1,014,050

PATENT SPECIFICATION

NO DRAWINGS

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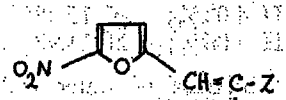
COMPLETE SPECIFICATION

New Nitrofuryl Derivatives

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., a body corporate organised under the laws of Germany, of Mannheim-Waldhof, Germany, 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 present invention is concerned with new nitrofuryl derivatives and with the preparation thereof.

In our Specification No. 11674/64 (Serial 1,010,582), there are described and claimed new nitrofuryl derivatives of the general formula:—



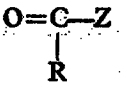
(I)

wherein R signifies a hydrogen atom or an alkyl radical and Z signifies a pyridyl radical linked with the vinyl group in the α- or γ-position, which carries one or more polar or hydrophilic substituents in the pyridyl nucleus; and their quaternary ammonium salts.

The compounds according to the said Specification show a marked action against pathogenic and non-pathogenic micro-organisms (bacteria, fungi, protozoa), the type and the position of the substituents in the pyridyl nucleus exercising a decisive influence on the spectrum of activity which can be made responsible for the formation of special ranges of indication.

As polar or hydrophilic substituents, there may be considered, for example, halogen atoms, nitro groups, alkoxy, alkylmercapto, alkyl - sulphonyl and polyhydroxy - alkoxy radicals, carboxylic acid groups, which may be esterified (especially polyhydroxy esters), carboxamido and carboxy-hydrazido radicals, which may be acylated or hydroxy-alkylated on the nitrogen atom as well as amino groups, which may be acylated, alkylated or hydroxy-alkylated.

The production of the new compounds takes place according to methods known *per se*. A preferred process is the condensation of 5-nitrofurfural or its diacetate with compounds of the general formula $R—CH_2—Z$, wherein R and Z have the meanings given above. However, in reversal of this reaction, 5-nitro-2-methyl-furan can be condensed with compounds of the general formula:—



wherein R and Z have the meanings given above.

Furthermore, for example, 5-nitrofurfural can be reacted with appropriate heterocyclic-substituted alkyl magnesium halides or, inversely, substituted heterocyclic aldehydes or ketones can be reacted with the Grignard compounds of 5 - nitro - 2 - halomethyl-furans, followed by dehydration, to produce the olefine.

Finally, it is possible to use, in the mentioned processes, the corresponding 5-unsubstituted furan derivatives as reaction components, and, after condensation has taken place, to carry out careful nitration in the 5-position of the furan nucleus.

In addition, for some of the above-mentioned substituents of the pyridine ring, it is expedient to introduce or to liberate these or to bring them into the final form by appropriate reactions only after condensation has taken place; thus, for example, amino-substituted compounds are advantageously produced by saponification of the corresponding acylamino compounds.

[*Price 4s. 6d.*]

The compounds can be converted in known manner into the quaternary ammonium salts.

We have now prepared a number of additional compounds coming within the scope of general formula (I) of the compounds accotding to the aforementioned Specification. These new compounds can be prepared in the manner described in the said Specification.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1.

1 - (5 - nitro - 2 - furyl) - 2 - (6 - carboxamido - 2 - pyridyl) - ethylene.

0.7 g. 2 - [2 - (5 - nitro - 2 - furyl)-vinyl] - pyridine - 6 - carboxylic acid chloride (prepared as in Example 7 of Specification No. 11674/64) (Serial 1,010,582) are dissolved in 10 ml. warm dioxan and, after cooling to room temperature, the solution is slowly added to a solution of 1 ml. concentrated aqueous ammonium solution and 1 drop triethylamine in 10 ml. dioxan, yellow crystals thereby precipitating out. After filtering off with suction and washing with dioxan, there are obtained 0.7 g. of product which are dissolved in 7 ml. hot formic acid, then mixed with 35 ml. water and the separated crystals, after standing in an ice bath, filtered off with suction. After recrystallisation from glacial acetic acid of the 0.6 g. of product so obtained, it decomposes, with foaming, on an aluminium block between 272 and 275°C.

$C_{12}H_9N_3O_4$ (M.W. 259) Calc.: C 55.6%; H 3.48%; N 16.22%
Found: C 55.46%; H 3.48%; N 15.76%

EXAMPLE 2.

1 - (5 - nitro - 2 - furyl) - 2 - (4 - acetamido-2 - pyridyl) - ethylene.

