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PATENT SPECIFICATION

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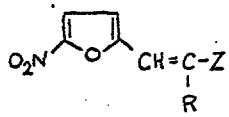
COMPLETE SPECIFICATION

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.

The new nitrofuryl derivatives according to the present invention are compounds of the general formula:—



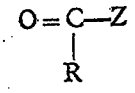
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wherein R signifies a hydrogen atom or an alkyl radical and Z signifies a pyridyl radical linked with the vinyl group in the α or γ-position, which carries one or more polar or hydrophilic substituents in the pyridyl nucleus; and their quaternary ammonium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

We have found that these compounds 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.

The new compounds can be converted in known manner into the quaternary ammonium salts and acid-addition salts.

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

[Price 4s. 6d.]

EXAMPLE 1.

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

26. g. 2 - methyl - pyridine - 6 - carboxylic acid methyl ester are heated under reflux at 160°C. (bath temperature) for 3 hours with 24.45 g. crude 5 - nitrofurfural in 172 ml. acetic anhydride. The reaction mixture is subsequently evaporated to dryness in a vacuum, the residue taken up in 160 ml. dioxan, water is added until cloudiness sets in and the mixture is then treated with active carbon at an elevated temperature. The reaction mixture is then filtered with suction, while hot, and the hot clear filtrate mixed with water until cloudiness sets in. The substance which crystallises out upon cooling is separated; yield: 9.3 g. of crystals of the above compound (m.p. 151—153°C.)

After recrystallisation of a sample from trichloroethylene in the presence of active carbon, the yellow crystals melt at 154—155°C.

$C_{13}H_{10}N_2O_5$ (M.W. 274) calc. C 56.90%; H 3.65%; N 10.22%
found C 56.52%; H 3.66%; N 9.82%

EXAMPLE 2.

2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid.

2.74 g. of the carboxylic acid methyl ester obtained according to Example 1 are dissolved in 50 ml. warm dioxan, 11 ml. 1N sodium hydroxide solution are added at room temperature and, after standing for 1 hour at room temperature, the crystals which have, in the meantime, separated out, are filtered off with suction and then washed with 80% aqueous dioxan. The sodium salt of the carboxylic acid obtained in this way by alkaline saponification of the methyl ester is dissolved in about 120 ml. warm water and mixed with 10 ml. 2N hydrochloric acid. The separated carboxylic acid is filtered off with suction, washed with water and recrystallised from 80 ml. dioxan in the presence of active carbon. There are obtained 1.55 g. of crystals of the above compound (m.p. 245—246°C.); a further 0.35 g. of the acid can be isolated from the mother liquor after considerable evaporation in a vacuum.

$C_{12}H_8N_2O_5$ (M.W. 260) calc. C 55.40%; H 3.08%; N 10.77%
found C 55.70%; H 3.55%; N 10.80%

EXAMPLE 3.

2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid β - hydroxyethylamide.

2.74 g. of the methyl ester produced according to Example 1 are dissolved in 30 ml. warm dioxan, 3.05 g. monoethanolamine are added thereto and the mixture is heated for 3 hours at 80°C. The dioxan solution is then separated from the oil which has, in the meantime, separated out, mixed with about 5 times its volume of water and the separated crystals are filtered off with suction; yield of the above compound: 1.15 g. (m.p. 136—138°C.). After recrystallisation from 30 ml. isopropanol, the yellow crystals melt at 146—148°C.

$C_{14}H_{13}N_3O_5$ (M.W. 303) calc. C 55.40%; H 4.29%; N 13.86%
found C 55.35%; H 4.39%; N 13.68%

EXAMPLE 4.

