

PATENT SPECIFICATION

(11)

1 462 424

1 462 424

- (21) Application No. 11706/74 (22) Filed 15 March 1974
 (31) Convention Application No. 349 805 (32) Filed 10 April 1973 in
 (33) United States of America (US)
 (44) Complete Specification published 26 Jan. 1977
 (51) INT. CL.² C07D 241/42
 (52) Index at acceptance
 C2C 1628 213 247 250 252 25Y 30Y 327 334 366 368 657
 742 ME



(54) PROCESS FOR PRODUCING A QUINOXALINE-DI-N-OXIDE DERIVATIVE

(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, 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 novel synthetic procedure and more particularly to a novel method for the preparation of methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide. The compound prepared by the novel subject process is well known as a urinary tract antiseptic, systemic anti-infective, animal growth promotant, as an agent for the control of chronic respiratory diseases in poultry and improvement of feed efficiency in animals. [Australian Vet. J. 48, No. 10 579, (1972) and Rec. Med. Vet. ecole Alfort 148 No. 3 365-73 (1972)].

Accordingly, the present invention discloses a process for the preparation of methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide which comprises contacting a 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide derivative with at least an equimolar proportion of a carbazate in acidic solvent medium at a temperature of from 30 to 200°C. until reaction is substantially complete, said derivative being selected from the nitron, acetal, oxime, semicarbazone and thiosemicarbazone derivatives of 2-quinoxalinecarboxaldehyde dioxide; and said carbazate being selected from methyl carbazate and the methyl 3-C₁-C₆ alkylidene-, cyclopentylidene-, cyclohexylidene-, and benzylidene-carbazates, with the proviso that when said derivative is acetal said carbazate is not methyl carbazate.

The new reaction of the present invention is carried out in a reaction-inert solvent. An inert solvent for purposes of this

invention contemplates any solvent which allows solubilization of the reactants and is free of adverse effect on the reagents and products under the conditions employed. Two preferred types include organic acids, such as acetic acid, and C₁-C₆ alcohols and esters such as ethanol and ethyl acetate. The novel reaction of the present invention requires the presence of a strong acid catalyst. Examples of such acids suitable for this purpose are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid and trifluoroacetic acid. It is usually satisfactory to employ 2-10% by weight of the total reaction mixture of the acid catalyst. (If a strong acid e.g., trifluoroacetic acid is used for a reaction solvent, an acid catalyst is unnecessary.) Often the presence of a small quantity of water in the reaction mixture is desirable and this may be conveniently introduced by employing as an acid catalyst such acids as concentrated hydrochloric or hydrobromic acid which contain water. However, any solvent possessing the qualities set forth above will be satisfactory. The temperature at which the reaction is performed may vary from 30°C to 200°C. and for the most part the optimum temperature will vary with the choice of reagents. The higher temperature ranges may require the use of an autoclave or other high-pressure vessel.

Depending upon the particular reagents and temperature, the reaction time can vary from a few minutes to as long as 24 hours. Generally, to ensure complete reaction the relatively long time periods are preferred. Optimum reaction conditions are readily determined by experiment.

The proportion of quinoxaline derivative relative to the carbazate may vary widely but for efficient conversion at least one equivalent of carbazate per mole of quinoxaline derivative is necessary and a molar excess of 50-100% of the carbazate is preferred.

The carbazate derivative is most frequently methyl carbazate although other carbazate derivatives such as methyl 3-isopropylidene carbazate are also satisfactory.

5 The starting materials for the process of the present invention are readily prepared by well known standard organic chemical techniques. For example, the quinoxaline di-
10 oxide acetals are prepared *via* the method of Issidorides and Haddadin, Brit. 1215815. The preferred acetals are the ethylene and propylene acetals, the corresponding methyl
15 substituted acetals and the C₁-C₃ alkyl acetals. The semicarbazone is prepared according to the procedure of J. D. Johnston, United States Patent 3,493,572. The thio-
20 semicarbazone and oxime are prepared in a similar manner using this semicarbazide hydrochloride and hydroxylamine hydrochloride, respectively.

The nitrones are prepared *via* the route described by H. K. Kim. United States Patent 3,644,363. The preferred nitrones are
25 N-C₁-C₃ alkyl, -hydroxy-C₁-C₃ alkyl, -phenyl and -benzyl nitrones. The methyl carbazate and its derivatives are available through the sequence described by N. Rabjohn and H. D. Barnstorff, *J. Am. Chem. Soc.*, 75, 2259 (1953).

30 The product is isolated by dilution of the reaction mixture with water, cooling and subsequent filtration. The solid thus collected is washed with water and dried to provide the desired methyl-3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide.
35

The valuable product of this invention exhibits activity as urinary tract systemic anti-infective in animals, including man,
40 against a wide variety of microorganisms including Gram-positive and Gram-negative bacteria. It is especially valuable against Gram-negative infections both *in vitro* and *in vivo*.

45 Further, the addition of a low level of the herein described Schiff base to the diet of animals, both ruminant and non-ruminant, such that these animals receive the product over an extended period of time, at a level
50 of from 0.04 mg/kg. to 10 mg./kg. of body weight per day, especially over a major portion of their active growth period, results in an acceleration of the rate of growth and improved feed efficiency. Included in
55 these two classes of animals are poultry (chickens, ducks, turkeys), cattle, sheep, dogs, cats, rats, swine, mice, horses, goats, mules, rabbits and mink. The beneficial effects in growth rate and feed efficiency are over and above what is normally obtained
60 with complete nutritious diets containing all the nutrients, vitamins, minerals and other factors known to be required for the maximum healthy growth of such animals. The animals thus attain market size sooner and
65 on less feed.