3.4 g. 4 - amino - 2 - methyl - pyridine are heated under reflux for 30 minutes with 31.4 ml. acetic anhydride, 4.5 g. 5-nitrofurfural then added and the reaction mixture refluxed for a further 3 hours at a bath temperature of 160°C. A further 1.5 g. 5-nitrofurfural are added, the reaction mixture maintained at a bath temperature of 160°C. for another 3 hours, finally another 1.5 g. 5-nitrofurfural added and heating continued for yet another 2 hours at the same bath temperature. After standing overnight at room temperature, the separated material is filtered off with suction, washed with a little glacial acetic acid, dried to give 4.5 g. of material which is boiled out three times with 50 ml. amounts of a mixture of dioxan and toluene (1:2) and the combined clear extract solutions evaporated in a vacuum. The evaporation residue is triturated with 80% aqueous ethanol to 0.2 g. of material which is then recrystallised from isopropanol. Yellow crystals are obtained which melt at 223—225°C. (decomp.).

$C_{13}H_{11}N_3O_4$ (M.W. 273) Calc.: C 57.1%; H 4.03%; N 15.38%
Found: C 57.62%; H 4.06%; N 14.92%.

EXAMPLE 3.

1 - (5 - nitro - 2 - furyl) - 2 - (4 - amino-2 - pyridyl) - ethylene.

0.25 g. of the compound prepared in Example 2 are dissolved in a mixture of 1.3 ml. 5N hydrochloric acid and 1.3 ml. dioxan and heated for 30 minutes at a bath temperature of 100°C. After evaporation in a vacuum, the residue obtained is dissolved with a small amount of a mixture of water and dioxan (1:1) and one drop of 2N hydrochloric acid, undissolved material filtered off and the clear filtrate mixed with a concentrated solution of ammonia until a basic reaction is obtained. The 0.12 g. of product which thereby separate out are washed with water and dried. Above 190°C. the compound shows a coloration and decomposes at about 203°C.

$C_{11}H_9N_3O_3$ (M.W. 231) Calc.: C 57.1%; H 3.9%; N 18.18%
found: C 56.74%; H 4.18%; N 18.02%

EXAMPLE 4.

1 - (5 - nitro - 2 - furyl) - 2 - (4 - carboxy-2 - pyridyl) - ethylene.

4 g. 2 - methyl - pyridine - 4 - carboxylic acid methyl ester are heated with 4.11 g. 5-nitrofurfural in a mixture of 4 g. acetic anhydride and 0.8 g. glacial acetic acid for 3 hours under reflux at a bath temperature of 160°C. After cooling, the reaction mixture is triturated with isopropyl ether and filtered with suction to give 6 g. of a solid crude product which is exhaustively boiled out with dioxan. Upon cooling the combined hot filtrates, there are obtained 3.9 g. of crystals and a further 0.45 g. of crystals are obtained from the mother liquor. After recrystallisation from 100 ml. dioxan, with the use of activated charcoal, there are obtained 3.8 g. of a yellow compound with a melting point of 225—226°C.

$C_{13}H_{10}N_2O_5$ (M.W. 274) Calc.: C 56.92%; H 3.65%; N 10.22%
found: C 56.85%; H 4.04%; N 10.25%

2.5 g. of the methyl ester so obtained are dissolved in 182 ml. of a mixture of dimethyl formamide and dioxan (2:1) and 11 ml. 1N sodium hydroxide solution added thereto at 30°C. After standing for 10 minutes at room temperature, a further 2 ml. 1N sodium

hydroxide solution are added and the reaction mixture left to stand for a further 10 minutes at room temperature, then acidified with 2N hydrochloric acid, mixed with three times its volume of water and, after standing for 1 hour, the yellow crystals formed are filtered off with suction and washed with water. There are obtained 2.3 g. 1 - (5 - nitro - 2-furyl) - 2 - (4 - carboxy - 2 - pyridyl) - ethylene which, after recrystallisation from dimethyl formamide, decomposes between 280 and 290°C.

$C_{12}H_8N_2O_5$ (M.W. 260) Calc.: C 55.4%; H 3.08%; N 10.78%
found: C 55.08%; H 3.44%; N 10.74%

EXAMPLE 5.

1 - (5 - nitro - 2 - furyl) - 2 - (2 - carboxy-4 - pyridyl) - ethylene.

