



PATENT SPECIFICATION

NO DRAWINGS

1,184,044

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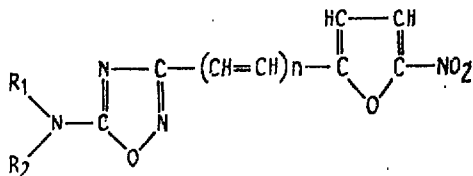
COMPLETE SPECIFICATION

Nitrofuryl-Oxadiazole Derivatives

We, E. R. SQUIBB & SONS INC., a Corporation organized and existing under the laws of the State of Delaware, United States of America, of 745, Fifth Avenue, 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 new, improved antimicrobial agents of the formula

(1)



wherein R₁ and R₂, within the limits defined in the appended claims, each represents hydrogen, lower alkyl, hydroxy-lower alkyl or acyl or, together with the nitrogen atom to which they are attached, they form a 6-membered heterocyclic ring which may also contain oxygen or sulfur, and wherein n is 0, 1 or 2.

By the term "lower" as used herein there is meant, unless otherwise stated, a radical having from 2 to 8 carbon atoms.

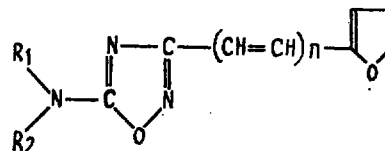
This invention is particularly concerned with new compounds of formula I wherein R₁ and R₂ each represents lower alkyl groups, which may be of straight or branched structure, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl and amyl, hydroxy-lower alkyl groups of the same type, such as 2-hydroxyethyl and 3-hydroxypropyl, and acyl radicals of the lower fatty acids, e.g., ones

having 2 to 8 carbons, such as acetyl, propionyl and butyryl. In addition, the N < R₂ grouping may represent a 6-membered saturated heterocyclic ring, in particular, piperidine, piperazine, morpholine or thiomorpholine.

The compounds of this invention show particular advantages over other known nitrofuran derivatives. These compounds are useful as antimicrobial agents to combat animal infections due to bacteria and fungi such as *Staphylococci*, *Escherichia*, *Klebsiella*, *Candida* and *Trichophyton*, and particularly effective against infections caused by *Trichomonas* organisms, such as *T. vaginalis* and *T. foetus*. They may be used orally in the conventional oral dosage forms in a range of about 10 mg. to 200 mg. per kilogram per day or topically in a cream or ointment vehicle at a concentration of about 0.05 to 2.0%. Especially active are those compounds with free amino groups and particularly those in which there is a single vinyl group (n=1).

The products of formula I may be produced by one of several methods. A compound of the general formula

(II)

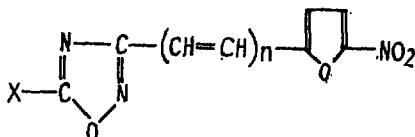


in which n, R₁ and R₂ have the above mentioned meaning, may be nitrated, e.g., with nitric acid. Acylation of the amine group may be simul-

taneously effected by nitrating in the presence of an acylating agent, e.g., an acid anhydride such as acetic anhydride.

Alternatively, a compound of the formula

(III)



in which n has the same meaning as above and X represents a group which may be replaced by an amine group, e.g., a halogen such as chlorine or a trichloromethyl group, is treated with ammonia or the appropriate amine, e.g., alkylamine, di-alkylamine, piperidine, morpholine, or thiamorpholine, in an inert organic solvent, like ethanol, or using the amine compound itself as the medium. If desired, acylation, e.g., with an acid anhydride, may follow.

The following examples are illustrative of the invention. Temperatures are expressed on the centigrade scale.

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EXAMPLE 1.

3.2 grams of 3-[2-(5-nitro-2-furyl)vinyl]-5-trichloromethyl-1,2,4-oxadiazole are added portionwise with stirring to 35 to 40 ml. of liquid ammonia. The product first forms a dark colored solution. Then later a thick crystalline slurry forms. The ammonia is permitted to evaporate and the residue is crystallized from dioxane. Yield: 2 grams of 3-[2-(5-nitro-2-furyl)vinyl]-5-amino-1,2,4-oxadiazole, m.p. 290° , with dec.

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EXAMPLE 2.

To a mixture formed from 30 ml. of acetic anhydride and 12 ml. of nitric acid ($d=1.52$) at -15° are added portionwise at the same temperature 5 grams of 3-[2-(2-furyl)vinyl]-5-acetylamino-1,2,4-oxadiazole. After the compound has been added, the mixture is stirred for an additional 2 hours, the precipitate is filtered under suction, washed with glacial acetic acid and dried. There are obtained 2 grams of 3-[2-(5-nitro-2-furyl)vinyl]-5-acetylamino-1,2,4-oxadiazole.

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EXAMPLE 3.

