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COMPLETE SPECIFICATION

New Nitrofuran Derivatives

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., a body corporate organised under the laws of Germany, of (17a) 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 5-nitrofuran derivatives and with the preparation thereof.

The new compounds according to the present invention may be represented by the general formula:—



wherein Z is a heterocyclic ring containing two or more hetero atoms of which at least one is a tertiary nitrogen atom, which ring may also be substituted or may be fused to a further ring system; and the N-oxides, quaternary ammonium compounds and acid addition salts thereof.

We have found that these new compounds possess outstanding bacteriostatic and fungistatic properties; in comparison with known nitrofuran derivatives, the new compounds shew, in particular, an improved effectiveness against *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus aureus*, *Microsporum gypseum* and *Trichophyton mentagrophytes*.

As examples of suitable heterocyclic compounds from which can be derived the substituent Z, there may be mentioned the pyridazines, pyrimidines, pyrazines, triazines, oxazoles, thiazoles, pyrazoles, triazoles, thiadiazoles and benzothiazoles. These heterocyclic

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compounds can also contain substituents such as halogen atoms or nitro, amino, acylamino, sulphonylamino, hydroxy, acyloxy or alkoxy radicals.

The new 5-nitrofuran derivatives according to the present invention can be prepared by methods known for the preparation of 5-nitrofuran derivatives. Preferably, 5-nitrofurfural is condensed with an alkyl-substituted heterocyclic compound of the general formula $\text{H}_2\text{C}-\text{Z}$ in which Z has the same meaning as above.

In the case of some of the above-mentioned substituents of the heterocyclic ring, it is expedient first to introduce or liberate these after the condensation reaction. Thus, for example, the amino-substituted compounds are advantageously prepared by saponification of the corresponding acylamino compounds.

The new heterocyclic-substituted 5-nitro-2-furyl ethylene compounds according to the present invention can be converted into their quaternary ammonium compounds or into their N-oxides by methods in actual use or described in the literature for the preparation of quaternary ammonium compounds or N-oxides.

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

EXAMPLE 1

1-(5-nitro-2-furyl)-2-(6-acetamido-3-pyridazinyl)-ethylene.

1.51 g. 3-methyl-6-acetamido-pyridazine are heated for 3 hours at a bath temperature of 160°C . with 1.41 g. 5-nitrofurfural, 10 ml. acetic anhydride and 10 ml. glacial acetic acid. The reaction mixture is then evaporated to dryness in a vacuum, the residue taken up in water, neutralised with sodium bicarbonate and filtered with suction. The precipitate is boiled five times with 15 ml. amounts of dioxan. Upon cooling the combined dioxan extracts, there are obtained 0.65 g. of crystals with a melting

point of 290—292°C. (decomp.); a further 0.5 g. of material with a melting point of 290—291°C. are obtained from the concentrated mother liquor. After recrystallisation from pyridine, the 1-(5-nitro-2-furyl)-2-(6-acetamido-3-pyridazinyl)-ethylene obtained melts at 292°C.

EXAMPLE 2.

1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene.

1 g. of the acetyl compound obtained according to Example 1 is hydrolysed for 1 hour at 110°C. with 30 ml. 5N hydrochloric acid; the initial suspension is converted after a few minutes into a clear solution from which, after some time and while still hot, crystals are precipitated. The reaction mixture is allowed to cool and then chilled in an ice bath, filtered with suction and the crystals obtained recrystallised from 50 ml. water with the addition of activated charcoal and 2.5 ml. concentrated hydrochloric acid. There are obtained 0.75 g. 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene in the form of its hydrochloride which melts at 290°C.

EXAMPLE 3.

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

2.82 g. 2-methyl-benzothiazole are heated for 2 hours at a bath temperature of 130°C. with 2.82 g. 5-nitrofurfural and 4 g. acetic anhydride; after cooling, the reaction mixture is mixed with water, neutralised with sodium bicarbonate, filtered off with suction and the precipitate washed with water. The precipitate is then boiled four times with benzene using, successively, 80 ml., 60 ml., 40 ml. and 20 ml. portions of benzene, and the clear benzene solution evaporated in a vacuum. The residue yields, after recrystallisation from 20 ml. dioxan, 1.75 g. 1-(5-nitro-2-furyl)-2-(2-benzothiazolyl)-ethylene with a melting point of 202—204°C. (decomp.).

