

PATENT SPECIFICATION

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(54) 3,4-DIHYDRO-2-METHYL-4-OXO-2H-1,2-BENZOTHAZINE-3-CARBOXYLIC ACID-1,1-DIOXIDE AND A PROCESS FOR ITS PREPARATION

(71) We, PFIZER INC., a corporation organised under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, City of New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to crystalline 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide, a valuable intermediate for the synthesis of non-steroidal antiinflammatory agents, and to a process for the preparation of said carboxylic acid compound by base hydrolysis of an alkyl or aralkyl ester of 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylic acid-1,1-dioxide.

The instability of β -keto carboxylic acids, evidenced by their tendency to undergo decarboxylation, is well known to those skilled in the art. U.S. Patent 3,892,740 and *J. Heterocyclic Chem.*, 13, 333 (1976) report that 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxylic acid-1,1-dioxides have been prepared by hydrolysis of the corresponding ester but they decarboxylate rapidly once formed. The observed instability arises from their β -keto structure.

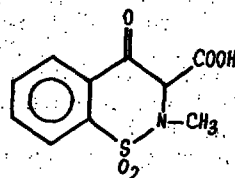
The preparation of N-substituted-3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxides useful as anti-inflammatory agents is described in U.S. Patents 3,591,584; 3,891,637 and 3,892,740.

The first patent discloses two routes for the synthesis of N-substituted-benzothiazine-carboxamide-1,1-dioxides: (a) reaction of the appropriate 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-1,1-dioxide with an organic isocyanate; and (b) ammonolysis of an ester of 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxylic acid-1,1-dioxide with ammonia or an appropriate

amine. The second patent describes the preparation of such compounds wherein the N-substituent is a heterocyclic moiety by a transamidation reaction. The third patent reports preparation of such carboxamide derivatives by contacting a 3,4-dihydro-4-alkoxy-2H-1,2-benzothiazine-3-carboxylic acid-1,1-dioxide with a coupling promoter (dicyclohexylcarbodiimide, POCl₃, N-ethoxycarbonyl-2-ethoxy-1,2'-dihydroquinoline) followed by contacting the resulting carboxamide with a mineral acid to convert the 4-alkoxy group to 4-oxo.

In each instance, the particular synthetic route employed carefully avoids the formation of 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxylic acid-1,1-dioxide, even as a transient intermediate, in order to circumvent the heretofore reported instability of the β -keto function of such acids. This reported instability of such acids is in keeping with the well-known tendency of β -keto acids to undergo decarboxylation.

It has now been unexpectedly and surprisingly found that 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylic acid-1,1-dioxide (formula I) can be prepared and isolated as a crystalline compound, stable at ambient temperatures, by hydrolysis of an ester thereof in the presence of a source of hydroxide ion, followed by acidification of the resulting product to a pH below 6.0.



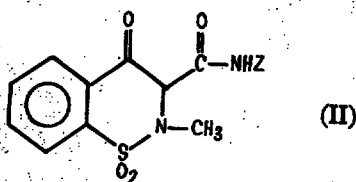
The acid thus produced is a valuable intermediate for the preparation of non-steroidal antiinflammatory agents such as those having formula II by acylation of the appropriate amine.

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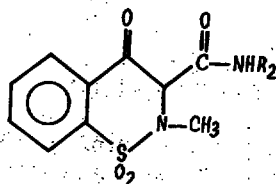
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In formula II, Z is 2 - pyridyl or 2 - thiazolyl. Our copending Application No. 32370/78 (Serial No. 1,544,359) provides a process for preparing a compound having the formula

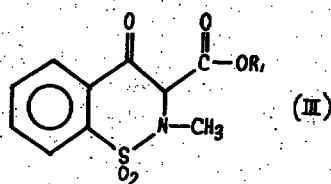


wherein R₂ is 2 - pyridyl or 2 - thiazolyl which comprises coupling at least substantially equimolar proportions of an amine having the formula



and 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide or a reactive functional derivative thereof selected from the acid chloride, the acid bromide, the acid azide, active esters or thio esters with N - hydroxysuccinimide, N - hydroxyphthalimide, a phenol or a thiophenol, or mixed anhydrides with alkoxy-carbonic acids or benzyloxycarbonic acid.

