

PATENT SPECIFICATION

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(54) PROCESS FOR PREPARING METHYL 3-(2-QUINOXALINYLMETHYLENE)CARBAZATE-N¹N⁴-DIOXIDE

(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 process for the preparation of methyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide. The compound prepared by the process of the invention is well known as a urinary tract anti-septic, systemic anti-infective, animal growth promotant as an agent for the control of chronic respiratory diseases in poultry in improvement of feed efficiency in animals. [Australian Vet J 48, No. 10 579, (1972) and Rec. Med Vet. école Alfort 148 No. 3 365—73 (1972)].

Accordingly the present invention discloses a process for the preparation of methyl 3 - (2 - quinoxalinyl - methylene) carbazate - N¹,N⁴ - dioxide which comprises contacting an alkyl 3 - (2 - quinoxalinylmethylene) carbazate - N¹,N⁴ - dioxide wherein the alkyl group has from 2 to 18 carbon atoms; cyclohexyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide or a tetrahydrofuryl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide with methanol in the presence of a catalytic amount of a strong acid, preferably sulfuric acid hydrochloric acid, hydrobromic acid, ortho phosphoric acid or *p* - toluene sulfonic acid, at a temperature of from 25 to 200°C until reaction is substantially complete and recovering the resulting crystalline product.

Among the alkyl precursors which may be employed are, for example, the 2 - ethylbutyl and the 2 - ethylhexyl esters.

The starting materials which are necessary to carry out the process of this invention are easily prepared by well known standard organic techniques. For example the starting materials may be prepared by reac-

tion of 2 - quinoxaline carboxaldehyde - N¹,N⁴ - dioxide and the appropriate carbazate in an inert solvent and in the presence of an acid catalyst, until the starting materials are substantially consumed.

The reaction of the invention is carried out in methanol. The reaction temperature may vary from 25 to 200°C, although at temperatures above reflux an autoclave must be employed. Since room temperature reaction may be inconveniently slow, it is preferable to employ a temperature from 50°C to the reflux temperature.

In performing the process a catalytic amount of a strong acid is required, and an amount of from 0.5 to 10% by weight based on the starting ester will ordinarily be entirely adequate, and little or nothing is gained in most cases by employing more.

The addition of such acid not only serves to accelerate the reaction but also to improve the yield of product.

The course of the reaction is readily followed by removal of aliquots for workup. The reaction is preferably continued to substantial completion, the time for which will of course vary with the particular temperature, catalyst, catalyst concentration and carbazate ester selected. Ordinarily reaction periods of from about one to 48 hours will suffice.

The product is a crystalline substance which precipitates from the reaction mixture either as the reaction proceeds or upon cooling depending on the concentration of the reactant. It is collected by suitable means, e.g. filtration or decantation, and dried.

The compound prepared by this invention exhibits activity as urinary tract and systemic anti-infective against Gram-negative infections both *in vitro* and *in vivo*. 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 of from about 1 mg./kg. to about 100 mg./kg., of body weight per day, results in an acceleration of the rate of growth

and improved feed efficiency. Included in these two classes of animals are poultry (chickens, ducks, turkeys), cattle, sheep, dogs, cats, rats, mice, swine, horses, goats, mules, rabbits and mink. The beneficial effects in growth rate and feed efficiency are over and above what is normally obtained 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 on less feed.

These feed compositions have been found to be particularly valuable for poultry, hogs, swine, lambs, and cattle. 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 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.

EXAMPLE I

Methyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide. To a solution of 1 - (2 - ethylbutyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide (66.4 g., 0.20 mole) in methanol (500 ml.) is added concentrated sulfuric acid (25 ml.). The resulting mixture is refluxed for 24 hours and then cooled. The precipitated solid is collected and dried to give methyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide.

EXAMPLE II

Following the procedure of Example I, methyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide may be prepared, substituting in turn, each of the following in place of the (2 - ethylbutyl) compound of the previous example: cyclohexyl 3 - (2 -

quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide, a tetrahydrofurfuryl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide, (2 - ethylhexyl) 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide, ethyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide, octadecyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide.

In like manner, the same reaction may be repeated, substituting hydrochloric, hydrobromic, ortho phosphoric or *p* - toluenesulfonic acid for the catalyst of Example I.

WHAT WE CLAIM IS:—

1. A process for the preparation of methyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide which comprises contacting an alkyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide wherein the alkyl group has from 2 to 18 carbon atoms; cyclohexyl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide or a tetrahydrofuryl 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide with methanol in the presence of a catalytic amount of a strong acid at a temperature of from 25° to 200°C, until reaction is substantially complete and recovering the resulting crystalline product.

2. A process according to claim 1, wherein the said strong acid is sulfuric acid, hydrochloric acid, hydrobromic acid, ortho phosphoric acid or *p* - toluene sulfonic acid.

3. The process of claim 1, wherein the said carbazate is 2 - ethylbutyl - 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide.

4. The process of claim 1, wherein the said carbazate is cyclohexyl - 3 - (2 - quinoxalinylmethylene)carbazate - N¹,N⁴ - dioxide.

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EXAMPLE I

Methyl 3 - (2 - quinoxalinylmethylene)-carbazate - N^1, N^4 - dioxide. To a solution of 1 - (2 - ethylbutyl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide (66.4 g., 0.20 mole) in methanol (500 ml.) is added concentrated sulfuric acid (25 ml.). The resulting mixture is refluxed for 24 hours and then cooled. The precipitated solid is collected and dried to give methyl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide.

EXAMPLE II

Following the procedure of Example I, methyl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide may be prepared, substituting in turn, each of the following in place of the (2 - ethylbutyl) compound of the previous example: cyclohexyl 3 - (2 -

quinoxalinylmethylenecarbazate - N^1, N^4 - dioxide, a tetrahydrofurfuryl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide, (2 - ethylhexyl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide, ethyl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide, octadecyl 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide.

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3. The process of claim 1, wherein the said carbazate is 2 - ethylbutyl - 3 - (2 - quinoxalinylmethylene)carbazate - N^1, N^4 - dioxide.

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