EXAMPLE 4.

1-(5-nitro-2-furyl)-2-(4-pyrimidinyl)-ethylene.

0.48 g. 4-methyl-pyrimidine are heated for 1 hour at a bath temperature of 130°C. with 0.92 g. glacial acetic acid, 1.05 g. acetic anhydride and 0.72 g. 5-nitrofurfural; after cooling, the reaction mixture is mixed with water, neutralised with sodium bicarbonate, filtered off with suction and washed with water. The crude product obtained is boiled three times with benzene using, successively, 30 ml., 15 ml. and 15 ml. portions of benzene, and the clear benzene solution evaporated. The residue yields, after recrystallisation from 8.5 ml. dioxan, 0.45 g. 1-(5-nitro-2-furyl)-2-(4-pyrimidinyl)-ethylene with a melting point of 223—224°C.

EXAMPLE 5.

1-(5-nitro-2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethylene.

7.44 g. 3-methyl-6-methoxy-pyridazine are heated for 3 hours at a bath temperature of 160°C. with 12.3 g. acetic anhydride and 8.5 g. 5-nitrofurfural; the reaction mixture is then evaporated to dryness in a vacuum, the black residue triturated with water and neutralised with sodium bicarbonate. After filtering off with suction, washing with water and drying, the material obtained is boiled five times with 100 ml. amounts of benzene and four times with 50 ml. amounts of benzene. 2.2 g. of crystals separate out from the chilled clear benzene filtrate and have a melting point of 185—190°C.; the mother liquor, after evaporation in a vacuum, leaves behind 3.4 g. of residue which, after recrystallisation from 60 ml. toluene, yields 2.2 g. of crystals with a melting point of 185—190°C. 1.6 g. of the combined crystals are dissolved in 20 ml. chloroform, the small amount of undissolved material separated off and the solution put on to a column (about 40 cm. long) of a benzene slurried neutral aluminium oxide (about 100 times the amount by weight). The column is eluted with benzene until there have formed two yellow zones well separated from one another. The column is then cut between these two zones and the lower zone extracted with chloroform. After removal of the solvent, there are obtained 1.1 g. 1-(5-nitro-2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethylene with a melting point of 202—203°C.

EXAMPLE 6.

N-oxide of 1-(5-nitro-2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethylene.

0.1 g. of the product obtained according to Example 5 are dissolved in 3.3 ml. chloroform and mixed with 4.3 ml. of a solution of 0.07 g. perbenzoic acid in chloroform. The reaction mixture is allowed to stand for 4 days at room temperature and the crystals which have separated out are subsequently filtered off with suction. After washing with chloroform and drying, there are obtained 0.1 g. of the N-oxide of 1-(5-nitro-2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethylene with a melting point of 244—245°C. (above 180°C. the orange-coloured compound gradually becomes dark brown).

EXAMPLE 7.

1-(5-nitro-2-furyl)-2-(6-methyl sulphonyl-amido-3-pyridazinyl)-ethylene.

a) 4.36 g. 6-amino-3-methyl-pyridazine are suspended in 60 ml. absolute dioxan and 30 ml. triethylamine and a solution of 10 g. methane sulphochloride in 50 ml. absolute dioxan added dropwise, with stirring, within a period of one hour; the reaction mixture is subsequently stirred for one hour at 50°C. The crystals obtained are filtered off with suction at room temperature and then washed with

dioxan. The filtrate, after evaporation in a vacuum, leaves behind 11.4 g. of residue which, after trituration with water, yields 5.6 g. 3 - methyl - 6 - (bis - methyl - sulphonyl)-amino - pyridazine with a melting point of 194—196°C.

1.9 g. of this compound are hydrolysed with excess 0.5N sodium hydroxide solution for 20 minutes at room temperature; the small amount of undissolved material is then filtered off, the filtrate acidified with concentrated hydrochloric acid to a pH of about 3, and finally the solution evaporated to dryness in a vacuum with the repeated addition of benzene. The completely dry residue is extracted three times with ethyl acetate and there are thus obtained 0.95 g. crude 3-methyl-6-methylsulphonylamido-pyridazine with a melting point of 146—150°C.