The process of this invention for producing 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid 1,1 - dioxide comprises hydrolysis, in the presence of a source of hydroxide ion, of a compound having formula III



wherein R₁ is alkyl having from one to twelve carbon atoms or phenylalkyl having up to three carbon atoms in the alkyl moiety, followed by acidification of the resulting product to a pH of from 0 to 6.0 to afford the compound of formula I.

Compounds having structures I, II and III exist as mixtures of keto and enol tautomers, as is taught in U.S. Patent No. 3,892,740. Formulae I, II and III depict the keto tautomers. It is intended to embrace both tautomers of compound I described herein within the scope of this invention. For convenience only the keto forms are illustrated.

The 3,4 - dihydro - 2 - methyl - 4 - oxo -

2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 dioxide esters of formula III are prepared according to the procedure described in U.S. Patent 3,591,584. The alkyl esters having from one to four carbon atoms and especially the methyl and ethyl esters are favoured as reactants in the hydrolysis process of the present invention because of their ease of preparation.

The hydrolysis of formula III esters is accomplished in the presence of hydroxide ions using, as the source of hydroxide ion a metal hydroxide such as an alkali metal hydroxide or alkaline earth metal hydroxide. The hydrolysis can be conducted in an aqueous or non-aqueous solvent system. When conducted in an aqueous solvent system, the hydrolysis is carried out at a temperature from 20°C. to the reflux temperature of the reaction medium. Of the metal hydroxides, alkali metal hydroxides are favoured—indeed, preferred because of their greater water solubility relative to that of the alkaline earth metal hydroxides. The preferred alkali metal hydroxides are sodium and potassium hydroxides because of their availability and, as regards large scale production, their more favourable economics relative to that of other alkali metal hydroxides.

The favoured alkaline earth metal hydroxides are calcium and magnesium hydroxides because of their cost and availability relative to that of other alkaline earth metal hydroxides.

In addition to metal hydroxides, quaternary ammonium hydroxides such as tetraalkyl ammonium hydroxides, trialkyl benzyl ammonium hydroxides and dialkyl dibenzyl ammonium hydroxides wherein the alkyl groups have from one to twelve carbon atoms can be used as the source of hydroxide ion. Representative of such bases are tetramethyl ammonium hydroxide, dimethyl dibenzyl ammonium hydroxide and trimethyl benzyl ammonium hydroxide.

The molar ratio of metal hydroxide to ester reactant is not critical but can vary from 1:1 to 10:1. In actual practice, molar ratios of from 1:1 to 5:1 have been found effective in achieving satisfactory rate and yield of hydrolysis.

When conducted in a non-aqueous solvent system, the same metal hydroxides as are enumerated above can serve as the source of hydroxide ion. In order to achieve efficient reaction, use is preferably made of the solubilizing effect afforded by the presence of a crown ether; that is, a macrocyclic ether, on the metal hydroxide in hydrocarbon solvents such as benzene or toluene. Representative of crown ethers useful in this process are 18 - crown - 6, dibenzo - 18 - crown - 6, cyclohexyl - 18 - crown - 6, dicyclohexyl - 18 - crown - 6 and cyclohexyl - 15 - crown - 5. The favoured hydroxide ion sources for use in

non-aqueous solvent systems are the alkali metal hydroxides because of the relatively strong tendency of crown ethers to complex the alkali metal cation, their ease of solubilization and enhanced reactivity in the presence of crown ethers. The preferred alkali metal hydroxides are potassium and sodium hydroxides.

This method, hydrolysis in a non-aqueous system with the assistance of a crown ether, is the preferred hydrolysis method since it affords substantial yields of the desired 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.

