AUSTRALIA

PATENTS ACT 1990

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

100 Independence Mall West, Philadelphia, Pennsylvania, 19106-2399, United States of America

[54] Invention Title:

Preparation of 3-isothiazolones

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

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[74] Address for service in Australia:

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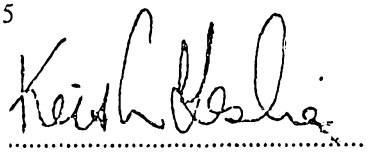
Basic Convention Application(s) Details:

[31] Application Number	[33] Country	Code	[32] Date of Application
220,763	United States of America	US	31 March 1994

DATED this TWENTY SEVENTH day of MARCH 1995



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/Nominated Person 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 inventor by assignment.

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 applicant in respect of the basic application.

DATED this TWENTY SEVENTH day of MARCH 1995

Keith L Gosling

.....

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

(DCC ref: 1730599)

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-15085/95
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(54) Title
PREPARATION OF 3-ISOTHIAZOLONES

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(56) Prior Art Documents
US 5068344
JP 3-095103

(57)

An especially commercially important 3-isothiazolone biocide is a mixture of 5-chloro-2-methyl-3-isothiazolone (CMI) and 2-methyl-3-isothiazolone (MI). All known processes to produce either of these compounds results in a mixture of the two. Therefore, in order to obtain either one essentially free of the other, the mixtures require separation. Until the present invention, this was both difficult and expensive.

Claim

1. A process for producing either (a) substantially separated 5-chloro-2-methyl-3-isothiazolone (CMI) and 2-methyl-3-isothiazolone (MI) from a mixture of their HCl salts, or (b) a mixture of CMI and MI having a higher CMI:MI ratio than said mixture of their HCl salts, comprising preparing a mixture of CMI•HCl and MI•HCl as a slurry in an organic solvent, and refluxing or distilling said slurry for a period of time sufficient to fully dissociate said CMI•HCl, but insufficient to fully dissociate said MI•HCl.

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COMPLETE SPECIFICATION

NAME OF APPLICANT(S):

Rohm and Haas Company

ADDRESS FOR SERVICE:

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

INVENTION TITLE:

Preparation of 3-isothiazolones

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

This invention is directed to preparation of 3-isothiazolone compounds.

3-isothiazolone compounds are highly effective microbicides and have generated much commercial interest to prevent spoilage of certain aqueous and non-aqueous products caused by microorganisms.

An especially commercially important 3-isothiazolone biocide is a mixture of 5-chloro-2-methyl-3-isothiazolone (CMI) and 2-methyl-3-isothiazolone (MI). All known processes to produce either of these compounds results in a mixture of the two. Therefore, in order to obtain either one essentially free of the other, the mixtures require separation. Until the present invention, this was both difficult and expensive.

US-A-5,028,620 discloses preparing substantially pure MI by recrystallization of a crude MI•hydrochloride (HCl) salt followed by neutralization, and substantially pure CMI by partial neutralization, with pyridine, of a mixture of MI•HCl and CMI•HCl. US-A-5,068,344 discloses preparing mostly pure CMI by partial neutralization of a mixture of MI•HCl and CMI•HCl with ammonia gas.

The methods taught in these U.S. patents for partially neutralizing the isothiazolone•HCl salt mixtures require the handling of an additional component (pyridine or ammonia) and provide CMI with a small amount of MI. Substantially pure MI must be obtained by other means (such as by recrystallization of the hydrochloride salt followed by neutralization).

Conventional methods of preparing the mixture of salts include, for example, cyclizing N,N'-dimethyl-3,3'-dithiopropionamide or N-methyl-3-mercaptopropionamide with a halogenating agent. The mixture of salts precipitates from the reaction mixture and can be isolated by filtration. Once isolated, the isothiazolone•HCl salts are generally washed before proceeding further. Normally, the washed mixture of CMI•HCl and MI•HCl is then neutralized with a base.

Typical halogenating agents are chlorine, sulfuryl chloride, N-chlorosuccinimide, and the like. Chlorine and sulfuryl chloride are the preferred halogenating agents.

The halogenation-cyclization is conducted in an organic solvent, typically aromatic hydrocarbons, aliphatic hydrocarbons, chlorinated aliphatic hydrocarbons, acetate esters, glycol ethers and glycol ether acetates. The preferred solvents are toluene, monochlorobenzene, ethyl acetate, ethylene dichloride, and butyl acetate.

