

PATENT SPECIFICATION

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- (21) Application No. 20800/77 (22) Filed 18 May 1977
 (31) Convention Application No. 696263 (32) Filed 15 Jun. 1976 in
 (33) United States of America (US)
 (44) Complete Specification Published 1 Jul. 1981
 (51) INT. CL.³ C07D 241/52
 A61K 31/495

(19)



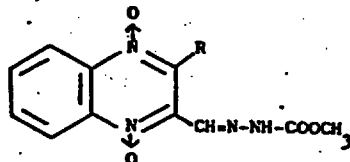
- (52) Index at Acceptance
 C2C 1628 213 220 22Y 247 250 252
 25Y 280 30Y 321 327 32Y 334 342
 34Y 351 355 360 361 362 366 368
 36Y 574 584 628 62X 657 658 65X
 742 802 805 80Y AB KN ME

(54) PROCESS FOR PRODUCING METHYL 3-(2-QUINOXALINYLMETHYLENE) CARBAZATE-N¹,N⁴-DIOXIDES

(71) We, PFIZER INC., a Corporation organised 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:-

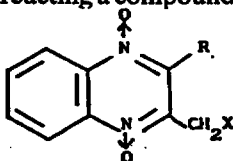
The invention relates to processes for preparing methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxides. It is particularly concerned with a process in which a 2-halomethyl-quinoxaline-N¹,N⁴-dioxide is reacted with novel aliphatic or aromatic sulphonyl derivatives of methyl carbazate to yield compounds with useful antibacterial properties and/or with growth promotant properties in animals.

According to the invention, a process for preparing a methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴-dioxide of the formula:



-- (I)

wherein R is hydrogen, alkyl, hydroxyalkyl, alkanoyl, benzoyl or -CONR¹R² wherein R¹ and R² are each hydrogen, alkyl, hydroxyalkyl or aminoalkyl, any such alkyl, hydroxyalkyl or aminoalkyl group containing 1 to 6 carbon atoms and any such alkanoyl group containing 2 to 7 carbon atoms, comprises reacting a compound of the formula:



--- (II)

wherein R is as defined above and X is chlorine or bromine, with a compound of the formula:



wherein R³ is an aliphatic or aromatic sulphonyl group, in a reaction-inert solvent, in the presence of anhydrous potassium carbonate.

Preferably X is bromine and preferably the reaction is carried out at a temperature of 75 to 85°C.

Suitable aliphatic and aromatic sulphonyl groups R³ include the methane sulphonyl (CH₃SO₂), trifluoromethane sulphonyl (CF₃SO₂), 2,2,2-trifluoroethane sulphonyl (CF₃CH₂SO₂) and para-toluene sulphonyl groups, commonly known as the mesyl, trifyl, tresyl and tosyl groups respectively. The preferred compound of formula (III) is that in which R³ is trifyl, i.e. N-methoxycarbonyl-N'-trifyl-hydrazine.

Suitable reaction-inert solvents are polar, non-aqueous solvent, such as acetonitrile and dimethylformamide.

The preferred solvent is acetonitrile.

The compound of formula (II) is preferably reacted with from one to two molar equivalents

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of the compound of formula (III) in the presence of from one to two molar equivalents of the anhydrous potassium carbonate. Most preferably, the reaction is carried out with an equimolar amount or a slight molar excess of the compound of formula (III) and of the anhydrous potassium carbonate.

A process for preparing certain methyl 3-(3-substituted-2-quinoxalinylmethylene)carbazate N¹, N⁴-dioxides is described in U.S. Patent No. 3839326 and British Patent Specification No. 1365441, wherein a 2-(bis-halo-methyl)-3-substituted-quinoxaline N¹, N⁴-dioxide is reacted with methyl carbazate in the presence of a primary or secondary amine and preferably also in the presence of water. The process of the present invention is broadly applicable to the preparation of methyl 3-(2-quinoxalinylmethylene)carbazate N¹, N⁴-dioxides, with a wide variety of substituents at the 3-position of the quinoxaline ring, from 2-(mono-halo-methyl) quinoxaline N¹, N⁴-dioxides, which are more easily and economically prepared than the corresponding 2-(bis-halo-methyl) compounds.

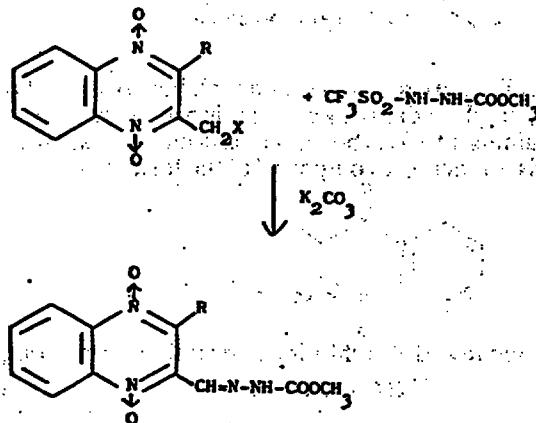
Compounds of formula (I), other than those in which R is hydrogen, alkyl or -CONR¹R², are novel compounds, which are the subject of our divisional application no. 80/00764 (Serial no. 1591873).