0.94 g. of this crude product are heated for 3 hours at a bath temperature of 160°C. with 0.7 g. 5-nitrofurfural and a mixture of 5 ml. glacial acetic acid and 5 ml. acetic anhydride; the cooled reaction mixture is treated with water, neutralised with sodium bicarbonate, the aqueous phase decanted off and the organic residue triturated with chloroform, 0.3 g. of material remain undissolved; they are boiled with dioxan and the filtrate evaporated. In this manner, there are obtained 0.06 g. 1 - (5-nitro - 2 - furyl) - 2 - (6 - methylsulphonylamido - 3 - pyridazinyl) - ethylene with a melting point of 242—244°C. After recrystallisation from ethylene glycol monomethyl ether, the compound melts at 255—257°C.

b) It is not necessary first to saponify the 3 - methyl - 6 - (bis - methylsulphonyl)-amino - pyridazine to the monomethylsulphonyl compound before the condensation reaction; on the contrary, the bis-methylsulphonyl compound can very advantageously be directly condensed with the 5-nitrofurfural, the same reaction conditions being used as described under a) above. There is thereby obtained 1 - (5 - nitro - 2 - furyl) - 2 - [6 - (bis-methylsulphonyl) - amino - 3 - pyridazinyl] - ethylene with a melting point of 198—199°C. If a dioxan solution of this bis compound is treated for a short time in the cold with a 0.1N sodium hydroxide solution, followed by acidification, then 1 - (5 - nitro - 2 - furyl) - 2 - (6 - methylsulphonylamido - 3 - pyridazinyl) - ethylene precipitates out; m.p. 253—255°C.

c) A further possibility for the preparation of 1 - (5 - nitro - 2 - furyl) - 2 - (6 - methylsulphonylamido - 3 - pyridazinyl) - ethylene consists in that the 1 - (5 - nitro - 2 - furyl) - 2 - (6 - amino - 3 - pyridazinyl) - ethylene hydrochloride obtained according to Example 2 is dissolved in pyridine and treated with methane sulphochloride at room temperature in the presence of triethylamine. After working up in a manner analogous to that described above for 6 - amino - 3 - methyl - pyridazine

(see under a)), there is obtained 1 - (5 - nitro - 2 - furyl) - 2 - [6 - (bis - methylsulphonyl)-amino - 3 - pyridazinyl] - ethylene with a melting point of 198°—199°C. which can be saponified, as described under b), to give 1 - (5 - nitro - 2 - furyl) - 2 - (6 - methylsulphonylamido - 3 - pyridazinyl) - ethylene.

EXAMPLE 8.

1-(5-nitro-2-furyl)-2-(5-amino-1,3,4-thiadiazolyl-2)-ethylene.

28.2 g. 5 - methyl - 2 - amino - 1,3,4-thiadiazole are heated for 10 minutes at 160°C. with 150° g. acetic anhydride, then 36.2 g. 5-nitrofurfural added thereto and the reaction mixture heated under reflux for 4 hours at a bath temperature of 160°C. After cooling, the reaction mixture is filtered with suction and the residue washed with glacial acetic acid. After drying, there are obtained 51.7 g. of the N-acetyl compound of 1 - (5-nitro - 2 - furyl) - 2 - (5 - amino - 1,3,4-thiadiazolyl - 2) - ethylene; the compound can be recrystallised from dimethyl formamide and then has a melting point of 290°C. (black coloration).

Analysis $C_{16}H_8N_4O_4S$ (M.W. 280)

calc.: N 20.0%; S 11.43%

found: 19.85%; 11.2%

51.7 g. of this N-acetyl compound are boiled under reflux for one hour, with stirring, with 1.52 litres of a mixture of concentrated hydrochloric acid and glacial acetic acid (1:1). After cooling, the reaction mixture is filtered with suction, the residue subsequently washed with water, acidified with hydrochloric acid and dried. In this manner, there are obtained 30 g. 1 - (5 - nitro - 2 - furyl) - 2 - (5-amino - 1,3,4 - thiadiazolyl - 2) - ethylene in the form of the hydrochloride with a melting point of 260°C. (decomp.); the decomposition point is unaltered after recrystallisation from approximately 3% hydrochloric acid or from a mixture of 10% hydrochloric acid and glycol (1:1).