It is well known in the art that the ratio of CMI•HCl to MI•HCl in the mixture can be varied between 4.5 and 0.02 by changing the cyclization conditions, the ratios of reactants used, and the rates of addition of the reactants.

Japanese Kokai Hei 3-095103 discloses a method of preparing a mixture of CMI and MI free of certain undesirable reaction by-products by heating a mixture of the 3-isothiazolone•HCl salts to dissociate said salts and to obtain the mixture of free base CMI and MI, rather than neutralizing with a base. This Kokai does not disclose a method for separating the individual isothiazolones.

It is an object of this invention to provide a process for obtaining in substantially pure form CMI, or MI, or special mixtures thereof.

Accordingly the present invention provides in one aspect a process for producing either (a) substantially separated 5-chloro-2-methyl-3-isothiazolone (CMI) and 2-methyl-3-isothiazolone (MI) from a mixture of their HCl salts, or (b) a mixture of CMI and MI having a higher CMI:MI ratio than said mixture of their HCl salts, comprising preparing a mixture of CMI•HCl and MI•HCl as a slurry in an organic solvent, and refluxing or distilling said slurry for a period of time sufficient to fully dissociate said CMI•HCl, but insufficient to fully dissociate said MI•HCl.

In the process of the invention a slurry of the mixture of CMI•HCl and MI•HCl salts is formed in an organic solvent, and heated in order to selectively crack, i.e., dissociate, the CMI•HCl salt, either leaving the MI•HCl salt essentially intact as an insoluble solid, or only dissociating a desired proportion. The free base CMI and any MI which is dissociated from its salt dissolve(s) in the organic solvent. The mixture can then be filtered to provide essentially pure MI•HCl as a solid. The filtrate may be stripped of the organic solvent to provide essentially pure CMI, or a mixture of CMI and MI at a desired ratio which is higher than the ratio of CMI•HCl to MI•HCl in the starting mixture. For best results, the solids content of the CMI•HCl and MI•HCl slurry formed should be no more than 20% by weight.

If substantially pure MI is the only desired product, a mixture of salts which is as rich as possible in MI•HCl should be used. In this case, the refluxing/distillation need not be continued beyond the point at which all the CMI has dissociated from the CMI•HCl salt, but none of the MI has yet done so. This point will depend on the relative proportions of CMI and MI in the initial salt mixture, the solvent, and the reflux temperature. Generally it is about one hour, though for example when ethyl acetate is the solvent the reflux time required to reach this point may be from half an hour to one and a half hours.

The isolated MI•HCl salt can be neutralized by a variety of methods, for example by reslurrying in a variety of solvents and then neutralized with an organic base such as pyridine and triethylamine, or with ammonia, which is the preferred base. The resulting precipitate, base•HCl, is removed by filtration. Removal of the solvent will provide MI as the free base. Alternatively, the MI•HCl salt can be reslurried and dissociated by heating the slurry, followed by removal of the solvent to provide substantially pure MI. When dissociating the MI•HCl, it is preferred that the slurry be dilute, less than 10% by weight solids, and preferably less than 5% solids.

If it is desired to obtain a particular mixture of CMI and MI, rather than separating them, the mixture of salts can be slurried as described above and refluxed/distilled to fully dissociate the CMI•HCl but only partially dissociate the MI•HCl. The ratio of the isothiazolones will depend upon the starting ratio of the mixture of the HCl salts, the temperature at which the salts are dissociated, and on the duration of the dissociation step. Due to the process of preparing the HCl salt mixture, the maximum practical ratio of CMI•HCl:MI•HCl in the mixture is usually about 82:18. By the process of this invention, greater ratios of CMI:MI (up to 99:1) can be obtained.

The solvents useful in the dissociation step are preferably acetate esters, such as ethyl acetate and butyl acetate; chlorinated aliphatic hydrocarbons, such as methylene dichloride,

ethylene dichloride, propylene dichloride, and chloroform; aromatic hydrocarbons, such as toluene; and chlorinated aromatic hydrocarbons, such as monochlorobenzene. The preferred solvents are ethyl acetate, butyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, and chloroform. Ethyl acetate, methylene dichloride, ethylene dichloride and chloroform are especially preferred, with ethyl acetate the solvent of choice.

The temperature for refluxing/distilling of the isothiazolone•HCl salts is generally at least 35°C. The preferred temperature is from about 35°C to about 85°C. The refluxing/distilling can also be done at reduced pressure. At temperatures above about 85°C, it is preferred to perform the dissociation step at reduced pressure.

