data on Compound A/Compound B Combinations (ppm)

Q_a	Q_b	Q_a/Q_b	SI
63(Q_A)	0	-	1.0
31	31	50/50	0.63
31	63	33/67	0.75
16	125	11/89	0.75
8	125	6/94	0.63
4	125	3/97	0.56
2	125	2/98	0.53
0	250(Q_B)	-	1.0

The block diagram illustrates the experimental protocol used to establish the synergy relationship for Compound A/Compound B combinations against *Pseudomonas aeruginosa*: X = growth of organism, blanks = no growth of organism.



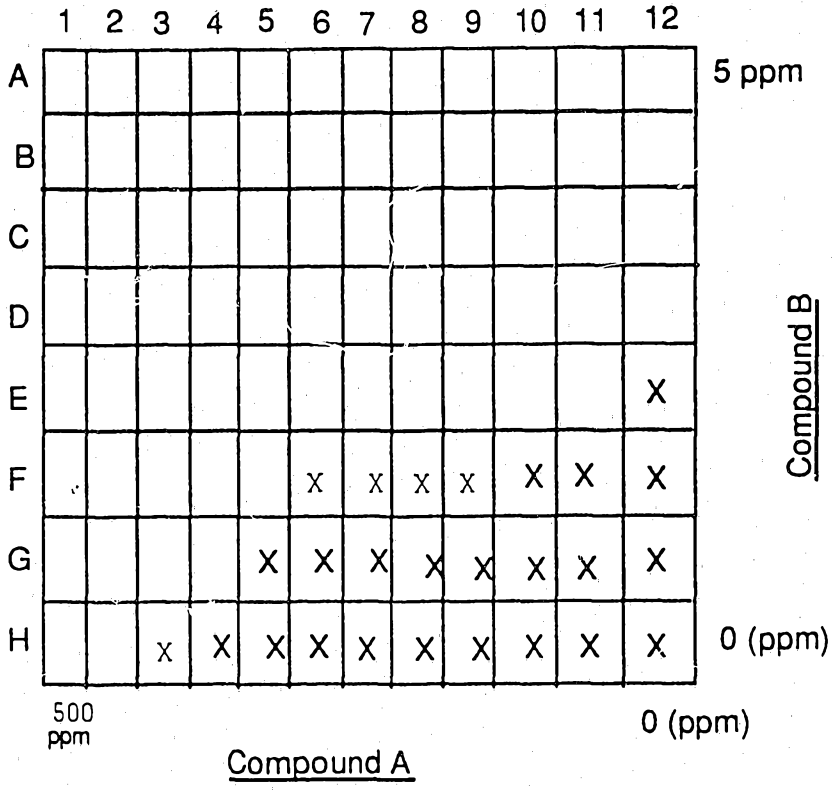
EXAMPLE 2 **Aspergillus niger**

In a manner similar to Example 1 another MIC study was conducted against *Aspergillus niger*.

MIC Data on Compound A/Compound B Combinations (ppm)

Q_a	Q_b	Q_a/Q_b	SI
250(Q_A)	0	-	1.0
125	0.08	1560/1	0.63
125	0.16	780/1	0.75
63	0.08	780/1	0.38
63	0.16	390/1	0.50
63	0.31	200/1	0.75
31	0.16	190/1	0.38
31	0.31	99/1	0.63
16	0.31	98/2	0.56
8	0.31	96/4	0.53
4	0.31	93/7	0.52
2	0.31	86/14	0.51
1	0.31	76/24	0.50
0.5	0.31	61/39	0.50
0	0.63 (Q_B)	-	1.0

The block diagram illustrates the experimental protocol used to establish the synergy relationship for Compound A/Compound B combinations against *Aspergillus niger*: X = growth of organism, blanks = no growth of organism.



Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Composition comprising a first component which is 1,2-benzisothiazolone, and a second component which is iodopropargyl butylcarbamate; the ratio of the first component to the second component being from 10000:1 to 1:1000.

2. Composition according to claim 1 wherein the ratio of the first component to the second component is from 2000:1 to 1:100.

3. Composition according to claim 1 or 2 further comprising an inert, agronomically acceptable or pharmaceutically acceptable carrier.

4. A coating or impregnant composition according to claim 3 comprising from 0.1 ppm to 2 percent by weight of said first and second components together.

5. A marine antifoulant composition according to claim 3 comprising from 1 to 10 percent by weight of said first and second components together.

6. A pharmaceutical composition according to claim 4 comprising from 0.1 ppm to 2 percent by weight of said first and second components togther.

7. A method for inhibiting or preventing the growth of bacteria, fungi, or algae in a locus subject or susceptible to contamination thereby, which comprises incorporating onto or into the locus, in an amount effective to adversely affect said growth, a composition according to any preceding claim.

8. Method according to claim 7 wherein the locus is an aqueous medium, cosmetic formulation or fuel system and the composition is used in an amount of from 0.1 ppm to 1 percent by weight.

9. Method according to claim 7 wherein the locus is a pharmaceutical formulation, a coating or impregnant composition, metal-working fluid or fabric, leather, paper or wood and the composition is used in an amount of from 0.1 ppm to 2 percent by weight.

10. Method according to claim 7 wherein the locus is a marine antifoulant composition and the composition is used in an amount of from 1 to

10 percent by weight.

11. Method according to claim 7 wherein the locus is a pulp or paper manufacturing process or cooling tower water, and the composition is used in an amount of from 0.1 to 1000 ppm by weight.

12. Composition comprising 1,2-benzisothiazolone and iodopropargyl butylcarbamate substantially as hereinbefore described.

13. A composition according to claim 1, or a method of use thereof, substantially as hereinbefore described with reference to the Examples.

~~14. The steps, features, compositions and compounds~~ disclosed herein or referred to or ~~indicated~~ in the specification and/or ~~claims of~~ this application, ~~individually or collectively~~, and any and all combinations ~~of any two or more of said steps or features.~~

DATED this TWENTY SEVENTH day of NOVEMBER 1991

Rohm and Haas Company

by DAVIES COLLISON CAVE
Patent Attorneys for the applicant(s)

ABSTRACT

A synergistic antimicrobial composition comprising 1,2-benzisothiazolin-3-one and iodopropargyl butylcarbamate in a ratio to each other which exhibits synergism is disclosed.