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

17.28 g. 2 - amino - 4 - methyl - pyridine are heated for 15 minutes under reflux (160°C. bath temperature) in 160 ml. acetic anhydride, 22.4 g. crude 5-nitrofurfural are then added thereto and the mixture is kept for a further 8 hours under reflux at a bath temperature of 160°C. After cooling, the separated material is filtered off with suction and the filtrate washed with glacial acetic acid and evaporated in a vacuum. The evaporation residue is boiled out twice with 100 ml. benzene and the combined clear benzene extracts are shaken with a solution of 10 g. sodium bisulphite in 100 ml. water in order to remove unreacted 5-nitrofurfural. After subsequent washing of the benzene solution with water and drying, it is evaporated in a vacuum, the residue taken up with about 100 ml. carbon tetrachloride, the undissolved material separated off and the clear organic solution evaporated. As residue, there remain behind 26.35 g. of an oil which contains 1 - (5 - nitro - 2 - furyl) - 2 - (2 - acetamido - 4 - pyridyl) - ethylene. (A sample of 6 g. of this oil yields 0.92 g. of crystals after trituration with 9 ml. 90% aqueous methanol; the pure acetamido compound of m.p. 188—189°C. is obtained therefrom by recrystallisation from a mixture of 6 ml. methanol + 2 ml. dioxan.).

26.35 g. of the oily crude product are now subjected to acidic hydrolysis by heating for 1

hour at 100°C. with a mixture of 70 ml. glacial acetic acid and 70 ml. 5N hydrochloric acid. The reaction mixture is then evaporated to dryness in a vacuum and the residue triturated with a little methanol. 3.3 g. of the crystals obtained in this way, after recrystallisation from 65 ml. 75% aqueous dioxan which contains 1.65 ml. concentrated hydrochloric acid, yield 2.3 g. of the practically pure hydrochloride of 1 - (5 - nitro - 2 - furyl) - 2 - (2 - amino - 4 - pyridyl) - ethylene.

7.5 g. of this hydrochloride are dissolved hot in a mixture of 120 ml. water and 30 ml. ethanol and rapidly mixed, with good stirring, with so much concentrated ammonia that the pH value is about 9—10, then rapidly cooled and left to stand for about 1 hour at room temperature. The resulting crystallisate is then filtered off with suction, washed neutral with water and dried; in this way, there are obtained 6.2 g. 1 - (5 - nitro - 2 - furyl) - 2 - (2 - amino - 4 - pyridyl) - ethylene of m.p. 181—183°C.

$C_{11}N_3N_3O_3$ (M.W. 231) calc. C 57.10%; H 3.90%; N 18.18%
found C 57.05%; H 4.05%; N 17.91%

EXAMPLE 5.

1 - (5 - nitro - 2 - furyl) - 2 - (6 - carbo - β,γ - dihydroxy - n - propoxy - 2 - pyridyl) - ethylene.

1.37 g. of the carboxylic acid methyl ester obtained according to Example 1 are brought into solution with 25 ml. anhydrous glycerol within about 15 minutes at 160 C. (bath temperature), then about 20 mg. *p*-toluene-sulphonic acid, dissolved in 5 ml. glycerol, are added thereto, the mixture is heated for a further 5 hours at 160°C., about 10 mg. *p*-toluene-sulphonic acid are again added thereto and the reaction is allowed to proceed for a further 2 hours at 160°C. The cooled reaction mixture is then mixed with about 7 times its volume of water, the precipitated material filtered off with suction and washed with water. There are obtained 1.45 g. of a yellow product which, after recrystallisation from 35 ml. isopropanol (and treatment of the hot solution with active carbon), melts at 172—173°C; yield: 0.9 g. of the above compound. A further 0.16 g. of crystals can be isolated from the mother liquor by concentration in a vacuum.

$C_{15}H_{14}N_2O_7$ (M.W. 334) calc. C 53.9%; H 4.19%
found C 54.11%; H 4.29%

The molecular weight was found to be 334 by potentiometric titration with perchloric acid in glacial acetic acid.

EXAMPLE 6.

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

1.13 g. 5-nitrofurfural are dissolved in a mixture of 0.8 g. acetic anhydride and 0.5 g. glacial acetic acid, 1.1 g. 2 - methyl - 5 - nitro - pyridine added thereto and the mixture is heated for 3 hours under reflux (bath temperature 160°C). The reaction mixture is then evaporated to dryness in a vacuum, the residue triturated with ether and the solid product obtained (1.9 g.) recrystallised from 20 ml. dioxan, whereby any undissolved material is separated off. In this way, there are obtained 0.85 g. of crystals of the above compound (m.p. 212—214°C.); by concentration of the mother liquor in a vacuum, a further quantity of the compound can be isolated.