Compounds of formula (I) in which R is hydrogen or alkyl containing 1 to 6 carbon atoms are described and claimed in British Patent Specification No. 1058047, while those in which R is -CONR¹R² are described and claimed in British Patent Specification No. 1365441.

The compounds of formula (II) used as starting materials in the process of the invention may be prepared by chlorination or bromination of 2-methyl-quinoxaline N¹, N⁴-dioxides by the general methods described in J. Chem. Soc. 2052, (1956), "Chemistry of Heterocyclic Compounds", 940 (1967) and in U.S. Patent No. 3753987. The 2-methyl-quinoxaline N¹, N⁴-dioxides are themselves prepared by methods as described in J. Chem. Soc., 322 (1943), U.S. Patents Nos. 3474097, 3553208 and 3660498 and British Patent Specification No. 1215815.

Some of the compounds of formula (III) are novel compounds, the subject of our divisional application no. 80/00765 (Serial no. 1591874), others are the subject of claims in British Patent No. 1505120.

The process for preparing compounds of formula (I) according to the invention may be illustrated by the reaction of the compound of formula (II) with N-methoxycarbonyl-N'-triflylhydrazine in the presence of anhydrous potassium carbonate as follows:-



A suspension of the 2-halomethylquinoxaline, N¹, N⁴-dioxide in a reaction-inert solvent such as acetonitrile is heated with stirring at a temperature of from 75 to 85°C., preferably at reflux temperature. One to two molar equivalents, preferably a slight molar excess, of anhydrous powdered potassium carbonate and N-methoxycarbonyl-N'-triflylhydrazine are added to the suspension in one portion. In those cases where a solid separates within a few minutes, heating is continued for 30-40 minutes, and then the solid is collected and dried. Where no solid separates, heating is continued until thin layer chromatography indicates the absence of the original 2-halomethylquinoxaline-di-N-oxide. The reaction mixture is filtered and the filtrate is concentrated under vacuum at room temperature to give an amber oil which crystallizes from absolute ethanol.

The quinoxaline derivatives of this invention show strong antibacterial effects against Gram-positive and Gram-negative bacteria. As a result of this activity, the compounds are useful as industrial antimicrobials, e.g., in water treatment, slime control, paint preservation and wood preservation as well as for topical application purposes as disinfectants.

Further, compounds of this invention are useful in veterinary medicine for the treatment of infections in animals. For oral administration dosages of from 1 mg/kg to 60 mg/kg of body

weight may be employed. In the case of poultry and domestic animals, a compound is conveniently administered by mixing with feed or as a dilute solution or suspension, e.g., 0.1% solution for drinking purposes.

The compounds of this invention are preferably administered by subcutaneous or intramuscular injection at a dosage of from 10 to 100 mg/kg of body weight. Vehicles suitable for parenteral injection may be either aqueous such as water, isotonic saline and isotonic dextrose or non-aqueous such as fatty oils of vegetable origin, glycerol, propylene glycol and sorbitol.

The compounds of this invention are useful for the promotion of weight gain and food consumption in animals, e.g., poultry and swine. The addition of a low level of one or more of the herein described quinoxaline-di-N-oxides in feed or drinking solution at a level of from 0.1 mg/kg to 100 mg/kg of body weight per day over a major portion of the animal's active growth period results in an acceleration of the rate of growth and improves feed efficiency (the number of pounds of feed required to produce a pound of weight gain).

The following Examples illustrate the preparation of compounds of formula (I) according to the invention.

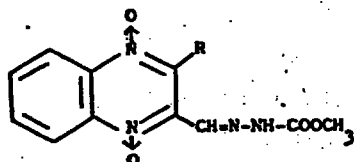
EXAMPLE 1

Methyl 3-(2-quinoxalinylmethylene) carbazate N¹,N⁴-dioxide

A suspension of 2-bromomethylquinoxaline, N¹,N⁴-dioxide (6 mmoles) in acetonitrile (70 ml) was heated to reflux with stirring. Powdered anhydrous potassium carbonate (6.52 mmoles) and N-methoxycarbonyl-N'-triflyl hydrazine (6.6 mmoles) were added to the suspension in one portion. A solid separated from the resulting incipient solution within a few minutes. The mixture was heated at reflux for a total of 1.5 hours. The solid was collected, washed successively with two 20 ml portions each of acetonitrile and ether, and dried to constant weight to give a dark yellow solid (1.89 g., ca 100%). The crude product was suspended in 5% sodium bicarbonate (50 ml) for 30 minutes, collected, washed with water, and then recrystallized from acetic acid (30 ml). The recrystallized product was washed with two 20 ml portions of acetic acid/ether (1:1) and then with two 20 ml portions of ether to yield the product as a yellow crystalline powder, m.p. 243°C.

