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PATENT SPECIFICATION

NO DRAWINGS

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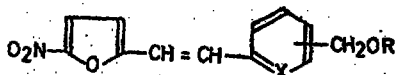
COMPLETE SPECIFICATION

2-[2-(5-Nitro-2-Furyl) Vinyl] Pyridine Derivatives and process for preparation thereof

We, DAINIPPON PHARMACEUTICAL CO., LTD, a Japanese body corporate of 25, 3-chome, Doshomachi, Higashi-ku, Osaka, Japan, 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 2-[2-(5-nitro-2-furyl)vinyl]pyridine derivatives and their production.

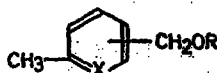
In one aspect the invention consists in 2-[2-(5-nitro-2-furyl)vinyl]-5- or -6-hydroxymethyl, or -alkanoyloxymethylpyridines and N-oxides thereof represented by the general formula:—



in which X is N or N → O, the radical —CH₂OR is at the 5- or 6-position of the pyridine ring, and R is hydrogen or lower alkanoyl such as acetyl or propionyl. (By "lower alkanoyl" is meant alkanoyl having 1—4 carbon atoms.) These compounds have been found to possess excellent antimicrobial activities.

Examples of the 2-[2-(5-nitro-2-furyl)vinyl] pyridines and N-oxides thereof represented by the above formula (1) include 2-[2-(5-nitro-2-furyl)vinyl]-6-hydroxymethylpyridine N-oxide, -6-acetoxymethylpyridine N-oxide, -6-hydroxymethylpyridine, -6-acetoxymethylpyridine, -6-propionyloxymethylpyridine, -5-hydroxymethylpyridine N-oxide, -5-acetoxymethylpyridine N-oxide, -5-hydroxymethylpyridine, and -5-acetoxymethylpyridine. Among those, the compounds having hydroxymethyl or alkanoyloxymethyl at the 6-position of the pyridine ring, particularly the first three of the above compounds, are preferred.

The invention comprises also the production of the compounds of formula (1) by condensing 5-nitrofurfural with a compound of the formula:—



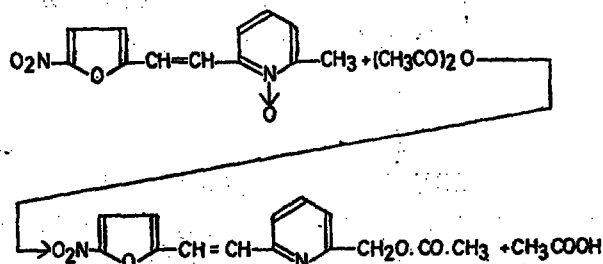
in which X and R have the above meanings, or reacting 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine N-oxide with a lower fatty acid anhydride (i.e. an anhydride of a fatty acid of 1—4 carbon atoms) and, if required, hydrolysing and/or oxidizing the product.

The condensation of 5-nitrofurfural with the compound of formula (2) can be performed in a manner known *per se*, advantageously by heating the reactants, for example to 70°C., in the presence of a lower fatty acid anhydride such as acetic anhydride or propionic anhydride, optionally in an inert solvent. When R is H in the compound of

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formula (2) the acid anhydride functions as an alkanoylating agent as well as a condensing agent. When X is N, other condensing agents such as hydrochloric acid, sulphuric acid, molten zinc chloride and anhydrous sodium acetate, which do not function as alkanoylating agents, may be used.

The reaction of 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine N-oxide with a lower fatty acid anhydride, such as acetic anhydride or propionic anhydride, to give a product having the substituted methyl group at the 6-position of the pyridine ring can be illustrated by the following equation, in which acetic anhydride is used as the lower fatty acid anhydride:—



This rearrangement reaction can be performed by heating the reactants in an inert solvent such as acetic acid or toluene, or, with advantage, by heating the N-oxide with an excess of the acid anhydride to a temperature of, say, at least $90^\circ C$. The 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine N-oxide can be readily prepared by oxidizing 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine with hydrogen peroxide in glacial acetic acid or condensing 5-nitrofurfural with 2,6-dimethylpyridine N-oxide.