$C_{11}H_7N_3O_5$ (M.W. 261) calc. C 50.6%; H 2.68%; N 16.1%
found C 50.54%; H 2.33%; N 16.0%

EXAMPLE 7.

2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid N^1 - hydroxyacetyl - hydrazide.

2.6 g. of the carboxylic acid obtained according to Example 2 are mixed with 26 ml. thionyl chloride and placed in a bath at 95°C. After about 30 minutes, a clear solution results which is boiled under reflux for a further hour and then evaporated to dryness. The residue yields, after recrystallisation from 60 ml. trichloroethylene, 2.4 g. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid chloride (m.p. 141—142°C.)

$C_{12}H_7ClN_2O_4$ (M.W. 278.5) calc. Cl 12.75%
found Cl 13.04%

2 g. of the acid chloride obtained in this way are dissolved warm in 22 ml. absolute pyridine, 1 ml. triethylamine and 0.72 g. glycollic acid hydrazide added thereto, the mixture is kept at 60°C. for 1.5 hours and then evaporated to dryness in a vacuum. The

residue is then boiled out with 120 ml. water, filtered off with suction while hot and 1.5 g. of undissolved material of melting point 190—209°C. are thus obtained; from the cooled aqueous filtrate, there can be isolated a further 0.15 g. of crystals (m.p. 203—218°C.). These two solid substances are combined and boiled out with 100 ml. dioxan. The clear, hot filtrate is concentrated to about 40 ml. and left to stand for crystallisation. Yield: 1.3 g. of the above hydrazide; m.p. 240—246°C. (decomp.). After recrystallisation from acetone, the compound melts at 253—260°C. (decomp., discoloration above 235°C.).

$C_{11}H_{12}N_4O_6$ (M.W. 332) calc. C 50.6% H 3.6% N 16.86%
found C 50.58% H 3.59% N 16.35%

EXAMPLE 8.

2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - diazomethyl ketone.

A solution of 7.5 g. of the carboxylic acid chloride obtained according to Example 7 (m.p. 141—142°C.) in a mixture of 80 ml. absolute dioxan and 120 ml. absolute ether is added dropwise at 0°C., with stirring within a period of 30 minutes to 85 ml. of an ethereal solution of 2.5 g. diazomethane and the resultant suspension left to stand overnight at room temperature. After filtering off with suction and washing with ether, there are obtained 6 g. of crystals of melting point 140—143°C. (decomp.); 1.3 g. thereof are recrystallised from 25 ml. nitrobenzene on a steam bath, treated with 0.1 g. active carbon and from the clear filtrate 0.6 g. of crystals of the above compound with a melting point of 141—143°C. (decomp.) are obtained. After again recrystallising from dioxan, the compound melts at 146—148°C. (decomp.).

$C_{13}H_8N_4O_4$ (M.W. 284) calc. C 54.92% H 2.82% N 19.72%
found C 54.91% H 3.34% N 19.2%

EXAMPLE 9.

Salt of 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - bromomethyl ketone with hexamethylene - tetramine.

0.2 g. of the diazo-ketone obtained according to Example 8 are dissolved in 3 ml. dimethyl formamide, the solution is diluted with 3 ml. dioxan and 2.6 ml. 48% aqueous hydrogen bromide solution are added thereto. After the nitrogen evolution has ended, the clear solution is neutralised with an aqueous sodium acetate solution and diluted with 25 ml. water. The resultant crystallisate is filtered off with suction, washed with water and 0.2 g. crude 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - bromomethyl - ketone of melting point 145—146°C. (decomp.) are thus obtained. This substance is dissolved in 5 ml. chloroform, a solution of 0.1 g. hexamethylene - tetramine in 2.5 ml. chloroform added thereto and the crystals obtained, after standing for some time, are filtered off with suction and then washed with chloroform; there are obtained 0.22 g. of the hexamethylene-tetramine salt which decomposes in the temperature range of 157 to 163°C. and is soluble in water.