15 grams of 3-(5-nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole are dissolved in 40 ml. of ethanol with warming. The solution is then quickly cooled with vigorous stirring and a fine crystalline suspension results. On cooling to 10° , 15 ml. of ethanolamine are dropped in. A red brown solution results from which the reaction product then crystallizes. The mixture is stirred for one hour, diluted with 100 ml. of water and filtered under suction. The yield is 11.6 grams of 3-(5-nitro-2-furyl)-5-(2-hydroxyethyl)amino-1,2,4-oxadiazole which, after recrystallization from isopropanol, melts at $135-138^{\circ}$.

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EXAMPLE 4.

15 grams of 3-(5-nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole are dissolved in 50 ml. of ethanol with warming and the solution is then quickly cooled with vigorous stirring. To the fine crystalline slurry are added dropwise, while cooling to 10° , 30 ml. of 40% aqueous dimethylamine solution. The mixture is warmed until a clear solution results and again quickly cooled. There are obtained 7.5 grams of 3-(5-nitro-2-furyl)-5-dimethyl-amino-1,2,4-oxadiazole, m.p. $181-182^{\circ}$.

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EXAMPLE 5.

15 grams of 3-[2-(5-nitro-2-furyl)vinyl]-5-trichloromethyl-1,2,4-oxadiazole are added to 50 ml. of dimethylamine at -20° over a period of 15 minutes and then stirred for an hour at this temperature. The reaction mixture becomes very viscous. The dimethylamine is then evaporated *in vacuo* and the residue is crystallized from 400 ml of ethanol. There are obtained 6 grams of 3-[2-(5-nitro-2-furyl)vinyl]-5-dimethylamino-1,2,4-oxadiazole, m.p. $186-187^{\circ}$.

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EXAMPLE 6.

15 grams of 3-(5-nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole are dissolved with warming in 45 ml. of ethanol and then quickly cooled. To the fine crystalline slurry are added dropwise with stirring at 20° 45 ml. of pyridine. A red brown solution results from which scaley crystals precipitate toward the end of the piperidine addition. The mixture is warmed until a clear solution results and this is again quickly cooled and the crystals are filtered under suction. There are obtained 10.2 grams of 3-(5-nitro-2-furyl)-5-(1-piperidinyl)-1,2,4-oxadiazole which are recrystallized from 40 ml. of acetone and 10 ml. of petroleum ether, m.p. $143-145^{\circ}$.

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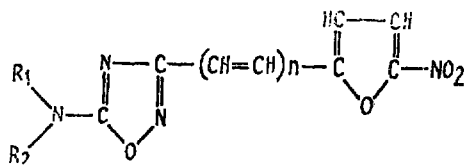
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WHAT WE CLAIM IS:—

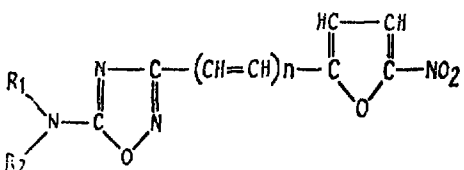
1. A compound of the formula



wherein R_1 and R_2 each is hydrogen or acyl and n is 0, 1 or 2.

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2. A compound of the formula

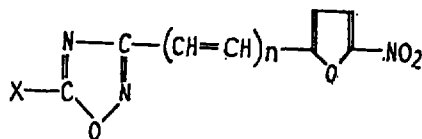


wherein R_1 and R_2 each is hydrogen, lower alkyl or hydroxy-lower alkyl with only one

taneously effected by nitrating in the presence of an acylating agent, e.g., an acid anhydride such as acetic anhydride.

Alternatively, a compound of the formula

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in which n has the same meaning as above and X represents a group which may be replaced by an amine group, e.g., a halogen such as chlorine or a trichloromethyl group, is treated with ammonia or the appropriate amine, e.g., alkylamine, di-alkylamine, piperidine, morpholine, or thiamorpholine, in an inert organic solvent, like ethanol, or using the amine compound itself as the medium. If desired, acylation, e.g., with an acid anhydride, may follow.

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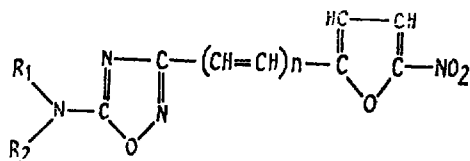
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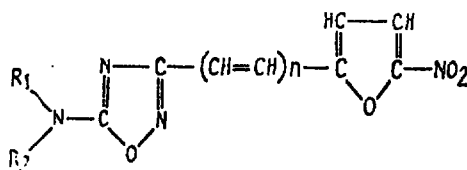
WHAT WE CLAIM IS:—

1. A compound of the formula



wherein R_1 and R_2 each is hydrogen or acyl and n is 0, 1 or 2.

2. A compound of the formula



wherein R_1 and R_2 each is hydrogen, lower alkyl or hydroxy-lower alkyl with only one

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of R_1 and R_2 being hydrogen, or R_1 and R_2 together with the nitrogen to which they are attached form a 6-membered, saturated monocyclic nitrogen heterocyclic ring containing only the single nitrogen atom and which may also contain oxygen or sulfur, and n is 0, 1 or 2.

