

PATENT SPECIFICATION

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(54) PROCESS FOR THE PREPARATION OF
 N-(2-PYRIDYL)- AND N(2-THIAZOLYL)-3,4-DIHYDRO-2-
 METHYL-4-OXO-2H-1,2-BENZOTHAZINE-3-
 CARBOXAMIDE-1,1-DIOXIDE AND NOVEL REACTIVE
 DERIVATIVES OF 3,4-DIHYDRO-2-METHYL-
 4-OXO-2H-1,2-BENZOTHAZINE-
 3-CARBOXYLIC ACID-1,1-DIOXIDE USED IN SAME

(71) We, PFIZER, INC., a Corporation organized 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 a process for producing the non-steroidal antiinflammatory agents N - (2 - pyridyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxides and N - (2 - thiazolyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxides and to reactive functional derivatives of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxides which are used in the preparation of said antiinflammatory compounds.

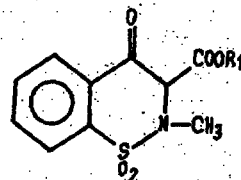
The preparation of N - substituted - 3,4 - dihydro - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxides useful as antiinflammatory agents is described in U.S. Patents 3,591,584; 3,891,637 and 3,892,740.

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 - dioxides 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 - dioxides 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 - dioxides 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.

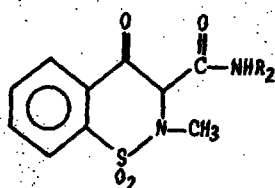
In each instance, the particular synthetic route employed carefully avoids the formation of 3,4 - dihydro - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxides, even as a transient intermediate, in order to circumvent the instability of the β - keto function of this acid. The instability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

Our copending Application No. 24161/77, Serial No. 1544358, provides a process for the preparation of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxides which comprises hydrolysis, in the presence of a source of hydroxide ion, of a compound having the formula



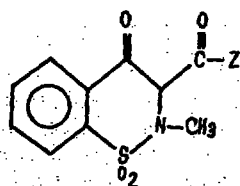
wherein R₁ is alkyl having from one to twelve carbon atoms or phenylalkyl having up to three carbon atoms in the alkyl moiety, followed by acidification of the resulting product to a pH of from 0 to 6.0.

The present invention provides a process for preparing a compound having the formula



wherein R_2 is 2 - pyridyl or 2 - thiazolyl which comprises coupling at least substantially equimolar proportions of an amine having the formula R_2NH_2 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 thioesters with N - hydroxysuccinimide, N - hydroxyphthalimide, a phenol or a thiophenol, or mixed anhydrides with alkoxy-carbonic acids or benzyloxy-carbonic acid.

Preferably, the amine is reacted with a compound having the formula (I)



wherein Z is chloro, bromo or OX wherein X is hydrogen benzyloxycarbonyloxy or alkoxy-carbonyloxy having from one to four carbon atoms.

N - (2 - pyridyl)- and N - (2 - thiazolyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxides, are both efficient antiinflammatory agents.

In the case where OX is hydroxy, the coupling reaction is preferably carried out in the presence of at least an equivalent proportion of a dehydrative coupling agent. Suitable dehydrative "coupling" agents are selected from N,N' - dicyclohexylcarbodiimide, N,N' - carbonyldiimidazole, N,N' - carbonylditriazole, N,N' - carbonyl - s - triazine, N - hydroxyphthalimide, N - hydroxysuccinimide, N - hydroxypiperidine, N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline, alkoxy-acetylene, diphenylketene p - tolylamine, and hexahalocyclotriphosphatriazines.

The most preferred dehydrative coupling agent is N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline.

The preferred reactive functional derivatives are the acid chloride and mixed anhydrides because of their ease of preparation. Especially useful is a compound of formula (I) wherein OX is ethoxycarbonyloxy.

The coupling reaction is conducted in an aqueous or non-aqueous solvent system. In aqueous systems, the reaction is generally

carried out at a pH of from 6 to 9 and a temperature of from 0°C to 50°C. It can, when using the acid chloride, also be performed in unstable emulsions of water and a water-immiscible organic solvent such as methyl isobutyl ketone and lower alkyl acetates over the pH range of from 2 to 4. When using a carbodiimide in an aqueous system, the pH is desirably adjusted to the range of 5 to 8, and preferably to 6 to 7. In a typical procedure, the acid reactant and carbodiimide are mixed in equimolar proportions in a suitable solvent (tetrahydrofuran, dioxan) and a water-water-miscible organic solvent solution (water plus dioxan or tetrahydrofuran) containing the amine is added at room temperature and the mixture stirred for several hours until reaction is complete. Temperatures of from -5°C to 30°C are generally used. In most instances, an excess up to 10% of the condensing agent is used. The desired product is recovered by methods known to the art.