EXAMPLE 2

The method of Example 1 was repeated employing the appropriate 3-substituted-2-bromomethylquinoxaline, N¹,N⁴-dioxide to obtain the following compounds having the formula



R	M.P. (°C)	% Yield
(A) CH ₂ OH	208-210 (dec.)	27
(B) CH(OH)CH ₃	145 (dec.)	12
(C) COC ₆ H ₅	220 (dec.)	57
(D) CONHCH ₃	244 (dec.)	9
(E) COCH ₃	238 (dec.)	5

Table I illustrates the antibacterial spectra of the hitherto unreported compounds. These tests were conducted by preparing tubes of nutrient broth with gradually increasing concentrations of each compound and then seeding the broths with the particular organism specified. The minimal inhibitory concentration indicated in Table I is the minimal concentration of the compound (in micrograms/ml) at which the microorganism failed to grow. The tests were conducted under standardized conditions as described in Proc. Soc. Exp. Biol. & Med., 122, 1107, (1966).

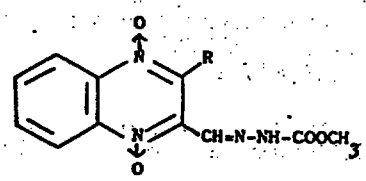
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Table I

Organism		Minimum Inhibitory Concentration (Micrograms/ml) of Example 2 Compound			
5	<i>Staphylococcus aureus</i>	01A005	5.12	3.12	< 0.39
		01A106	3.12	3.12	< 0.39
10	<i>Escherichia coli</i>	51A203	3.12	6.25	6.25
		51A266	0.78	6.25	6.25
		51A218	3.12	6.25	6.25
15	<i>Streptococcus pyogenes</i>	020203	< 0.39	0.78	< 0.39
	<i>Streptococcus equi</i>	02I001	< 0.39	1.56	< 0.39
20	<i>Salmonella typhimurium</i>	58D001	3.12	12.5	25
		58D011	1.56	12.5	50
25	<i>Salmonella dublin</i>	58U001	3.12	6.25	12.5
	<i>Salmonella cholerae-suis</i>	58B242	3.12	6.25	12.5
	<i>Pasteurella multocida</i>	59A001	< 0.39	3.12	6.25
30		59A002	< 0.39	3.12	12.5
		59A006	< 0.39	---	---

EXAMPLE 3

The method of Example 1 may be repeated employing appropriate 3-substituted-2-chloromethylquinoxaline, N¹,N⁴-dioxides to obtain compounds with comparable antibacterial activities having the formula

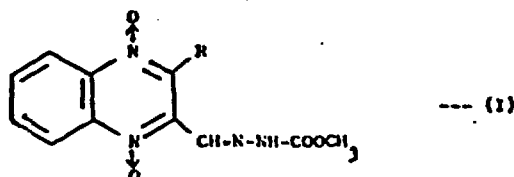


- R
- CONH₂
 - CONHCH₂CHOH CH₃
 - CONHCH₂CH₃
 - CON(CH₃)₂
 - CONHCH₂CH₂CH₃
 - CONH-n-C₄H₉
 - CONHCH₂CH₂NH₂
 - CH₂CH₂OH
 - CHOHCH₂CH₃
 - COCH₂CH₃
 - COCH₂CH₂CH₃
 - CH₃
 - C₂H₅
 - η-C₄H₉

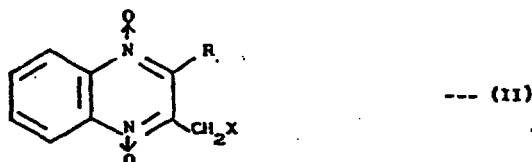


WHAT WE CLAIM IS:-

1. A process for preparing a methyl 3-(2-quinoxalinylmethylene)carbazate N¹,N⁴ dioxido of the formula:



wherein R is hydrogen, alkyl, hydroxyalkyl, alkanoyl, benzoyl or -CONR¹R² wherein R¹ and R² are each hydrogen, alkyl, hydroxyalkyl or aminoalkyl, any such alkyl, hydroxyalkyl or aminoalkyl group containing 1 to 6 carbon atoms and any such alkanoyl group containing 2 to 7 carbon atoms, which comprises reacting a compound of the formula:



wherein R is as defined above and X is chlorine or bromine, with a compound of the formula:



wherein R³ is an aliphatic or aromatic sulphonyl group, in a reaction-inert solvent, in the presence of anhydrous potassium carbonate.

2. A process as claimed in claim 1, in which R³ is a mesyl, trifyl, tresyl or tosyl group.
3. A process according to any preceding claim, in which the reaction-inert solvent is acetonitrile.
4. A process according to claim 1 or claim 2, in which X is bromine.
5. A process according to any preceding claim, in which the reaction is carried out at a temperature of 75 to 85°C.
6. A process according to any preceding claim in which the compound of formula (II) is reacted with from one to two molar equivalents of the compound of formula (III) in the presence of from one to two molar equivalents of anhydrous potassium carbonate.
7. A process for preparing compounds of formula (I), substantially as hereinbefore described in any of Examples 1 to 3.
8. A compound of formula (I) prepared by a process as claimed in any preceding claim.

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