Analysis $C_8H_6N_4O_4S \cdot HCl$ (M.W. 274.5)

calc.: S 11.63%; Cl 12.9%

found: 11.5%; 12.77%

The amino compound liberated from the hydrochloride by treatment with a dilute sodium hydroxide solution, is a red product which decomposes at 228°C.

EXAMPLE 9.

1-(5-nitro-2-furyl)-2-(4,6-diacetamido-2-s-triazinyl)-ethylene.

7.05 g. 5-nitrofurfural are boiled under reflux for 3 hours at a bath temperature of 190°C. with 10.45 g. 2-methyl-4,6-diacetamido-s-triazine and 5 ml. acetic anhydride; the reaction mixture is then evaporated in a vacuum and the residue triturated with isopropyl ether. The undissolved material is boiled with 200 ml. glacial acetic acid, undissolved material separated off and the filtrate allowed to crystallise; this crystallisate and the residue which remained undissolved in the

glacial acetic acid are recrystallised from dioxan. In this manner, there are obtained 6 g. 1 - (5 - nitro - 2 - furyl) - 2 - (4,6-diacetamido - 2 - s - triazinyl) - ethylene with a melting point of 260—262°C.; a further

1.5 g. of material with a melting point of 260—262°C. can be obtained from the dioxan and glacial acetic acid mother liquors by concentration thereof.

Analysis $C_{13}H_{12}N_6O_5$ (M.W. 332)

calc: C 46.95%; H 3.61%; N 25.32%; CH_3CO 25.9%
found: 46.73%; 3.59%; 24.99%; 26.12%

EXAMPLE 10.

15 1-(5-nitro-2-furyl)-2-(2-thiazolyl)-ethylene.
1.5 g. 2-methyl-thiazole, 3 g. acetic anhydride, 0.9 g. glacial acetic acid and 2.1 g. 5-nitrofurfural are heated for 2 hours at 160°C., the reaction mixture cooled, the produce which thereby separates out filtered off with suction and subsequently washed with glacial acetic acid. The substance (1.5 g.) is dissolved in hot benzene, undissolved material separated off and the solution evaporated to dryness in a vacuum. In this manner, there are obtained 25 1.25 g. 1 - (5 - nitro - 2 - furyl) - 2 - (2-thiazolyl) - ethylene with a melting point of 154—156°C. (from acetonitrile).

Analysis $C_8H_6N_2O_3S$ (M.W. 222)

calc.: N 12.61%; S 14.43%
found: 12.68%; 14.4%

EXAMPLE 11.

1-(5-nitro-2-furyl)-2-(6-methylmercapto-3-pyridazinyl)-ethylene.
35 12.85 g. 3-methyl-6-chloropyridazine are dissolved in 150 ml. methanol and mixed, with stirring, within a period of 30 minutes at 50°C. with 150 ml. of a solution of 5.8 g. sodium and 12 g. methyl mercaptan in 250 ml. methanol. The reaction mixture is further stirred for 1½ hours, evaporated in a vacuum and the residue taken up in chloroform. After evaporation of the organic solvent, the clear solution is fractionated in a vacuum; b.p. 40 110—125°C./12 mm.Hg. Yield: 5 g. 3-methyl-6-methylmercapto-pyridazine.

Analysis $C_{11}H_9N_3O_2S$ (M.W. 295)

calc: C 44.75%; H 3.05%; N 14.23%; S 10.85%
found: 44.64%; 3.32%; 13.97%; 10.9%

EXAMPLE 13.

1-(5-nitro-2-furyl)-2-(5-methylsulphonyl-amido-1,3,4-thiadiazolyl-2)-ethylene.
85 0.55 g. of the compound prepared according to Example 8 are suspended in 12.5 ml absolute pyridine and 0.73 g absolute triethylamine added thereto. 0.5 g. methane sulphochloride dissolved in 2 ml. absolute dioxan are then introduced dropwise, with stirring, into this suspension at 50°C. within a period of 30 minutes and the mixture subsequently stirred for 1½ hours at 50°C. After cooling, the reaction mixture is filtered with suction, the residue washed with dioxan and the washings added to the filtrate, and the combined filtrate and dioxan washings evaporated to dryness in a vacuum. The residue (1 g.) is taken up with water, 2N sodium carbonate solution added

1.4 g. of this liquid pyridazine derivative are boiled under reflux for 3 hours at a bath temperature of 160°C. with 10 ml. acetic anhydride; 5 ml. glacial acetic acid and 1.41 g. 5-nitrofurfural. The reaction mixture is then evaporated to dryness, the residue triturated with ether, subsequently boiled with dioxan and the dioxan solution evaporated. In this manner, there is obtained 1 g. 1 - (5 - nitro - 2-furyl) - 2 - (6 - methylmercapto - 3 - pyridazinyl) - ethylene with a melting point of 208—209°C.