When the acid chloride is used an acid acceptor, desirably an organic base such as triethylamine, pyridine, N - methylaniline, or an excess of the amine reactant (R_2NH_2) or an inorganic base such as sodium carbonate or bicarbonate, is preferably present.

The present invention also provides novel intermediates which are reactive functional derivatives of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide 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, reactive intermediates formed with N,N' - dicyclohexylcarbodiimide, N,N' - carbonyldiimidazole, N,N' - carbonylditriazole, N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline, an alkoxyacetylene or hexahalocyclotriphosphatriazines, and mixed anhydrides with alkoxy-carbonic acids or benzyloxycarbonic acid.

The invention is illustrated by the following Examples.

EXAMPLE 1

N - (2 - Pyridyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - Carboxamide - 1,1 - dioxide

A 25 ml. three-neck, round-bottom flask equipped with magnetic stirrer, reflux condenser and glass stoppers is charged with thionyl chloride (1.82 ml.), isopropyl ether (12.8 ml.) and 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide (1.28 g.). The mixture is heated at reflux and stirred for five hours and is then evaporated under reduced pressure. The residue is taken up in N,N - dimethylformamide (10 ml.) and the resulting solution used directly in the following step.

To the N,N - dimethylformamide solution of the acid chloride formed above is added, with stirring, 2 - aminopyridine (1.03 g.). An exothermic reaction occurs with development of a red color which changes to orange-yellow within about five minutes. The reaction mixture is stirred overnight and is then diluted by slow addition of water (40 ml.). The resulting precipitate is granulated for one-half hour and is then filtered, washed with water and air-dried (1.3 g., 79%). M.p. 160°—175°C. It is purified by dissolution in N,N - dimethylacetamide (1 ml. per 0.1 g.) at 50°—60°C. and precipitation therefrom by addition of a five-fold volume of methanol and chilling. Yield of pure product=30%; M.p. 198°—200°C. The identity of the compound is confirmed by infrared and mass spectrometry.

A similar result is achieved by substitution of thionyl bromide for thionyl chloride.

EXAMPLE 2

N - (2 - Thiazolyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxide

The procedure of Example 1 is repeated by using 510 mg. of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,1 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide, 1.45 ml. of thionyl chloride, 10.0 ml. of isopropyl ether and 2.0 ml. of N,N - dimethylformamide to prepare the acid chloride of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.

The acid chloride is then reacted with 2 - aminothiazole (400 mg.) according to the acylation procedure of Example 1 to afford 532 mg. (79%, crude) of the title product.

It is purified by dissolution in N,N - dimethylacetamide (3 ml.) at 60°C., filtration of the solution followed by dilution of the filtrate with methanol (15 ml.) to precipitate the product. Yield=208 mg. (33%). M.p. 234°—240°C. Repetition of this treatment affords the pure product.

The identity of the product is confirmed by infrared and mass spectrometry.

EXAMPLE 3

N - (2 - Pyridyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxide

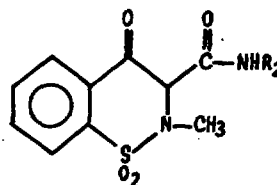
To a solution of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide (127 mg.) and 2 - aminopyridine (52 mg.) in tetrahydrofuran (5 ml.) is added, with stirring, a solution of N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline (148 mg.) in tetrahydrofuran (1 ml.). The mixture is stirred at room temperature (23°—25°C) for four hours and is then concentrated under reduced pressure to an oil. Thin layer chromatography on silica

gel plates in the system—benzene:acetic acid (65:5) and visualization of the plate under a 366 mu lamp showed, by comparison with an authentic sample, the title compound is present.

Repetition of this procedure but using N,N' - dicyclohexylcarbodiimide, N,N' - carbonyl - s - triazine, N,N - carbonyldiimidazole, ethoxyacetylene, diphenylketene p - tolylamine, N - hydroxysuccinimide, N - hydroxyphthalimide or N - hydroxypiperidine as coupling agents in place of N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline achieves similar results.

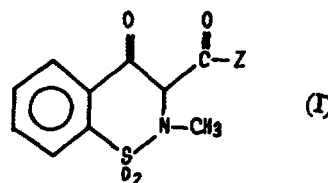
WHAT WE CLAIM IS:—

1. 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 R₂NH₂ 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 alkoxycarbonic acids or benzyloxycarbonic acid.

2. A process as claimed in claim 1 wherein the amine is reacted with a compound having the formula (I)



wherein Z is chloro, bromo or OX wherein X is hydrogen benzyloxycarbonyloxy or alkoxy-carbonyloxy having from one to four carbon atoms.