In general, when using crown ethers, the molar ratio of alkali metal or alkaline earth metal hydroxide to crown ether and ester reactant can vary from 1:0.1:1 to 100:1:10. In actual practice, an excess of the metal hydroxide is used since it tends to minimize the reaction time and afford more complete hydrolysis of the ester than does lesser amounts of metal hydroxide. Larger proportions of crown ether can, of course, be used. The reaction is normally carried out at about the reflux temperature of the solvent used. In general, temperatures ranging from 80°C. to 150°C. depending, of course, on the solvent (e.g. benzene, toluene, xylene) are used.

The crown - ether - alkali metal complexes can be preformed or can be formed *in situ*. For ease of operation, it is generally advantageous to form the complexes *in situ*, and to use an excess of alkali metal hydroxide in order to accelerate the reaction. The preformed complexes are prepared by reacting the appropriate base, e.g. potassium hydroxide, and the appropriate crown ether in methanol or benzene. The methanol or benzene is then removed and toluene or benzene added to the residue.

The hydrolysis product is recovered by adjusting the pH of an aqueous solution of the hydrolysis product to a pH of from 0 to 6.0. Mineral acids, and especially hydrochloric acid, are generally used for reasons of economy. Of course, when the hydrolysis is conducted in a non-aqueous solvent system, the solid hydrolysis product is separated by an appropriate method (e.g. filtration, centrifugation) from the solvent system and is then taken up in water prior to pH adjustment. The favoured pH range is from 1 to 4; the preferred range is from pH 2 to pH 3.

As noted above, 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide is a valuable intermediate for the preparation of N - (2 - pyridyl) - and N - (2 - thiazolyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxides, both of which are efficient antiinflammatory agents.

The invention is illustrated by the following Examples.

EXAMPLE 1

3,4 - Dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic Acid - 1,1 - dioxide

(Hydrolysis in Aqueous Medium)

Methyl 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylate - 1,1 - dioxide (50 g.) is added to a solution of sodium hydroxide (160 g.) in water (500 ml.) at 70°C. The resulting lemon-yellow slurry is then heated at 90°—95°C. for 45 minutes and then cooled to room temperature in an ice-water bath. The pH of the reaction mixture is adjusted to 1—1.5 by gradual addition of concentrated hydrochloric acid (350 ml.). Ice chips are added as necessary to keep the temperature below 35°C. The acid product precipitates and is granulated by stirring at 10°—15°C. for 15 minutes. It is recovered by suction filtration, washed with water (100 ml.) and reslurried in water (250 ml.) for a half hour to remove excess hydrochloric acid. It is again filtered with suction and washed with water (100 ml.). Twenty-five grams of the wet filter cake (total wet filter cake is 25.5 g.) is dissolved in warm methanol (150 ml.), the solution filtered and water (50 ml.) added to the filtrate. The addition of seed crystals causes immediate precipitation of product. The slurry is granulated by stirring at about 10°C. for a half hour. The white crystalline product is separated by filtration, washed with water and air-dried. Yield=13.2 g., M.p. 144°—146°C.

Evaporation of the filtrate to half-volume affords additional product (3.2 g.). A third crop is recovered by repetition of this procedure (2.6 g.).

Total yield=16.4 g. (34.6%).

MS (mol. ion)=255.

IR (KBr): 3535 cm⁻¹ (enolic OH), 2900—2000 cm⁻¹ (acid OH), 660 cm⁻¹ (C=O), 1340, 1170 cm⁻¹ (SO₂).

Repetition of this procedure but using potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide or barium hydroxide as base affords similar results.