The condensation or rearrangement reaction product can be converted to the corresponding hydroxymethyl compound or N-oxide compound by hydrolysis and/or oxidation processes known *per se*, if so desired. For hydrolysing a lower alkanoyloxymethyl compound to the corresponding hydroxymethyl compound, such known acidic hydrolysing agents as sulphuric acid, phosphoric acid, hydrohalic acids and organic acids can be used. Although basic hydrolysing agents such as caustic soda and sodium carbonate are also effective, they do not result in such good yields. The hydrolysis can be performed in an inert solvent such as an alcohol or dioxane, and can be accelerated by heating.

The pyridine compounds of formula (1) in which X is N can be oxidized to the corresponding N-oxide compounds by means known *per se*, for example by oxidizing the pyridine compound at room temperature or at an elevated temperature with an oxidizing agent such as hydrogen peroxide or an organic peroxide. While such oxidation may be performed in an inert solvent such as water or an alcohol, it is preferred to perform the oxidation in glacial acetic acid with hydrogen peroxide.

The invention is illustrated by the following Examples.

EXAMPLE 1

A mixture of 1.4 g. of 5-nitrofurfural, 1.7 g. of 2-methyl-5-acetoxymethylpyridine and 3.1 g. of acetic anhydride was heated to $120-130^\circ C$. for 4.5 hours on an oil bath. Acetic anhydride was then distilled off under reduced pressure, and an aqueous solution of sodium bicarbonate was added to the residue. Crystals precipitated, which were then separated by filtration, washed with water, and recrystallized from ethanol. 1.2 g. of 2-[2-(5-nitro-2-furyl)vinyl]-5-acetoxymethylpyridine (Compound No. 1) having a melting point of $127-128^\circ C$. were obtained.

EXAMPLE 2

Example 1 was repeated except that the 2-methyl-5-acetoxymethylpyridine was replaced by the same quantity of 2-methyl-6-acetoxymethylpyridine, and that the product was recrystallized from acetone. 1 g. of 2-[2-(5-nitro-2-furyl)vinyl]-6-acetoxymethylpyridine (Compound No. 2) having a melting point of $120-121^\circ C$. was obtained.

EXAMPLE 3

100 mg. of 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine N-oxide and 5 ml. of acetic anhydride were reacted at $100-110^\circ C$. for an hour under anhydrous conditions. The acetic anhydride was then distilled off under reduced pressure, water was added to the residue, and the mixture was then ice-cooled. The crystals which precipitated

were recrystallized from ethanol to yield 70 mg. of 2-[2-(5-nitro-2-furyl)vinyl]-6-acetoxymethylpyridine (m.p. 120—121°C.).

EXAMPLE 4

A mixture of 2.8 g. of 5-nitrofurfural, 2.5 g. of 2,6-dimethylpyridine N-oxide and 7.8 g. of propionic anhydride was heated for 4 hours to 70°C. The reaction mixture was then further heated to 110—120°C. for an additional 2 hours, the 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine N-oxide formed remaining in it. Residual propionic anhydride was distilled off under reduced pressure, and the residue was hot-extracted with 20 ml. of methanol. After treating the extract with decolorizing carbon and then cooling it, crystals precipitated, which were recrystallized from methanol. 1.5 g. of 2-[2-(5-nitro-2-furyl)vinyl]-6-propionyloxypyridine (Compound No. 3) having a melting point of 107—108°C. were obtained.

EXAMPLE 5

0.5 g. of 2 - [2 - (5 - nitro - 2 - furyl)vinyl] - 5 - acetoxymethylpyridine and 10 ml. of 15% sulphuric acid were heated together for 4 hours at 140°C. Then the reaction mixture was made alkaline with an aqueous solution of sodium bicarbonate, and the resulting crystalline precipitate was separated by filtration, washed with water and recrystallized from methanol. 0.4 g. of 2 - [2 - (5 - nitro - 2 - furyl)vinyl] - 5 - hydroxymethylpyridine (Compound No. 4) having a melting point of 150—151°C. was obtained.