3. A process as claimed in claim 2 wherein OX is hydroxy and the coupling reaction is carried out in the presence of at least an equivalent proportion of a dehydrative coupling agent.

4. A process as claimed in claim 3 wherein the dehydrative coupling agent is selected from N,N' - dicyclohexylcarbodiimide, N,N' - carbonyldiimidazole, N,N' - carbonyldi-triazole, N,N' - carbonyl - s - triazine, N -



To the N,N - dimethylformamide solution of the acid chloride formed above is added, with stirring, 2 - aminopyridine (1.03 g.). An exothermic reaction occurs with development of a red color which changes to orange-yellow within about five minutes. The reaction mixture is stirred overnight and is then diluted by slow addition of water (40 ml.). The resulting precipitate is granulated for one-half hour and is then filtered, washed with water and air-dried (1.3 g., 79%). M.p. 160°—175°C. It is purified by dissolution in N,N - dimethylacetamide (1 ml. per 0.1 g.) at 50°—60°C. and precipitation therefrom by addition of a five-fold volume of methanol and chilling. Yield of pure product=30%; M.p. 198°—200°C. The identity of the compound is confirmed by infrared and mass spectrometry.

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EXAMPLE 2

N - (2 - Thiazolyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxide

The procedure of Example 1 is repeated by using 510 mg. of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,1 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide, 1.45 ml. of thionyl chloride, 10.0 ml. of isopropyl ether and 2.0 ml. of N,N - dimethylformamide to prepare the acid chloride of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 - dioxide.

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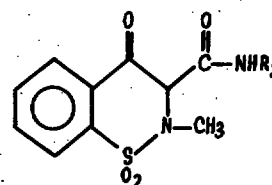
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Repetition of this procedure but using N,N' - dicyclohexylcarbodiimide, N,N' - carbonyl - s - triazine, N,N - carbonyldiimidazole, ethoxyacetylene, diphenylketene p - tolylamine, N - hydroxysuccinimide, N - hydroxyphthalimide or N - hydroxypiperidine as coupling agents in place of N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline achieves similar results.

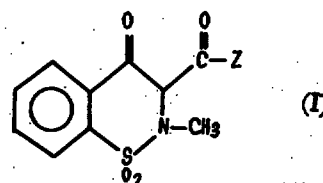
WHAT WE CLAIM IS:—

1. A process for preparing a compound having the formula



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2. A process as claimed in claim 1 wherein the amine is reacted with a compound having the formula (I)



wherein Z is chloro, bromo or OX wherein X is hydrogen benzyloxycarbonyloxy or alkoxy-carbonyloxy having from one to four carbon atoms.

3. A process as claimed in claim 2 wherein OX is hydroxy and the coupling reaction is carried out in the presence of at least an equivalent proportion of a dehydrative coupling agent.

4. A process as claimed in claim 3 wherein the dehydrative coupling agent is selected from N,N' - dicyclohexylcarbodiimide, N,N' - carbonyldiimidazole, N,N' - carbonyldi-triazole, N,N' - carbonyl - s - triazine, N -



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4. hydroxyphthalimide, N - hydroxysuccinimide, N - hydroxypiperidine, N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline, alkoxyacetylene, diphenylketene p - tolylamine, and
5 hexahalocyclotriphosphatriazines.

5. A process as claimed in claim 4 wherein the dehydrative coupling agent is N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline.

6. A process as claimed in claim 2 wherein
10 OX is ethoxycarbonyloxy.

7. A process as claimed in claim 2 wherein Z is chloro and the coupling reaction is carried out in the presence of an acid acceptor.

8. A process as claimed in claim 7 wherein
15 the acid acceptor is 2 - aminopyridine.

9. A process as claimed in claim 7 wherein the acid acceptor is 2 - aminothiazole.

10. A reactive functional derivative of 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxylic acid - 1,1 -
20 dioxide 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, reactive intermediates formed with N,N' - dicyclohexylcarbodiimide, N,N' - carbonyldiimidazole, N,N' - carbonylditriazole, N - ethoxycarbonyl - 2 - ethoxy - 1,2 - dihydroquinoline, an alkoxyacetylene or hexahalocyclotriphosphatriazines, and mixed
30 anhydrides with alkoxy-carbonic acids or benzyloxycarbonic acid.

11. N - (2 - pyridyl)- and N - (2 - thiazolyl) - 3,4 - dihydro - 2 - methyl - 4 - oxo - 2H - 1,2 - benzothiazine - 3 - carboxamide - 1,1 - dioxide, when prepared by the
35 process of any one of claims 1 to 9.

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