Analysis $C_{11}H_9N_3O_3S$ (M.W. 263)

calc: C 50.2%; H 3.42%; S 12.17%
found: 50.3%; 3.37%; 12.2%

EXAMPLE 12.

1-(5-nitro-2-furyl)-2-(6-methylsulphonyl-3-pyridazinyl)-ethylene.

132 g. of the compound prepared according to Example 11 are dissolved in 100 ml. warm chloroform, 104 ml. of a solution of 2.21 g. perbenzoic acid in 104 ml. chloroform added thereto at room temperature, the crystallisate obtained by allowing the reaction mixture to stand overnight at room temperature filtered off with suction and washed with chloroform. In this manner, there is obtained 1 g. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - methylsulphonyl - 3 - pyridazinyl) - ethylene with a melting point of 218—219°C.

The oxidation can also be carried out with potassium permanganate instead of with perbenzoic acid.

thereto, insoluble material is filtered off with suction and the filtrate acidified with concentrated hydrochloric acid; the yellow crystals which thereby precipitate out melt, after washing with water, at 259—260°C. (decomp.). Yield of 1 - (5 - nitro - 2 - furyl) - 2 - (5-methylsulphonylamido - 1,3,4 - thiadiazolyl-2) - ethylene: 0.45 g.

Analysis $C_9H_8N_4O_3S_2$ (M.W. 316)

calc.: C 34.18%; H 2.53%; S 20.27%
found: 34.22%; 2.49%; 20.2%

EXAMPLE 14.

1-(5-nitro-2-furyl)-2-(6-dimethylol-methylamino-3-pyridazinyl)-ethylene.

2.84 g. of a mixture of 3-methyl-6-chloropyridazine and 3-methyl-6-bromopyridazine (about ½ : ½) are heated for 4 hours at a bath temperature of 120°C. with 14.5 g. 2-amino-

propan-1,3-diol. After cooling, the clear solution is diluted with 50 ml. water, 25 ml. concentrated sodium hydroxide solution added thereto, with cooling, and the reaction mixture repeatedly extracted with benzene in order to remove unreacted 3-methyl-6-halopyridazine. After the addition of 10 g. anhydrous sodium carbonate, the aqueous phase is extracted five times with 30—50 ml. amounts of dioxan and the combined dioxan extracts, after drying over anhydrous sodium carbonate, evaporated in a vacuum. As residue there is obtained 1 g. of syrupy 3-methyl-6-(dimethylol-methylamino)-pyridazine; 0.8 g. of the compound can be obtained from the aqueous alkaline phase by the addition of a further 10 g. anhydrous sodium carbonate and extracting five times with dioxan.

1 g. of this crude product is heated for 30 minutes at 120°C. with 5.5 ml. acetic anhydride, 0.77 g. 5-nitrofurfural added thereto and the reaction mixture maintained at a bath temperature of 120°C. for a further 3 hours. After cooling, the reaction mixture is mixed with 70 ml. benzene, the resultant precipitate (0.14 g.) filtered off and the solution evaporated in a vacuum. The residue is repeatedly triturated with isopropyl ether (for the removal of glacial acetic acid, acetic anhydride and possibly unreacted nitrofurfural) and decanted off each time. The residue which was not dissolved in the isopropyl ether is then boiled under reflux for one hour with 17 ml. 5N hydrochloric acid, the solution diluted with water and treated with 0.8 g. activated charcoal; after filtering, a 2N sodium carbonate solution is added to the clear aqueous solution until a pH of about 8—9 is reached, the solution then exhaustively extracted with ethyl acetate and the combined ethyl acetate extracts evaporated to dryness in a vacuum (0.35 g. of residue). After recrystallisation from 10 ml. isopropanol, there are obtained 0.15 g. 1 - (5-nitro - 2 - furyl) - 2 - (6 - dimethylolmethylamino - 3 - pyridazinyl) - ethylene with a melting point of 170—172°C. The red crystals can be recrystallised from water; they dissolve in dilute hydrochloric acid with a yellow colour and can be precipitated out again as red crystals by the addition of sodium bicarbonate.