EXAMPLE 10.

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

0.77 g. 2 - methyl - 5 - nitro - 6 - amino - pyridine are heated for 15 minutes at 160°C. (bath temperature) with 7.5 ml. acetic anhydride, 0.7 g. crude 5-nitrofurfural are then added thereto and the mixture is boiled for a further 6 hours under reflux (160°C. bath temperature). The reaction mixture is then evaporated in a vacuum, the residue triturated with isopropyl ether and the undissolved material boiled out several times with benzene. The benzene extracts, evaporated in a vacuum yield, 1 g. of residue which is first boiled out with 10 ml. and then with 5 ml. isopropanol. The residue hereby obtained (0.7 g.) is treated for 1 hour at 100°C. with 3 ml. glacial acetic acid and 3 ml. 5N hydrochloric acid. Upon cooling, 0.5 g. of the crude hydrochloride of 1 - (5 - nitro - 2 - furyl) - 2 - (6 - amino - 5 - nitro - 2 - pyridyl) - ethylene precipitate (m.p. 213—214°C., decomp).

The free base is obtained by dissolving this salt in dioxan and a little water at an elevated temperature, adding excess aqueous ammonia and filtering off with suction the separated yellow crystallisate; after recrystallisation from 3 ml. dioxan, the above compound is obtained which melts at 219—220°C. (decomp.).

$C_{11}H_8N_4O_5$ (M.W. 276) calc. C 47.75% H 2.9% N 20.27%
found C 47.53% H 2.93% N 19.76%

EXAMPLE 11.

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

17.28 g. 2 amino - 6 - methyl - pyridine are reacted with 5 - nitrofurfural in an analogous manner to that described for the isomeric compound in Example 4; however, the addition of the 22.4 g. 5-nitrofurfural takes place in 4 portions of 5.6 g. each (at intervals of 2 hours). After evaporation of the benzene solution, taking up the evaporation residue in 100 ml. carbon tetrachloride, separating undissolved material (0.7 g.) and evaporating the clear filtrate, there are obtained 25.5 g. of oily residue.

The 0.7 g. of undissolved material obtained [crude 1 - (5 - nitro - 2 - furyl) - 2 - (6 - acetamido - 2 - pyridyl) - ethylene] are hydrolysed with 2 ml glacial acetic acid and 2 ml. 6N hydrochloric acid for 1 hour at 100°C. and the solution then evaporated. The residue is then dissolved hot in water and a little dilute hydrochloric acid, undissolved material is separated, the filtrate treated with active carbon and, after filtration, brought to a pH of about 10 with ammonia, while still hot. The orange-coloured crystals which thereby separate out (0.25 g.) melt at 191—192°C. and are 1 - (5 - nitro - 2 - furyl) - 2 - (6 - amino - 2 - pyridyl) - ethylene.

The oily evaporation residue (25.5 g.) is also acidically saponified by heating with a mixture of 70 ml. glacial acetic acid and 70 ml. 5N hydrochloric acid for 1 hour at 100°C. and then evaporated in a vacuum. The residue is dissolved hot in 120 ml. 50% aqueous methanol and treated with active carbon. By the addition of excess ammonia, 0.6 g. of substance (m.p. 178—183°C.) can be precipitated out from the clear, still hot filtrate. This product is dissolved in hot benzene, some undissolved material separated off and the filtrate evaporated; the evaporation residue yields, after recrystallisation from 10 ml. 50% aqueous dioxan, 0.3 g. of crystals of m.p. 189—190°C. which are identical with the above product.

$C_{11}H_9N_3O_3$ (M.W. 231) calc. C 57.1% H 3.9% N 18.18%
found C 56.6% H 3.88% N 17.93%

EXAMPLE 12.