By substantially pure CMI is meant CMI having a purity of at least 95% and containing less than 1% of MI. By substantially pure MI is meant MI having a purity of at least 95% and containing less than 0.4% CMI. It is preferred that MI have a purity of 98%.

Either CMI or MI can be formulated in a variety of solvents, such as water or glycols, such as propylene glycol, dipropylene glycol, and the like. It is also known that in certain solvents it is necessary to add stabilizers to prevent decomposition of CMI or MI. Suitable stabilizers include metal nitrates, such as magnesium nitrate; trialkyl orthoesters, such as triethyl orthoformate; anhydrides; epoxides; antimony salts; olefins; and the like.

Example 1 - Preparation of isothiazolone•HCl salts

Into a one-litre, 4-necked, round bottom flask equipped with a mechanical stirrer, thermometer, gas dispersion tube, and dry ice condenser with nitrogen inlet adapter, was placed methyl-3-mercaptopropionate (504.7 g, 4.20 mol). The vessel was purged with nitrogen and the liquid was cooled to 10°C. Monomethylamine (163.0 g, 5.25 mol) was added through the gas dispersion tube with stirring at 10° - 20°C over a one hour period. Following the addition, the mixture was stirred at 20°C for 20 hours to complete the reaction. Unreacted monomethylamine and the methanol by-product was then removed under reduced pressure (100 mmHg). The resultant mixture was then further reduced on a rotary evaporator to give crude N-methyl-3-mercaptopropionamide (500.8 g, 100% yield).

A one-liter, 5-necked, jacketed resin kettle was equipped with an agitator, fritted glass dispersion tube, thermometer, condenser attached to an off-gas scrubber, and a feed line for N-methyl-3-mercaptopropionamide slurry. The jacket was connected to a temperature control bath for coolant circulation. The cooling system maintained the reaction temperature at 25° - 30°C. The flask was charged with 59.5 g of ethyl acetate. A slurry (398.9 g) of N-methyl-3-mercaptopropionamide in ethyl acetate (31%) was added to the flask over a 55 minute period at a rate of 7.1 g/minute. Concurrently, 220 g of Cl_2 were added at a rate of 4.0 g/minute. Following the complete addition of N-methyl-3-mercaptopropionamide and Cl_2, the reaction mixture was filtered, and the cake washed with ethyl acetate to yield a mixture of CMI•HCl and MI•HCl.

Example 2 - Selective Dissociation of CMI•HCl

To a one-litre, jacketed, resin flask equipped with an overhead agitator, thermometer, condenser, and a temperature control bath, was added 60 g of an 81:19 mixture of CMI•HCl and MI•HCl, prepared according to Example 1, in 340g of ethyl acetate. The slurry (containing 15% solids) was heated to 78-80°C for 2 hours. After heating, the reaction mixture was cooled to room temperature, the slurry was filtered and the solid was washed with ethyl acetate. The filtrate was stripped to yield 42g of substantially pure CMI. The ratio of CMI:MI in the filtrate was 99.2/0.8.

The solid contained 96.4% MI•HCl and only 1.4% CMI•HCl.

Example 3 - Dissociation of both CMI•HCl and MI•HCl

Example 2 was repeated using a more dilute slurry (9%) of the isothiazolone•HCl salt mixture. The slurry was heated at 78-80°C until most of the solids had disappeared. At the end of this period, the mixture was filtered and the filtrate removed to provide a mixture of CMI and MI in a ratio of 80:20, essentially the same ratio as in the starting isothiazolone•HCl salt mixture.

Example 4 - Selective Dissociation of both CMI•HCl and MI•HCl

To a 500 ml jacketed flask equipped with an overhead agitator, thermometer, condenser fitted with a drying tube, and a temperature control bath, was added 31.3g of an 82:18 mixture of CMI•HCl and MI•HCl, prepared according to Example 1, in 468g of methylene dichloride. The slurry (6.25% solids) was heated to 36.5° - 37°C. Aliquots of the mother liquor were taken at various time points, stripped and analyzed for the amount of free base isothiazolones. After 16 hours heating, the reaction mixture was cooled to room temperature, the slurry was filtered and a small amount of the solid was washed with methylene dichloride. The filtrate was stripped and the resulting material was analyzed for free base isothiazolone content. The results are shown in Table 1.