EXAMPLE 15.

The quaternary ammonium salt from 1 - (5-nitro - 2 - furyl) - 2 - (6 - amino - 3-pyridazinyl) - ethylene and ethylene chlorohydrin.

0.93 g. 1 - (5 - nitro - 2 - furyl) - 2 - (6-amino - 3 - pyridazinyl) - ethylene (prepared by treating the hydrochloride obtained according to Example 2 with dilute sodium hydroxide solution) are suspended in 10 ml. ethylene chlorohydrin and then heated for 3 hours at a bath temperature of 135°C. The clear solution is subsequently evaporated in a vacuum to about half its original volume, ether added and the precipitate obtained filtered off with

suction. The crystallisate obtained is recrystallised from 7.5 ml. of a mixture of 85% dioxan and 15% 1N hydrochloric acid, insoluble material being separated off. The product obtained (0.65 g.; m.p. 225°C. (decomp.)) is dissolved in 15 ml. warm water, sodium bicarbonate added at room temperature until a pH of 7—8 is reached and the reaction mixture allowed to stand at room temperature for 30 minutes. The precipitate is then filtered off with suction and subsequently washed with water; yield; 0.45 g. The substance melts, after recrystallisation from 4 ml. 80% aqueous dioxan (whereby somewhat insoluble material is separated off), at 914°C., with decomposition (0.32 g.); the compound is ~~difficultly~~ soluble in cold water but readily soluble in very dilute aqueous acetic acid.

EXAMPLE 16.

1-(5-nitro-2-furyl)-2-(5-methylureido-1,3,4-thiadiazolyl-2)-ethylene.

0.69 g. methyl isocyanate are dissolved in 40 ml. dry pyridine and mixed with 1.9 g. 1 - (5 - nitro - 2 - furyl) - 2 - (5 - amino-1,3,4 - thiadiazolyl - 2) - ethylene (prepared according to Example 8). The mixture is stirred for 15 minutes at 80°C.; after cooling, the yellow crystallisate obtained is filtered off with suction and then washed with pyridine. In this manner, there are obtained 2 g. (1 - (5 - nitro-2 - furyl) - 2 - (5 - methylureido - 1,3,4 - thiadiazolyl - 2) - ethylene; after recrystallisation from 10 ml. dimethyl formamide, the compound melts at 267—268°C., with decomposition (above 220°C. there appears a brown coloration). For purification, 1 g. of this urea derivative is suspended in water and mixed with 2N sodium hydroxide solution until solution is obtained. The small amount of undissolved material is filtered off and the dark red solution acidified with glacial acetic acid, whereby an amorphous mass precipitates out; the reaction mixture is then briefly heated to 60°C., allowed to cool, the precipitate obtained filtered off with suction, then washed with water and subsequently with ether. Yield: 0.8 g.; after again recrystallising from dimethyl formamide, the melting point remains unaltered at 267—268°C. (decomp.).

Analysis $C_{10}H_9N_5O_4S$ (M.W. 295)

calc.: S 10.85%

found: 10.8%

The equivalent weight was found to be 298 (titrated with tetrabutyl ammonium hydroxide in methyl ethyl ketone).

EXAMPLE 17.

1-(5-nitro-2-furyl)-2-[6-(β,γ -dihydroxy-n-propoxy)-3-pyridazinyl]-ethylene.

8.7 g. of monosodium glycerine are dissolved in 48 ml. of warm dry glycerine, and 10.85 g. of a mixture of 3-methyl-6-chloropyridazine and 3-methyl-6-bromopyridazine (ca. 2:1) are added thereto. The resulting mixture is heated for 2 hours at a bath temperature of 150°C. After cooling, 150—200 ml. water are



difficulty

added, and the solution is saturated with potassium carbonate, while cooling. The oil which has separated is extracted with chloroform, and the extract, after drying over sodium sulphate, evaporated in a vacuum. As residue there are obtained 9.2 g. (65.7% of theory) of a viscous oil which becomes crystallized after some hours standing. This product is the 3-methyl-6-(β,γ -dihydroxy-*n*-propoxy)-pyridazine which after trituration with dioxane/chloroform (1:1) melts at 74–76°C.