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

4 g. crude 2-methyl-5-amino-pyridine, such as is obtained after the catalytic hydrogenation of the corresponding nitro compound with a palladium catalyst are heated under reflux for 30 minutes (160°C. bath temperature) with 40 ml. acetic anhydride and mixed with 5.2 g. 5-nitrofurfural. Heating is then continued for 3 hours at 160°C. bath temperature, a further 1.75 g. 5-nitrofurfural are added and the mixture again maintained for 3 hours at 160°C. After cooling, the precipitated black material is filtered off with suction, this is boiled out 3 times with 20 ml. portions of dioxan, after washing with glacial acetic acid, the undissolved material filtered off with suction and the dioxan filtrates evaporated in a vacuum (0.7 g. residue). The acetic anhydride mother liquor is also evaporated in a vacuum and the evaporation residue boiled out with 150 ml. benzene and then twice with 60 ml. portions of dioxan. Upon cooling, the combined dioxan extracts precipitate 0.85 g. of yellow crystals of melting point 269—271°C. (decomp.) which consist of crude 1 - (5 - nitro - 2 - furyl) - 2 - (5 - acetamido - 2 - pyridyl) - ethylene. Calc. acetyl 15.75% found 15.17%.

The dioxan filtrate is evaporated and the residue so obtained (0.9 g.) combined with the 0.7 g. of dioxan evaporation residue mentioned earlier. This amorphous product is also crude 1 - (5 - nitro - 2 - furyl) - 2 - (5 - acetamido - 2 - pyridyl) - ethylene; a further 5 g. of this compound (as semicrystalline crude product) are obtained by evaporation of the previously mentioned clear benzene solution, trituration of the residue thereby obtained with 15 ml. isopropanol and filtering off with suction the undissolved material.

0.85 g. of the 1 - (5 - nitro - 2 - furyl) - 2 - (5 - acetamido - 2 - pyridyl) - ethylene obtained in this way are hydrolysed with 29 ml. 5N hydrochloric acid for 30 minutes at 100°C. After cooling, 0.7 g. crude 1 - (5 - nitro - 2 - furyl) - 2 - (5 - amino - 2 - pyridyl) - ethylene hydrochloride of melting point 260—266°C. (decomp.) can be filtered off with suction. This salt (0.5 g.) can be converted into the dark red, free amine by dissolving in 25 ml. hot acidified water, treatment of the hot solution with 0.2 g. active carbon and mixing the warm acidic filtrate with concentrated ammonia up to about pH 10. Yield, after filtering off with suction and washing with water; 0.35 g.; m.p. 255—258°C. (decomp.)

$C_{11}H_9N_3O_3$ (M.W. 231) calc. C 57.1% H 3.9% N 18.18%
found C 57.04% H 3.8% N 18.13%

Found: molecular weight 230 (with perchloric acid in glacial acetic acid, potentiometric titration).

EXAMPLE 13.

1 - (5 - nitro - 2 - furyl) - 2 - (3 - acetoxy - 2 - pyridyl) - ethylene.

1.74 g. of the hydrochloride of 3-hydroxy-2-methyl-pyridine are boiled under reflux for 1.5 hours with 4.8 ml. glacial acetic acid, 7.2 ml. acetic anhydride and 0.96 g. sodium acetate, 1.8 g. 5-nitrofurfural are then added and the mixture is maintained under reflux for a further 3 hours. After cooling, black material is filtered off with suction, the filtrate washed with glacial acetic acid and the clear solution evaporated in a vacuum. The residue is well triturated with benzene, the undissolved material filtered off and the benzene filtrate evaporated in a vacuum. The oily residue so obtained yields, after trituration with a little methanol, 0.4 g. of yellow crystals which melt at 137—140°C.

$C_{13}H_{10}N_2O_5$ (M.W. 274)	calc.	C 56.8%	H 3.65%	N 10.23%	acetyl 15.7%
	found	C 57.33%	H 4.07%	N 10.16%	acetyl 15.7%

EXAMPLE 14.

1 - (5 - nitro - 2 - furyl) - 2 - (3 - hydroxy - 2 - pyridyl) - ethylene.