4.6 g. 4 - methyl - pyridine - 2 - carboxylic acid methyl ester are heated for 3 hours under reflux at a bath temperature of 160°C. with 4.73 g. 5-nitrofurfural in a mixture of 4.6 g. acetic anhydride and 0.9 glacial acetic acid. After cooling, the reaction mixture is triturated with diisopropyl ether and filtered with suction. There are obtained 7.9 g. of filter residue which, after drying, is exhaustively boiled out with dioxan. The combined extracts are evaporated in a vacuum to give 4.7 g. of residue which, after recrystallisation from 120 ml. 60% aqueous dioxan, with the use of activated charcoal, gives 2.3 g. of crystals melting at 204—205°C.

1.5 g. of the 1 - (5 - nitro - 2 - furyl) - 2-(2 - carbomethoxy - 4 - pyridyl) - ethylene so obtained are dissolved in a mixture of dimethyl formamide and dioxan (2:1), 6.6 ml. 1N sodium hydroxide solution added thereto, the reaction mixture allowed to stand for 10 minutes at room temperature, a further 1.1 ml. 1N sodium hydroxide solution then added to the resultant suspension and, after again standing for 10 minutes at room temperature, filtered with suction and washed with the above-mentioned solvent mixture. The filter residue is well triturated with 150 ml. water containing 5.5 ml. 2N hydrochloric acid, filtered with suction and washed with water to give 1 g of material. After recrystallisation from a mixture of dimethyl formamide and dioxan (1:1), using activated charcoal, there are obtained 0.6 g. of yellow crystals which decompose between 242 and 244°C.

$C_{11}H_8N_2O_4$ (M.W. 232) Calc.: C 56.9%; H 3.45%; N 12.07%
Found: C 56.36%; H 3.8%; N 12.04%.

The compound dissolves with a deep orange-red colour in excess dilute sodium hydroxide solution and precipitates out upon acidification of this solution with dilute hydrochloric acid.

$C_{12}H_8N_2O_5$ (M.W. 260) Calc.: N 10.78%
found: N 10.65%

By titration with 0.1 N sodium hydroxide solution in aqueous dioxan, the equivalent weight is found to be 264±1%.

EXAMPLE 6.

1 - (5 - nitro - 2 - furyl) - 2 - (6 - hydroxy-2 - pyridyl) - ethylene.

0.92 g. 1 - (5 - nitro - 2 - furyl) - 2 - (6-amino - 2 - pyridyl) - ethylene (produced as in Example 11 of Specification No. 11674/64) (Serial 1,010,582) are dissolved in 36 ml. of a warm mixture of 20 ml. water, 8 ml. concentrated sulphuric acid and 28 ml. dioxan. A solution of 1 g. sodium nitrite in 5 ml. water is added thereto, with stirring, at room temperature, the reaction mixture left to stand for 15 to 30 minutes at room temperature and then slowly heated to about 100°C. The reaction mixture is then concentrated *in vacuo*, diluted with water, adjusted to a pH of 3 with a concentrated aqueous solution of ammonia, the orange-yellow crystals obtained filtered off with suction, washed with water and dried *in vacuo*. There is obtained about 1 g. of crystals. After recrystallisation from a mixture of dioxan and dimethyl formamide (3:1), the compound melts, with decomposition, at 279°C.

WHAT WE CLAIM IS:—

1. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - carboxamido - 2 - pyridyl) - ethylene.
2. 1 - (5 - nitro - 2 - furyl) - 2 - (4 - acetamido - 2 - pyridyl) - ethylene.
3. 1 - (5 - nitro - 2 - furyl) - 2 - (4-amino - 2 - pyridyl) - ethylene.
4. 1 - (5 - nitro - 2 - furyl) - 2 - (4-carboxy - 2 - pyridyl) - ethylene.
5. 1 - (5 - nitro - 2 - furyl) - 2 - (2 - carboxy - 4 - pyridyl) - ethylene.
6. 1 - (5 - nitro - 2 - furyl) - 2 - (6-hydroxy - 2 - pyridyl) - ethylene.
7. Process for the preparation of compounds according to any of claims 1 to 6, substantially as hereinbefore described and exemplified.
8. Compounds according to any of claims 1 to 6, whenever prepared by the process according to claim 7.

hydroxide solution are added and the reaction mixture left to stand for a further 10 minutes at room temperature, then acidified with 2N hydrochloric acid, mixed with three times its volume of water and, after standing for 1 hour, the yellow crystals formed are filtered off with suction and washed with water. There are obtained 2.3 g. 1 - (5 - nitro-2-furyl) - 2 - (4 - carboxy - 2 - pyridyl)-ethylene which, after recrystallisation from dimethyl formamide, decomposes between 280 and 290°C.