9.2 g. of the oily crude product are heated for 10 minutes at a bath temperature of 160°C. with 67.5 ml. acetic anhydride, 7.05 g. of crude 5-nitrofurfural added thereto and the reaction mixture boiled under reflux at a bath temperature of 160°C. for a further 3 hours. The excess acetic anhydride is evaporated in a vacuum, and the residue triturated with benzene. The small amount of undissolved material is separated off and the benzene solution evaporated in a vacuum. The residue is again dissolved in benzene and diluted with much ether. The precipitated flocculent material is filtered off and the filtrate evaporated in a vacuum. The oily residue is the 1-(5-nitro-2-furyl)-2-[6-(β,γ -diacetoxy-*n*-propoxy)-3-pyridazinyl]-ethylene. Yield: 16.25 g. (83.3% of theory).

This crude product is dissolved in 172 ml. methanol and 92 ml. of 1N soda lye are added thereto with cooling. After 10 minutes standing at room temperature, concentrated hydrochloric acid is added until a pH value of 1 is reached. The resulting solution is evaporated in a vacuum and the residue triturated twice with about 100 ml. water. The water is decanted off and the remaining oil is dissolved in methanol. The small amount of undissolved material is separated off, the solution diluted with benzene and again evaporated in a vacuum. The residue is dissolved in few methanol, the solution diluted with much ether and the precipitated brown amorphous mass filtered off. After evaporation, the clear filtrate yields 3.45 g. of an orange-yellow amorphous residue, which is purified by recrystallization from dioxane-chloroform (1:1). The compound melts at 147–148°C. (decomp.).

Analysis $C_{13}H_{13}N_3O_6$ (M.W. 307)
calc.: C 50.8%; H 4.23; N 13.68%
found: 50.65%; 4.22; 13.38%

EXAMPLE 18.

1-(5-nitro-2-furyl)-2-(pyrazinyl)-ethylene.
2.4 g. 2-methyl-pyrazine are heated for 2 hours at a bath temperature of 130°C., under reflux, with 4.6 g. glacial acetic acid, 5.22 g. acetic anhydride and 3.6 g. 5-nitrofurfural. A further 2.5 ml. acetic anhydride are then added and the reaction mixture heated for a further 2 hours at a bath temperature of 160°C. The crystals (1 g.) which separate out from the cooled reaction mixture are filtered off with suction, washed with glacial acetic acid, boiled out several times with benzene and the com-

bined extracts evaporated. The residue (0.6 g.) melts, after recrystallisation from 7.5 ml. dioxan, at 210°C. By the addition of water to, and possible neutralisation of, the mother liquor, further amounts of the desired product can be isolated. Total yield: 3.4 g.

Analysis $C_{10}H_7N_3O_5$ (M.W. 217)
Calc.: C 55.3%; H 3.23%; N 19.36%
Found: 55.38%; 3.36%; 19.07%

The following compounds are obtained in an analogous manner: 1-(5-nitro-2-furyl)-2-(5-amino-1,3,4-oxadiazolyl-2)-ethylene of melting point 272°C. (decomp.).

Analysis $C_8H_6N_4O_4$ (M.W. 222)
Calc.: C 43.25%; H 2.7%; N 25.2%
Found: 43.2%; 3.1%; 25.2%

and 1-(5-nitro-2-furyl)-2-(5-methylol-1,2,4-triazolyl-3)-ethylene of melting point 202–205°C. (decomp.).

Analysis $C_9H_8N_4O_4$ (M.W. 236)
Calc.: C 45.75%; H 3.39%; N 23.73%
Found: 45.74%; 3.51%; 23.86%

EXAMPLE 19.

N-oxide of 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene.

38.5 g. of the hydrochloride prepared in Example 2 (m.p. 290°C.) are dissolved in aqueous ethanol and converted into the base by the addition of the calculated amount of dilute ammonia solution. Yield: 32.8 g. 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene of melting point 264–266°C. (decomp.).