2 g. of the compound produced according to Example 13 are heated with 20 ml. 2N hydrochloric acid for 1 hour at 70°C.; after cooling to room temperature, the separated hydrochloride of 1 - (5 - nitro - 2 - furyl) - 2 - (3 - hydroxy - 2 - pyridyl) - ethylene is filtered off with suction, suspended in water and neutralised with sodium bicarbonate. The solution is now filtered, the residue washed with water and the solid product (1.6 g.) so obtained recrystallised from 13 ml. of a mixture of dimethyl formamide/dioxan (2:1), 1.3 g. of red crystals being obtained which decompose in a melting point block at 238—258°C., with foaming. The substance readily dissolves in dilute aqueous sodium hydroxide solution with a dark red colour and again precipitates out as a yellow hydrochloride upon acidification with dilute hydrochloric acid; m.p. 235—245°C. (decomp.).

$C_{11}H_8N_2O_4 . HCl$ (M.W. 268.5)	calc.	C 49.15%	H 3.35%	N 10.42%	Cl 13.22%
	found	C 49.43%	H 3.38%	N 10.19%	Cl 13.28%

EXAMPLE 15.

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

3.3 g. 2 - methyl - 5 - carbethoxy - pyridine are boiled under reflux (160°C. bath temperature) for 4 hours with 2.82 g. 5-nitrofurfural and 20 ml. acetic anhydride. The reaction mixture is then evaporated in a vacuum and the crystallisate formed after cooling and standing, filtered off with suction and washed with some glacial acetic acid to give 3.7 g. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - carbethoxy - 2 - pyridyl) - ethylene (m.p. 183—187°C.).

0.77 g. of this ester are dissolved in 56 ml. tetrahydrofuran and 16 ml. ethanol, a mixture of 12 ml. methanol and 2 ml. 2N sodium hydroxide solution is then added at room temperature and the mixture left to stand for 15 minutes. 4 ml. water are subsequently added thereto, the mixture is left to stand for a further 5 minutes and a further two 4 ml. portions of water are added, with an interval of 5 minutes. The reaction mixture is then mixed with 8 ml. water, a little undissolved material filtered off with suction and the clear solution left to stand for 30 minutes at room temperature. It is now acidified with 2N hydrochloric acid, the separated yellow crystals, after standing for some time, are filtered off with suction (0.48 g.) and recrystallised from a mixture of dimethyl formamide and dioxan (1:1); there are thus obtained 0.32 g. of crystals of the above compound which decompose, with foaming, at 269°C. in an aluminium melting point block.

$C_{12}H_8N_2O_5$ (M.W. 260)	calc.	C 55.40%;	H 3.08%;	N 10.77%	
	found	C 55.05%;	H 3.10%;	N 10.38%	

The compound dissolves in dilute aqueous ammonia and again precipitates upon the addition of dilute hydrochloric acid.

EXAMPLE 16.

1 - (5 - nitro - 2 - furyl) - 2 - (3,5 - dicarboxy - 6 - methyl - 2 - pyridyl) - ethylene.

5 g. 2,6 - dimethyl - 3,5 - dicarbethoxy - pyridine are boiled under reflux for 3 hours (bath temperature 160°C.) with 2.82 g. 5-nitrofurfural and 20 ml. acetic anhydride. The reaction mixture is then concentrated in a vacuum, the yellow crystallisate which separates out after standing for some time at room temperature, is filtered off with suction and washed with some glacial acetic acid to give 5.7 g. crude 1 - (5 - nitro - 2 - furyl) - 2 - (3,5 - dicarbethoxy - 6 - methyl - 2 - pyridyl) - ethylene.