EXAMPLE 2

3,4 - Dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic Acid - 1,1 - Dioxide

(Hydrolysis in Non-Aqueous Medium, (Crown Ether Method))

To a mechanically stirred mixture of potassium hydroxide (2.8 g.), methyl 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylate - 1,1 - dioxide (6.73 g.) and benzene (100 ml.) is added a solution of dicyclohexyl - 18 - crown - 6 ether (0.93 g.) in benzene (10 ml.) over a period of one minute. The reaction mixture is then

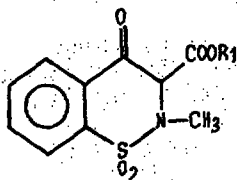
heated at reflux for two hours. Additional potassium hydroxide (2.8 g.) is then added and refluxing continued for a total of 50 hours. The yellow-brown slurry is filtered while hot, and the filter cake washed with benzene (50 ml.) and dried. It is then dissolved in water (100 ml.) and the solution adjusted to pH 1.0 with hydrochloric acid while maintaining the temperature at about 15°C. The resulting precipitate is granulated for a half-hour, filtered, washed with water and dried (4.4 g. of crude product).

The crude product is dissolved in warm methanol (49 ml.), the solution filtered and then diluted by slow addition of water (63 ml.). The precipitate which forms is granulated for a half-hour at 10°–15°C. and is then filtered, washed with water (2×10 ml.) and dried in air. Yield=3.5 g., 61.9%. M.p. 134°–141°C.

Repetition of this procedure but using 18 - crown - 6, dibenzo - 18 - crown - 6, cyclohexyl - 18 - crown - 6, cyclohexyl - 15 - crown - 5 and sodium or potassium hydroxides; lithium hydroxide and dibenzo - 14 - crown - 4; barium or strontium hydroxides and binaphthyl - 20 - crown - 6; or calcium hydroxide and dibenzo - 30 - crown - 10 affords the acid.

EXAMPLE 3

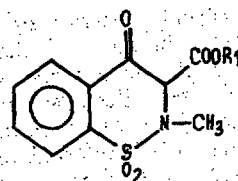
Following the procedures of Examples 1 or 2, the esters tabulated below are hydrolyzed to 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.



R ₁	Method of Example
C ₂ H ₅	1
t-C ₄ H ₉	2
n-C ₈ H ₁₇	1
n-C ₈ H ₁₇	2
n-C ₁₂ H ₂₅	1
n-C ₁₂ H ₂₅	2
C ₆ H ₅ CH ₂	1
C ₆ H ₅ (CH ₂) ₃	1
C ₆ H ₅ (CH ₂) ₂	2

WHAT WE CLAIM IS:—

1. A process for the preparation of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide which comprises hydrolysis, in the presence of a source of hydroxide ion, of a compound having the formula



wherein R₁ is alkyl having from one to twelve carbon atoms or phenylalkyl having up to three carbon atoms in the alkyl moiety, followed by acidification of the resulting product to a pH of from 0 to 6.0.

2. A process according to claim 1 wherein the hydrolysis is conducted in an aqueous solvent system.

3. A process according to claim 2 wherein the hydrolysis is conducted at a temperature of from 20°C. to the reflux temperature of the solvent.

4. A process according to claim 3 wherein R₁ is alkyl.

5. A process according to claim 4 wherein R₁ is methyl.

6. A process according to claim 5 wherein an alkali metal hydroxide is the source of hydroxide ion.

7. The process according to claim 6 wherein the alkali metal hydroxide is sodium hydroxide.

8. A process according to claim 1 wherein the hydrolysis is conducted in a non-aqueous solvent system in the presence of a crown ether.

9. A process according to claim 8 wherein the hydroxide ion source is an alkali metal hydroxide.

10. A process according to claim 9 wherein the alkali metal hydroxide is potassium hydroxide, the non-aqueous solvent is benzene or toluene, and the crown ether is 18 - crown - 6, dicyclohexyl - 18 - crown - 6, dibenzo - 18 - crown - 6 or cyclohexyl - 18 - crown - 6.

11. The process according to claim 10 wherein the solvent is benzene, the crown ether is dicyclohexyl - 18 - crown - 6 and the alkali metal hydroxide is potassium hydroxide.