EXAMPLE 6

0.5 g. of 2 - [2 - (5 - nitro - 2 - furyl)vinyl] - 6 - acetoxymethylpyridine and 10 ml. of 15% sulphuric acid were heated together for 6 hours at 140°C. The subsequent procedure of Example 5 was followed, except that the recrystallization was performed from acetone, and 0.3 g. of 2 - [2 - (5 - nitro - 2 - furyl)vinyl] - 6 - hydroxymethylpyridine (Compound No. 5) having a melting point of 170—171°C. was obtained.

EXAMPLE 7

2 g. of 2 - [2 - (5 - nitro - 2 - furyl)vinyl] - 6 - methylpyridine N-oxide were heated with 2.5 ml. of acetic anhydride for an hour at 120°C. Thereafter the acetic anhydride was distilled off under reduced pressure, and the residue was hot-extracted with 10 ml. of 10% hydrochloric acid. The extract was made alkaline with aqueous sodium bicarbonate, and the resulting crystalline precipitate was filtered off and recrystallized from acetone. 1.1 g. of 2-[2-(5-nitro-2-furyl)vinyl]-6-hydroxymethylpyridine (m.p. 170—171°C.) were obtained.

EXAMPLE 8

A mixture consisting of 5 g. of 2-[2-(5-nitro-2-furyl)vinyl]-5-acetoxymethylpyridine, 60 ml. of acetic acid, and 6 ml. of 30% aqueous hydrogen peroxide was heated for 6 hours on a water bath at 70°C. Then the acetic acid was distilled off under reduced pressure, and water was added to the residue, which was then neutralised with sodium bicarbonate. The precipitated crystals were filtered off, washed with water, dried and recrystallized from ethanol. 2 g. of yellow needles of 2-[2-(5-nitro-2-furyl)vinyl]-5-acetoxymethylpyridine N-oxide (Compound No. 6) having a melting point of 178—179°C. were obtained.

EXAMPLE 9

A mixture consisting of 1.4 g. of 5-nitrofurfural, 1.8 g. of 2-methyl-5-acetoxymethylpyridine N-oxide and 3.1 g. of acetic anhydride was heated for 15 hours on a water bath at 70°C. Then the acetic anhydride was distilled off under reduced pressure, and the residue was ice-cooled. The crystals which precipitated were recrystallized from ethanol to yield 0.65 g. of 2-[2-(5-nitro-2-furyl)vinyl]-5-acetoxymethylpyridine N-oxide having a melting point of 178—179°C.

EXAMPLE 10

A mixture of 9 g. of 2-[2-(5-nitro-2-furyl)vinyl]-6-acetoxymethylpyridine, 110 ml. of acetic acid and 12 ml. of 30% aqueous hydrogen peroxide was heated for 20 hours on a water bath at 60°C. The subsequent procedure of Example 8 was followed, except that the crystals obtained were recrystallized from acetone, and 4.5 g. of yellow needles of 2-[2-(5-nitro-2-furyl)vinyl]-6-acetoxymethylpyridine N-oxide (Compound No. 7) having a melting point of 195—197°C. were obtained.

EXAMPLE 11

A mixture of 1.4 g. of 5-nitrofurfural, 1.4 g. of 2-methyl-6-hydroxymethylpyridine N-oxide and 3.1 g. of acetic anhydride was heated for 17.5 hours on a water bath at

70°C. Then the acetic anhydride was distilled off under reduced pressure, and the residue was ice-cooled. The precipitated crystals were washed with 5 ml. ether, and were recrystallized from acetone to yield 0.6 g. of 2-[2-(5-nitro-2-furyl)vinyl]-6-acetoxymethylpyridine N-oxide having a melting point of 195—197°C.