4.5 g. of this ester are dissolved in 75 ml. hot dioxan a mixture of 24 ml. methanol and 17.2 ml. 2N sodium hydroxide solution added thereto at room temperature and the solution left to stand for 3 minutes at room temperature. The reaction mixture is now mixed with 480 ml. water, left to stand for 8 minutes, a little undissolved material is rapidly filtered off with suction, the mixture is then immediately acidified with about 30 ml. 2N hydrochloric acid and the precipitated olive-yellow crystallisate filtered off with suction. After washing with water and drying in a vacuum, these crystals (3.2 g.) are dissolved in 30 ml. dioxan, 150 ml. benzene added thereto and the dark brown material which precipitates after standing for about 10 minutes is filtered off with suction. The filtrate is evaporated in a vacuum and the evaporation residue (2.8 g.) recrystallised from 60 ml. glacial acetic acid. Yield: 1.8 g. of crystals of the above compound which decompose in an aluminium block between 210 and 244°C. A sample thereof is recrystallised from dioxan and there is obtained a crystallisate which decomposes, with foaming, in an aluminium block at 250°C.

$C_{15}H_{11}N_2O_5$ (M.W. 302) Calc. : C 59.6%; H 4.63%; N 9.27%
Found : C 59.66%; H 4.61%; N 9.11%

EXAMPLE 17

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

4g. 2 - ethyl - 4 - carbethoxy - pyridine are dissolved in 7.5 ml. acetic anhydride and, after the addition of 3.2g. 5-nitrofurfural, boiled under reflux for 3 hours at a bath temperature of 160°C. After standing for a long time at room temperature, the separated material is filtered off with suction, washed with some glacial acetic acid and the 3.1g. of product obtained recrystallised from 40 ml. dioxan, with the use of activated charcoal. There are thus obtained 2.2 g. of crystals with a melting point of 152—154°C., which is the ethyl ester of 1 - (5 - nitro - 2 - furyl) - 2 - (4 - carboxy - 2 - pyridyl) - 2 - methyl - ethylene.

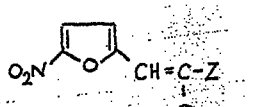
1.3 g. of this ethyl ester are dissolved in a warm mixture of 10.5 ml. dimethyl formamide and 4 ml. dioxan, 5.2 ml. 1N sodium hydroxide solution added at 35°C., the reaction mixture left to stand for 10 minutes at room temperature, then acidified with 2N hydrochloric acid and the solution diluted with an equal volume of water, 1.15 g. of yellow crystals thereby separating out which, after washing with water and drying, decompose when heated, foaming occurring between 248 and 255°C., after the appearance of a brown colour at 240°C. The carboxylic acid so obtained can be recrystallised from aqueous dioxan.

$C_{13}H_{10}N_2O_5$ (M.W. 274) Calc. : C 56.9%; H 3.65%; N 10.2%
Found : C 56.98%; H 3.75%; N 9.85%

By titration with 0.1N sodium hydroxide solution in aqueous dioxan, the equivalent weight is found to be 278±1%.

WHAT WE CLAIM IS:—

1. Nitrofuryl derivatives of the general formula:—



wherein R is a hydrogen atom or an alkyl radical and Z is 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 the quaternary ammonium salts and acid-addition salts thereof.

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

3. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid.

4. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid β - hydroxy-ethylamide.

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

6. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - carbo - β,γ - dihydroxy - *n* - propyl - 2 - pyridyl) - ethylene.

7. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - nitro - 2 - pyridyl) - ethylene.

8. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid N^1 - hydroxy-acetyl - hydrazide.

9. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - diazomethyl ketone.

10. 1 - (5 - nitro - 2 - furyl) - 2 - (4 - carboxy - 2 - pyridyl) - 2 - methyl - ethylene.

11. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - bromomethyl ketone hexamethylene - tetramine salt.

12. 1 - (5 - nitro - 2 - furyl) - 2 - (2 - acetamido - 4 - pyridyl) - ethylene.