These feed compositions have been found to be particularly valuable and outstanding in the case of such animals as poultry, rats, hogs, swine, lambs and cattle. In some instances the degree of response may vary
70 with respect to the sex of the animals. The products, may, of course, be administered in one component of the feed or they may be blended uniformly throughout a mixed feed; alternatively, as noted above, they may
75 be administered in an equivalent amount *via* the animal's water ration. It should be noted that a variety of feed components may be of use in the nutritionally balanced feeds.
80

The following examples are merely illustrative and in no way limit the scope of the appended claims.

EXAMPLE I

85 A solution of 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide oxime (41.0 g., 0.20 mol) and methyl carbazate (27 g., 0.30 mol) in trifluoroacetic acid (400 ml.) is refluxed for about 20-24 hours. The mixture is cooled
90 and diluted with water (1200 ml.). The precipitated solid is collected and dried to give the desired methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide.
95

EXAMPLE II

To a solution of 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide semicarbazone (49.4 g., 0.2 mol) and methyl 3-isopropylidene carbazate (39 g., 0.30 mol) in acetic acid (400
100 ml.) is added concentrated hydrochloric acid (20 ml.). The mixture is heated to about 80-100°C. for about 16 to 18 hours. After cooling, the mixture is diluted with water (1200 ml.) and the precipitated solid collected and washed with water to afford, after
105 air drying, the desired methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide.

EXAMPLE III

110 To a solution of 43.8 g. (0.20 mol) N-methyl-2-(quinoxalinylmethylene)nitron N¹,N⁴-dioxide and methyl carbazate (27 g., 0.30 mol) in acetic acid (400 ml.) is added concentrated sulfuric acid (20 ml.). The resulting
115 mixture is heated at about 90-100°C. for about 20-24 hours. After cooling and dilution with water (1200 ml.), the precipitated solid is collected and dried to give methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide.
120

EXAMPLE IV

125 To a solution of 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide dimethylacetal (47.2 g., 0.20 mol) and methyl 3-isopropylidene carbazate (39 g., 0.30 mol) in acetic acid (500 ml.) is added concentrated hydrochloric acid (20 ml.). The resulting mixture is heated on a steam bath for about 3 to 4
130

hours and then stirred at room temperature for about 24 hours. The precipitated product is collected and dried to give methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide.

WHAT WE CLAIM IS:—

1. A process for the preparation of methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide, which comprises contacting a 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide derivative with at least an equimolar proportion of a carbazate in reaction-inert solvent in the presence of strong acid catalyst, at a temperature of from 30 to 200°C. until reaction is substantially complete, said derivative being selected from the nitron, acetal, oxime, semicarbazone and thiosemicarbazone derivatives of 2-quinoxalinecarboxaldehyde dioxide; and said carbazate being selected from methyl carbazate and the methyl 3-C₁-C₂ alkylidene-, -cyclopentylidene-, cyclohexylidene-, and -benzylidene-carbazates, with the proviso that when said derivative is acetal said carbazate is not methyl carbazate.

2. The process of claim 1, wherein said nitron is selected from N-C₁-C₂ alkyl, -hydroxy-C₁-C₂ alkyl, -phenyl and -benzyl nitrons.

3. The process of claim 1, wherein said acetal is selected from the ethylene and propylene acetals, the corresponding methyl-substituted acetals, and the C₁-C₂ alkyl acetals.

4. The process of claim 1, wherein said derivative is the oxime, semicarbazone, or thiosemicarbazone of 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide.

5. A process for preparing methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide in accordance with claim 1, substantially as described.

6. Methyl 3-(2-quinoxalinylmethylene)carbazate whenever prepared by the process substantially as herein described and claimed.

STEVENS, HEWLETT & PERKINS,

Chartered Patent Agents,

5, Quality Court,
Chancery Lane,
London, W.C.2.
Tel. 01-405 8393.

Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 1 058 047.



hours and then stirred at room temperature for about 24 hours. The precipitated product is collected and dried to give methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide.

WHAT WE CLAIM IS:—

1. A process for the preparation of methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide, which comprises contacting a 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide derivative with at least an equimolar proportion of a carbazate in reaction-inert solvent in the presence of strong acid catalyst, at a temperature of from 30 to 200°C. until reaction is substantially complete, said derivative being selected from the nitron, acetal, oxime, semicarbazone and thiosemicarbazone derivatives of 2-quinoxalinecarboxaldehyde dioxide; and said carbazate being selected from methyl carbazate and the methyl 3-C₁-C₅ alkylidene-, -cyclopentylidene-, cyclohexylidene-, and -benzylidene-carbazates, with the proviso that when said derivative is acetal said carbazate is not methyl carbazate.

2. The process of claim 1, wherein said nitron is selected from N-C₁-C₅ alkyl-, -hydroxy-C₁-C₅ alkyl-, -phenyl and -benzyl nitrones.

3. The process of claim 1, wherein said acetal is selected from the ethylene and propylene acetals, the corresponding methyl-substituted acetals, and the C₁-C₅ alkyl acetals.

4. The process of claim 1, wherein said derivative is the oxime, semicarbazone, or thiosemicarbazone of 2-quinoxalinecarboxaldehyde N¹,N⁴-dioxide.

5. A process for preparing methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide in accordance with claim 1, substantially as described.

6. Methyl 3-(2-quinoxalinylmethylene)carbazate whenever prepared by the process substantially as herein described and claimed.

STEVENS, HEWLETT & PERKINS,

Chartered Patent Agents,

5, Quality Court,
Chancery Lane,
London, W.C.2.
Tel. 01-405 8393.

Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 1 058 047.