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EXAMPLE 12

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A mixture consisting of 0.1 g. of 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxymethylpyridine, 5 ml. of acetic acid and 0.2 ml. of 30% aqueous hydrogen peroxide was heated for 5.5 hours on a water bath at 70°C. Then the acetic acid was distilled off under reduced pressure. Water was added to the residue, the solution obtained was neutralized with sodium bicarbonate, and the resulting crystals were filtered off, washed with water, dried and recrystallized from acetone. 0.065 g. of orange needles of 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxymethylpyridine N-oxide (Compound No. 8) having a melting point of 210—211°C. (decomposed) were obtained.

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EXAMPLE 13

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0.3 g. of 2-[2-(5-nitro-2-furyl)vinyl]-5-acetoxymethylpyridine N-oxide and 15 ml. of 10% hydrochloric acid were heated together for an hour on a steam bath. After being cooled, the reaction mixture was brought to a pH of 8 with sodium bicarbonate, and the crystals thereby precipitated were filtered off, washed with water and recrystallized from acetone, to yield 0.2 g. of orange needles of 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxymethylpyridine N-oxide having a melting point of 210—211°C. (decomposed).

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EXAMPLE 14

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A mixture of 2.4 g. of 2-[2-(5-nitro-2-furyl)vinyl]-6-hydroxymethylpyridine, 5 ml. of acetic acid and 5 ml. of 30% aqueous hydrogen peroxide was heated for 7 hours on a water bath at 70°C. The subsequent procedure of Example 12 was followed and 1.6 g. of yellow needles of 2-[2-(5-nitro-2-furyl)vinyl]-6-hydroxymethylpyridine N-oxide (Compound No. 9) having a melting point of 210—211°C. (decomposed) were obtained.

EXAMPLE 15

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20 mg. of 2-[2-(5-nitro-2-furyl)vinyl]-6-acetoxymethylpyridine N-oxide and 2 ml. of 10% hydrochloric acid were heated together for 0.5 hour on a steam bath at 100°C. After cooling, the pH of the reaction mixture was adjusted to 8 with an aqueous sodium bicarbonate solution, and the crystals thereby precipitated were filtered off, washed with water and recrystallized from acetone, to yield 10 mg. of 2-[2-(5-nitro-2-furyl)vinyl]-6-hydroxymethylpyridine N-oxide having a melting point of 210°—211°C. (decomposed).

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The new compounds have high *in vitro* activities against Gram positive bacteria such as *Staphylococcus aureus*, *Staphylococcus albus* and *Streptococcus haemolyticus*; Gram negative bacteria such as *Escherichia coli*, *Salmonella enteritidis* and *Shigella flexneri*; *Mycobacterium tuberculosis*; fungi such as *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton asteroides* and *Microsporum gypseum*; and protozoa such as *Trichomonas vaginalis*.

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The *in vivo* activities of the compounds against *Salmonella typhimurium* are shown in Table 1. (In all the following Tables, Compounds Nos. 1 to 9 are those so identified in the Examples, and Compounds Nos. 10 to 12 are controls as follows:

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Compound No. 10 2-[2-(5-nitro-2-furyl)vinyl]pyridine
Compound No. 11 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine
Compound No. 12 2-[2-(5-nitro-2-furyl)vinyl]pyridine N-oxide.

TABLE I
Therapeutic Effect in Male Mice
Infection : ip
(survived/tested)

a) Per Os treatment		No. 1	No. 2	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11
compound	dose*										
100 mg/kg		10/10	6/10	10/10	7/10	—	—	—	—	1/10	—
50		7/10	3/10	9/10	2/10	10/10	10/10	—	10/10	0/10	3/10
25		5/10	1/10	5/10	0/10	4/10	6/10	—	10/10	—	—
12.5		3/10	0/10	1/10	—	2/10	3/10	—	8/10	—	—
6.3		1/10	—	0/10	—	0/10	0/10	5/10	2/10	—	—
3.1		0/10	—	—	—	—	—	—	0/10	—	—
non-treated control		(0/10)									
ED ₅₀		23.3	±70.7	25.0	±75.8	23.3	18.9	—	8.8	>100	—