$C_{12}H_8N_2O_5$ (M.W. 260) Calc.: C 55.4%; H 3.08%; N 10.78%
found: C 55.08%; H 3.44%; N 10.74%

EXAMPLE 5.

1 - (5 - nitro - 2 - furyl) - 2 - (2 - carboxy-4 - pyridyl) - ethylene.

4.6 g. 4 - methyl - pyridine - 2 - carboxylic acid methyl ester are heated for 3 hours under reflux at a bath temperature of 160°C. with 4.73 g. 5-nitrofurfural in a mixture of 4.6 g. acetic anhydride and 0.9 glacial acetic acid. After cooling, the reaction mixture is triturated with diisopropyl ether and filtered with suction. There are obtained 7.9 g. of filter residue which, after drying, is exhaustively boiled out with dioxan. The combined extracts are evaporated in a vacuum to give 4.7 g. of residue which, after recrystallisation from 120 ml. 60% aqueous dioxan, with the use of activated charcoal, gives 2.3 g. of crystals melting at 204—205°C.

1.5 g. of the 1 - (5 - nitro - 2 - furyl) - 2-(2 - carbomethoxy - 4 - pyridyl) - ethylene so obtained are dissolved in a mixture of dimethyl formamide and dioxan (2:1), 6.6 ml. 1N sodium hydroxide solution added thereto, the reaction mixture allowed to stand for 10 minutes at room temperature, a further 1.1 ml. 1N sodium hydroxide solution then added to the resultant suspension and, after again standing for 10 minutes at room temperature, filtered with suction and washed with the above-mentioned solvent mixture. The filter residue is well triturated with 150 ml. water containing 5.5 ml. 2N hydrochloric acid, filtered with suction and washed with water to give 1 g of material. After recrystallisation from a mixture of dimethyl formamide and dioxan (1:1), using activated charcoal, there are obtained 0.6 g. of yellow crystals which decompose between 242 and 244°C.

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$C_{12}H_8N_2O_5$ (M.W. 260) Calc.: N 10.78%
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By titration with 0.1 N sodium hydroxide solution in aqueous dioxan, the equivalent weight is found to be 264±1%.

EXAMPLE 6.

1 - (5 - nitro - 2 - furyl) - 2 - (6 - hydroxy-2 - pyridyl) - ethylene.

0.92 g. 1 - (5 - nitro - 2 - furyl) - 2 - (6-amino - 2 - pyridyl) - ethylene (produced as in Example 11 of Specification No. 11674/64) (Serial 1,010,582) are dissolved in 36 ml. of a warm mixture of 20 ml. water, 8 ml. concentrated sulphuric acid and 28 ml. dioxan. A solution of 1 g. sodium nitrite in 5 ml. water is added thereto, with stirring, at room temperature, the reaction mixture left to stand for 15 to 30 minutes at room temperature and then slowly heated to about 100°C. The reaction mixture is then concentrated *in vacuo*, diluted with water, adjusted to a pH of 3 with a concentrated aqueous solution of ammonia, the orange-yellow crystals obtained filtered off with suction, washed with water and dried *in vacuo*. There is obtained about 1 g. of crystals. After recrystallisation from a mixture of dioxan and dimethyl formamide (3:1), the compound melts, with decomposition, at 279°C.

WHAT WE CLAIM IS:—

1. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - carboxamido - 2 - pyridyl) - ethylene.
2. 1 - (5 - nitro - 2 - furyl) - 2 - (4 - acetamido - 2 - pyridyl) - ethylene.
3. 1 - (5 - nitro - 2 - furyl) - 2 - (4-amino - 2 - pyridyl) - ethylene.
4. 1 - (5 - nitro - 2 - furyl) - 2 - (4-carboxy - 2 - pyridyl) - ethylene.
5. 1 - (5 - nitro - 2 - furyl) - 2 - (2 - carboxy - 4 - pyridyl) - ethylene.
6. 1 - (5 - nitro - 2 - furyl) - 2 - (6-hydroxy - 2 - pyridyl) - ethylene.
7. Process for the preparation of compounds according to any of claims 1 to 6, substantially as hereinbefore described and exemplified.
8. Compounds according to any of claims 1 to 6, whenever prepared by the process according to claim 7.



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