Table 1 - Dissociation of Isothiazolone•HCl Salt Mixture in Methylene Dichloride: free base isothiazolone content

Time (hrs)	CMi (wt %)	MI (wt %)	CMI:MI
0*	62.0*	13.3*	82.3:17.7*
1	95.3	1.4	98.5:1.5
2	95.3	2.5	97.5:2.5
4	92.5	4.3	95.5:4.5
8	87.1	7.9	96.1:3.9
12	89.0	7.4	92.3:7.7
15	88 7	7.7	92.0:8.0
16	84.0	9.3	90.0:10.0

* These data represent the amounts in the starting isothiazolone•HCl salt mixture.

The data in Table 1 clearly show that CMI•HCl can be selectively dissociated from the mixture of the two isothizolone•HCl salts, or both salts may be dissociated to yield a special mixture of the free base isothiazolones, CMI and MI in any ratio higher in CMI than the ratio of salts in the starting mixture.

Example 5 - Selective Dissociation of both CMI•HCl and MI•HCl

To a 500 ml jacketed flask equipped with an overhead agitator, thermometer, condenser fitted with a drying tube, and a temperature control bath, was added 50.6 g of a 73:27 mixture of CMI•HCl and MI•HCl, prepared according to Example 1, in 349.4 g of ethyl acetate. The slurry (10% solids) was heated to reflux and the solvent partially distilled (rate = 20 ml/min) while replenishing the kettle with fresh ethyl acetate. Aliquots of the mother liquor were taken at various time points. These were filtered and the solids washed with ethyl acetate and analyed for isothiazolone content. The filtrates from these aliquots were stripped and analyzed for the amount of free base isothiazolones. After 7 hours of refluxing, essentially all of the solids had dissolved. The reaction mixture was cooled to room temperature and then the solvent was stripped under reduced pressure. The results are shown in Table 2.

Table 2 - Dissociation of Isothiazolone•HCl Salt Mixture in Ethyl Acetate

	Filtrate			Solids		
	Wt %			Wt %		
Time (hrs)	CMI	MI	CMI:MI	CMI•HCl	MI•HCl	CMI•HCl:MI•HCl
-*	-	-	-	53.9	18.0	73:27
0**	86.9	1.2	98.6:1.4	37.2	32.4	53.4:46.6
1	90.0	2.8	97.0:3.0	0.31	64.7	0.5:99.5
2	82.0	10.8	88.4:11.6	0.29	65.1	0.4:99.6
3	77.2	14.6	83.9:16.1	0.42	65.2	0.6:99.4
4	76.5	18.2	80.5:19.5	-	-	-
5	72.8	20.0	78.4:21.6	-	-	-
6	73.6	20.8	78.0:22.0	-	-	-
7	69.4	25.7	73.0:27.0	-	-	-

* These data are from the solid at the time of slurry preparation.

** The 0 hour sample was taken at the start of reflux

The data in Table 2 clearly show a surprisingly high degree of selectivity favouring CMI•HCl dissociation during the first hour of reflux, giving essentially pure CMI containing only

a small amount of MI. Importantly, it is possible to obtain a special CMI:MI mix with any desired ratio from about 99:1 to the starting ratio of 73:27, depending on the duration of this dissociation step.

Example 6 - Isolation of Substantially Pure MI•HCl

A mixture of CMI•HCl and MI•HCl was prepared according to Example 1 except that the cyclization reaction was carried out at 45°- 50°C and 384.9 g of a 31% solution of N-methyl-3-mercaptopropionamide in ethyl acetate were added concurrently with 138.5 g Cl_2 over a 2 hour period to the flask charged with 132.5 g of ethyl acetate. At the end of this time, the reaction mixture was filtered and the cake washed with ethyl acetate to yield a mixture of CMI•HCl and MI•HCl in a 9:91 ratio.

Example 2 was repeated using 400g of a 20% solids slurry of this 9:91 mixture of CMI•HCl and MI•HCl in ethyl acetate. The slurry was heated at reflux for 1 hour. The mixture was allowed to cool to room temperature and filtered. The wet cake was washed with 100 g of ethyl acetate and dried to give substantially pure MI•HCl (87.4 g) containing only a trace amount of CMI•HCl in a CMI:MI ratio of 0.2:99.8.

Example 7 - Isolation of Substantially Pure MI

Substantially pure MI was prepared by slurrying the MI•HCl from Example 6 in ethyl acetate (20% solids) and neutralizing with ammonia. The solids were filtered and the filtrate was concentrated under reduced pressure (50°C/20 mmHg) to provide substantially pure MI (99.0%) containing only a small amount of CMI (0.12%). The ratio of CMI:MI was 0.4:99.6.