* 2 times per day for 4 days

b) Intraperitoneal treatment		(survived/tested)								
compound	dose*	No. 1	No. 2	No. 4	No. 5	No. 6	No. 7	No. 9	No. 10	No. 11
	100 mg/kg	—	—	—	—	—	—	—	6/10**	—
	50	—	10/10	—	—	—	—	—	9/10	10/10
	25	10/10	10/10	10/10	10/10	—	—	—	7/10	—
	12.5	9/10	8/10	8/10	7/10	10/10	10/10	—	6/10	—
	6.3	8/10	2/10	5/10	5/10	9/10	9/10	10/10	1/10	—
	3.1	2/10	1/10	3/10	2/10	8/10	5/10	10/10	0/10	—
	1.6	0/10	0/10	1/10	1/10	5/10	3/10	5/10	—	—
	0.8	—	—	0/10	0/10	2/10	1/10	0/10	—	—
	0.4	—	—	—	—	0/10	0/10	0/10	—	—
non-treated control		(0/10)								
ED ₅₀		4.7	8.3	5.4	6.3	1.7	2.5	1.6	>12.5	—

*2 times per day for 4 days. **death by toxicity

5 Plasma levels of some active compounds were measured by a microbioassay, cup-plate method using *Bacillus subtilis*. In the tests, 100 mg/kg of each of the active compounds was administered to male rats weighing 300—400 g. The plasma levels of the compounds in the rats were measured one, two, three, six and twenty four hours after oral administration. The average plasma levels (mcg/ml) in six rats are given in Table II. 5

TABLE II
PLASMA LEVEL

Compound	Time after administration				
	1 hr.	2 hrs.	3 hrs.	6 hrs.	24 hrs.
No. 7	1.1	0.8	0.8	0.3	<0.3
No. 9	4.0	2.5	1.1	0.2	<0.2
No. 12	<0.3	<0.3	<0.3	<0.3	<0.3

10 No nitrofurantoin derivatives have been known hitherto to exert active plasma level. As is clear from Table II, the preferred compounds of this invention show considerable plasma level in their active form. 10

Acute toxicity in mice of some of the compounds of this invention and that of the control compounds are shown in Table III.

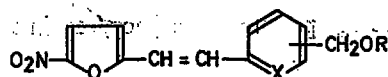
TABLE III
Acute Toxicity in Mice

(LD₅₀ : mg/kg)

Compound	ip	po
No. 1	707	933
No. 2	>2000	>2000
No. 5	>2000	>2000
No. 6	1150	1620
No. 7	1410	2000
No. 9	707	1310
No. 10	1275	>2000
No. 11	>1000	>1000
No. 12	900	900

WHAT WE CLAIM IS:—

1. Compounds of the formula



wherein X is N or N → O, the radical —CH₂OR is at the 5 or 6-position of the pyridine ring, and R is hydrogen or lower alkanoyl (as hereinbefore defined).

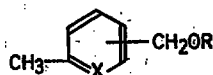
2. 2-[2-(5-Nitro-2-furyl)vinyl]-6-hydroxymethylpyridine N-oxide.

3. 2-[2-(5-Nitro-2-furyl)vinyl]-6-acetoxymethylpyridine N-oxide.

4. 2-[2-(5-Nitro-2-furyl)vinyl]-6-hydroxymethylpyridine.

5. Compounds according to claim 1 substantially as hereinbefore described.

6. A process for the preparation of the compounds claimed in any one of the preceding claims, which comprises either condensing 5-nitrofurfural with a compound of formula



in which X and R have the meanings given in Claim 1, or reacting 2-[2-(5-nitro-2-furyl)vinyl]-6-methylpyridine N-oxide with a lower fatty acid anhydride as hereinbefore defined), and, if required, hydrolysing and/or oxidizing the product.

7. A process according to claim 6 substantially as hereinbefore described.

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