12. Crystalline 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.

13. 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide when prepared by the process of any one of claims 1 to 11.

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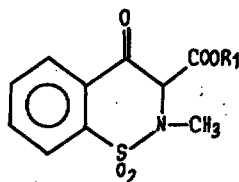
heated at reflux for two hours. Additional potassium hydroxide (2.8 g.) is then added and refluxing continued for a total of 50 hours. The yellow-brown slurry is filtered while hot, and the filter cake washed with benzene (50 ml.) and dried. It is then dissolved in water (100 ml.) and the solution adjusted to pH 1.0 with hydrochloric acid while maintaining the temperature at about 15°C. The resulting precipitate is granulated for a half-hour, filtered, washed with water and dried (4.4 g. of crude product).

The crude product is dissolved in warm methanol (49 ml.), the solution filtered and then diluted by slow addition of water (63 ml.). The precipitate which forms is granulated for a half-hour at 10°—15°C. and is then filtered, washed with water (2×10 ml.) and dried in air. Yield=3.5 g., 61.9%. M.p. 134°—141°C.

Repetition of this procedure but using 18 - crown - 6, dibenzo - 18 - crown - 6, cyclohexyl - 18 - crown - 6, cyclohexyl - 15 - crown - 5 and sodium or potassium hydroxides; lithium hydroxide and dibenzo - 14 - crown - 4; barium or strontium hydroxides and binaphthyl - 20 - crown - 6, or calcium hydroxide and dibenzo - 30 - crown - 10 affords the acid.

EXAMPLE 3

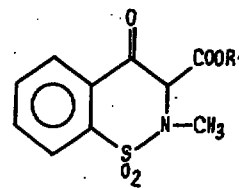
Following the procedures of Examples 1 or 2, the esters tabulated below are hydrolyzed to 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.



R ₁	Method of Example
C ₂ H ₅	1
t-C ₄ H ₉	2
n-C ₈ H ₁₇	1
n-C ₈ H ₁₇	2
n-C ₁₂ H ₂₅	1
n-C ₁₂ H ₂₅	2
C ₆ H ₅ CH ₂	1
C ₆ H ₅ (CH ₂) ₃	1
C ₆ H ₅ (CH ₂) ₂	2

WHAT WE CLAIM IS:—

1. A process for the preparation of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide which comprises hydrolysis, in the presence of a source of hydroxide ion, of a compound having the formula



wherein R₁ is alkyl having from one to twelve carbon atoms or phenylalkyl having up to three carbon atoms in the alkyl moiety, followed by acidification of the resulting product to a pH of from 0 to 6.0.

2. A process according to claim 1 wherein the hydrolysis is conducted in an aqueous solvent system.

3. A process according to claim 2 wherein the hydrolysis is conducted at a temperature of from 20°C. to the reflux temperature of the solvent.

4. A process according to claim 3 wherein R₁ is alkyl.

5. A process according to claim 4 wherein R₁ is methyl.

6. A process according to claim 5 wherein an alkali metal hydroxide is the source of hydroxide ion.

7. The process according to claim 6 wherein the alkali metal hydroxide is sodium hydroxide.

8. A process according to claim 1 wherein the hydrolysis is conducted in a non-aqueous solvent system in the presence of a crown ether.

9. A process according to claim 8 wherein the hydroxide ion source is an alkali metal hydroxide.

10. A process according to claim 9 wherein the alkali metal hydroxide is potassium hydroxide, the non-aqueous solvent is benzene or toluene, and the crown ether is 18 - crown - 6, dicyclohexyl - 18 - crown - 6, dibenzo - 18 - crown - 6 or cyclohexyl - 18 - crown - 6.

11. The process according to claim 10 wherein the solvent is benzene, the crown ether is dicyclohexyl - 18 - crown - 6 and the alkali metal hydroxide is potassium hydroxide.

12. Crystalline 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.

13. 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide when prepared by the process of any one of claims 1 to 11.

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