Example 8 - Isolation of Substantially Pure MI

Substantially pure MI•HCl was dissociated to yield MI according to the procedure of Example 2. The MI•HCl (4.4 g) from Example 6 was slurried in 345.6 g of ethyl acetate (1.25% solids) and heated under reflux for 2 hours and then subjected to distillation for 30 minutes. The mixture was then allowed to cool and the remaining solids were filtered. The filtrate was concentrated under reduced pressure (50°C/20 mmHg) to give an oil. The oil was substantially pure MI containing only 0.21% CMI.

Example 9 - Isolation of Substantially Pure MI•HCl

Example 6 was repeated except using a mixture of CMI•HCl and MI•HCl in a 2:98 ratio, to obtain essentially the same ratio of CMI:MI. This example has the advantage of sacrificing only a small amount of CMI.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for producing either (a) substantially separated 5-chloro-2-methyl-3-isothiazolone (CMI) and 2-methyl-3-isothiazolone (MI) from a mixture of their HCl salts, or (b) a mixture of CMI and MI having a higher CMI:MI ratio than said mixture of their HCl salts, comprising preparing a mixture of CMI•HCl and MI•HCl as a slurry in an organic solvent, and refluxing or distilling said slurry for a period of time sufficient to fully dissociate said CMI•HCl, but insufficient to fully dissociate said MI•HCl.

2. Process according to claim 1 wherein said solvent comprises one or more of acetate esters, chlorinated aliphatic hydrocarbons, aromatic hydrocarbons, or chlorinated aromatic hydrocarbons; preferably ethyl acetate, butyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride or chloroform.

3. Process according to claim 1 or 2 wherein the reflux/distillation temperature is from 35°C to 85°C.

4. Process according to claim 1 or 2 wherein the reflux/distillation temperature is above 85°C, and preferably the refluxing is conducted under reduced pressure.

5. Process according to any preceding claim, wherein the slurry contains up to 20% by weight of solids.

6. Process according to any preceding claim, further comprising separating the resultant dissociated CMI from the solid MI•HCl by filtration, and then neutralizing the MI•HCl to form substantially pure MI.

7. Process according to any preceding claim, wherein a stabilizer for the CMI is added to the separated CMI or to the special mixture of CMI and MI, or to a solution thereof.

8. Process according to any preceding claim wherein the initial mixture of CMI•HCl and MI•HCl has a CMI•HCl : MI•HCl ratio of at least 70:30, and a CMI:MI mixture is prepared having a CMI:MI ratio of from 80:20 to 99:1.

9. Process according any one of claims 1 to 7, wherein the refluxing/distillation is continued for a period of time sufficient to fully dissociate the CMI•HCl, but insufficient to dissociate any of the MI•HCl.

10. Process according to claim 9 wherein said period of time is less than one hour.

11. Process according to claim 9 wherein said organic solvent is ethyl acetate and said period of time is from half an hour to one and a half hours.

12. Process according to any one of claims 9 to 11, further comprising separating the resultant dissociated CMI from the solid MI•HCl by filtration, and then removing the solvent from the filtrate to obtain substantially pure CMI.

13. Process according to any preceding claim comprising separating the resultant dissociated CMI from said MI•HCl by filtration, reslurrying said MI•HCl, and refluxing the resultant slurry of MI•HCl to substantially dissociate said MI•HCl to a solution of MI.

14. Process according to claim 13 wherein the MI•HCl slurry has a solids content of less than 10% by weight, preferably less than 5% by weight.

15. Process according to claim 13 or 14 wherein the ratio of CMI•HCl to MI•HCl in said slurry is from 2:98 to 10:90.

16. A process for producing isothiazolones substantially as hereinbefore described with reference to the Examples.

17. Isothiazolones when produced by the process claimed in any one of the preceding claims.

18. 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 MARCH 1995

Rohm and Haas Company

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

Abstract

PREPARATION OF 3-ISOTHIAZOLONES

Process for producing substantially separated 5-chloro-2-methyl-3-isothiazolone (CMI) and 2-methyl-3-isothiazolone (MI) from a mixture of their hydrochloride salts, or in a special mixture having a higher ratio of CMI to MI, comprising heating a mixture of CMI•HCl and MI•HCl for a period of time necessary to fully dissociate said CMI•HCl, but insufficient to fully dissociate said MI•HCl.