3. A compound according to claim 1 wherein R_1 and R_2 are both hydrogen and n is 1.

4. A compound according to claim 1 wherein R_1 is lower alkanoyl, R_2 is hydrogen and n is 1.

5. A compound according to claim 4 wherein the lower alkanoyl group is acetyl.

6. A compound according to claim 2 wherein R_1 is hydroxy-lower alkyl, R_2 is hydrogen and n is 0.

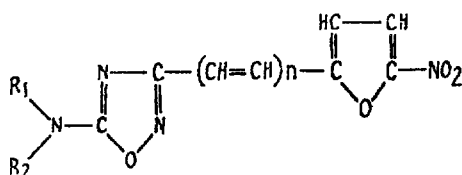
7. A compound according to claim 6 wherein the hydroxy-lower alkyl group is hydroxyethyl.

8. A compound according to claim 2 wherein R_1 and R_2 are both lower alkyl.

9. A compound according to claim 8 wherein each lower alkyl group is methyl.

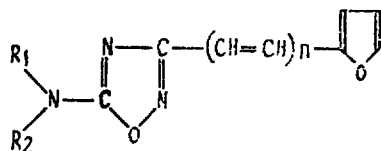
10. A compound according to claim 2 wherein R_1 and R_2 form a piperidine group with the nitrogen.

11. A process for preparing antimicrobial agents of the formula (I)



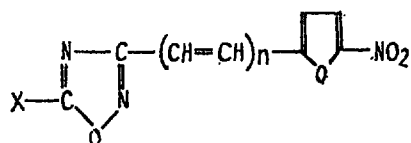
wherein R_1 and R_2 each represents hydrogen or acyl and wherein n is 0, 1 or 2, which comprises nitrating or simultaneously nitrating and acylating a compound of the formula

(II)



in which n , R_1 and R_2 are as defined above to form compound (I) or reacting a compound of the formula

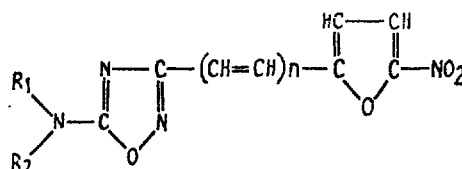
(III)



in which n has the same meaning as above and X represents halogen with ammonia and

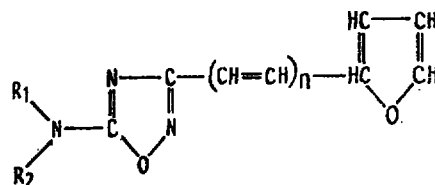
if desired acylating to form compound (I).

12. A process for preparing antimicrobial agents of the formula (I)



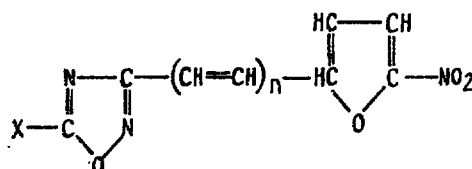
wherein R_1 and R_2 each represents hydrogen, lower alkyl or hydroxy-lower alkyl with only one of R_1 and R_2 being hydrogen, or R_1 and R_2 together with the nitrogen to which they are attached form a 6-membered saturated monocyclic nitrogen heterocyclic ring containing only the single nitrogen atom and which may also contain oxygen or sulfur and n is 0, 1 or 2, which comprises nitrating a compound of the formula

(II)



in which n , R_1 and R_2 are as defined above, to form compound I or reacting a compound of the formula

(III)



in which n has the same meaning as above and X represents halogen, with an amine.

13. The process according to claim 11, wherein R_1 and R_2 are both hydrogen and n is 1.

14. The process according to claim 11, wherein R_1 is lower alkanoyl, R_2 is hydrogen and n is 1.

15. The process according to claim 12, wherein R_1 is hydroxy-lower alkyl, R_2 is hydrogen and n is 0.

16. The process according to claim 12, wherein R_1 and R_2 are both lower alkyl.

17. The process according to claim 12, wherein R_1 and R_2 form a piperidine group with the nitrogen.

18. A compound according to any of claims 1, 3, 4 and 5, substantially as herein described with reference to the Examples given.

19. A compound according to any of

claims 2, and 6 to 10, substantially as herein described with reference to the Examples given.

5 20. A process as claimed in any of claims 11, 13 and 14 for preparing a compound as therein defined, substantially as herein described.

10 21. A process as claimed in any of claims 12, 15, 16 and 17, for preparing a compound as therein defined, substantially as herein described.

22. A compound according to any of claims 1, 3, 4 and 5, which has been prepared using

a process as claimed in any of claims 11, 13 and 14.

23. A compound according to any of claims 2, and 6 to 10 which has been prepared using a process as claimed in any of claims 12, 15, 16 and 17.

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