13. 1 - (5 - nitro - 2 - furyl) - 2 - (4 -

4.5 g. of this ester are dissolved in 75 ml. hot dioxan a mixture of 24 ml. methanol and 17.2 ml. 2N sodium hydroxide solution added thereto at room temperature and the solution left to stand for 3 minutes at room temperature. The reaction mixture is now mixed with 480 ml. water, left to stand for 8 minutes, a little undissolved material is rapidly filtered off with suction, the mixture is then immediately acidified with about 30 ml. 2N hydrochloric acid and the precipitated olive-yellow crystallisate filtered off with suction. After washing with water and drying in a vacuum, these crystals (3.2 g.) are dissolved in 30 ml. dioxan, 150 ml. benzene added thereto and the dark brown material which precipitates after standing for about 10 minutes is filtered off with suction. The filtrate is evaporated in a vacuum and the evaporation residue (2.8 g.) recrystallised from 60 ml. glacial acetic acid. Yield: 1.8 g. of crystals of the above compound which decompose in an aluminium block between 210 and 244°C. A sample thereof is recrystallised from dioxan and there is obtained a crystallisate which decomposes, with foaming, in an aluminium block at 250°C.

EXAMPLE 17

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

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$C_{13}H_{11}N_2O_5$ (M.W. 302) Calc. : C 59.6%; H 4.63%; N 9.27%
Found : C 59.66%; H 4.61%; N 9.11%

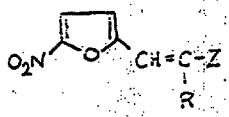
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6. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - carbo - β,γ - dihydroxy - *n* - propyl - 2 - pyridyl) - ethylene.

7. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - nitro - 2 - pyridyl) - ethylene.

8. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - carboxylic acid N¹ - hydroxy-acetyl - hydrazide.

9. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - diazomethyl ketone.

10. 1 - (5 - nitro - 2 - furyl) - 2 - (4 - carboxy - 2 - pyridyl) - 2 - methyl - ethylene.

11. 2 - [2 - (5 - nitro - 2 - furyl) - vinyl] - pyridine - 6 - bromomethyl ketone hexamethylene - tetramine salt.

12. 1 - (5 - nitro - 2 - furyl) - 2 - (2 - acetamido - 4 - pyridyl) - ethylene.

13. 1 - (5 - nitro - 2 - furyl) - 2 - (4 -

carboxyl - 2 - pyridyl) - 2 - methyl - ethylene ethyl ester.

14. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - acetamido - 2 - pyridyl) - ethylene.

15. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - acetamido - 2 - pyridyl) - ethylene.

16. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - carbethoxy - 2 - pyridyl) - ethylene.

17. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - amino - 5 - nitro - 2 - pyridyl) - ethylene.

18. 1 - (5 - nitro - 2 - furyl) - 2 - (3,5 - dicarbethoxy - 6 - methyl - 2 - pyridyl) - ethylene.

19. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - amino - 2 - pyridyl) - ethylene.

20. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - amino - 2 - pyridyl) - ethylene.

21. 1 - (5 - nitro - 2 - furyl) - 2 - (3 - acetoxy - 2 - pyridyl) - ethylene.

22. 1 - (5 - nitro - 2 - furyl) - 2 - (3 - hydroxy - 2 - pyridyl) - ethylene.

23. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - carboxy - 2 - pyridyl) - ethylene.

24. 1 - (5 - nitro - 2 - furyl) - 2 - (3,5 - dicarboxy - 6 - methyl - 2 - pyridyl) - ethylene.

25. Process for the production of nitrofuryl derivatives of the general formula given in claim 1, wherein 5-nitrofurfural or its diacetate is condensed with a compound of the general formula $R—CH_2—Z$, in which R and Z have the same meanings as in claim 1.

26. Modification of the process according to claim 25, wherein the substituent or substituents in the pyridine ring is or are introduced or liberated after the condensation reaction.

27. Process according to claim 25 or 26, wherein the product obtained is converted into a quaternary ammonium salt.

28. Process for the production of nitrofuryl derivatives of the general formula given in claim 1, substantially as hereinbefore described and with reference to any of the specific Examples.

29. Nitrofuryl derivatives according to claim 1, whenever prepared by the process according to any of claims 25 to 28.

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ERRATUM

SPECIFICATION No. 1,010,582
Amendment No. 1

Page 3, line 24, *for* "$C_{11}N_9N_3O_3$" *read* "$C_{11}H_9N_3O_3$"

THE PATENT OFFICE
4th February 1966