0.93 g. of this base are dissolved in 20 ml. warm dimethyl formamide, a solution of 0.67 g. perbenzoic acid in chloroform added thereto at room temperature and the reaction mixture left to stand for some time at room temperature. The dark red-brown crystals obtained are filtered off with suction and washed with chloroform. After recrystallisation from 10 ml. dimethyl formamide, there are obtained 0.65 g. of the N-oxide which decomposes at about 275°C.

Analysis $C_{10}H_8N_4O_4$ (M.W. 248)
calc.: C 48.4%; H 3.23%; N 22.58%
found: 48.61%; 3.56%; 21.30%

In contradistinction to the starting material, the product does not dissolve in 2 N aqueous hydrochloric acid.

In an analogous manner, there is obtained, from the compound produced in Example 17, the N-oxide of 1-(5-nitro-2-furyl)-2-[6-(β,γ -dihydroxy-*n*-propoxy)-3-pyridazinyl]-ethylene of melting point 202–204°C. (decomp.).

Analysis $C_{11}H_{13}N_3O_7$ (M.W. 323)
calc.: C 48.3%; H 4.025%; N 13.0%
found: 47.93%; 3.9%; 11.27%

EXAMPLE 20.

1-(5-nitro-2-furyl)-2-(5-formamido-1,3,4-thiadiazolyl-2)-ethylene.

2.5 g. of the red 1-(5-nitro-2-furyl)-2-(5-amino-1,3,4-thiadiazolyl-2)-

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ethylene obtained according to Example 8 are dissolved in 25 ml. 98% formic acid at 100°C. and then maintained at this temperature for 3 hours. After cooling, the yellow crystals are filtered off with suction, then washed with 98% formic acid to give 1.55 g. of the desired substance which decomposes at 283°C.

Analysis $C_9H_6N_4O_4S$ (M.W. 266)

calc.: 40.6%; H 2.25%; N 12.02%

found: 40.14%; 2.24%; 11.9%

EXAMPLE 21.

1-(5-nitro-2-furyl)-2-(6-β-hydroxyethoxy-3-pyridazinyl)-ethylene.

2.5 g. sodium are carefully dissolved in 60 ml. absolute ethylene glycol. 14.2 g. of a mixture of 3-methyl-6-chloropyridazine and 3-methyl-6-bromo-pyridazine (about 2:1) are introduced into this solution and the reaction mixture heated for 2 hours at a bath temperature of 150°C. After cooling, 250 ml. water is added, the mixture saturated with potassium carbonate and the oil which separates from the aqueous solution extracted with chloroform. After drying and evaporating, the chloroform extracts yield 15.6 g. of an oily residue which gradually becomes crystalline.

The crude 3-methyl-6-β-hydroxyethoxy-pyridazine obtained in this manner is reacted with 5-nitrofurfural to give 1.4 g. of the desired product with a melting point of 145—146°C.

Analysis $C_{12}H_{11}N_5O_5$ (M.W. 277)

calc.: C 52%; H 3.97%; N 15.15%

found: 52.37%; 4.10%; 14.83%

EXAMPLE 22.

1-(5-nitro-2-furyl)-2-(6-β-hydroxyethyl-amino-3-pyridazinyl)-ethylene.

5.68 g. of a mixture of 3-methyl-6-chloropyridazine and 3-methyl-6-bromopyridazine (about 2:1) are heated with 12.2 g. monoethanolamine for 4 hours at 120°C. After cooling, the reaction mixture is diluted with 100 ml. water, 50 ml. concentrated sodium hydroxide are added thereto, with cooling, followed by repeated extraction with dioxan. The dioxan extracts are then combined, dried with anhydrous sodium carbonate and evaporated to give an oily residue which quickly crystallises. After repeated trituration with ether, the crystals (4.5 g.) are recrystallised from 20 ml. dioxan and then melt at 92—94°C.

The 3-methyl-6-β-hydroxyethylamino-pyridazine obtained in this manner is reacted with 5-nitrofurfural. There is obtained 0.1 g. of the desired product in the form of orange-red crystals of melting point 200°C. (decomp.).

Analysis $C_{12}H_{12}N_4O_4$ (M.W. 276)

calc.: C 52.2%; H 4.35%; N 20.28%

found: 52.1%; 4.19%; 18.95%

EXAMPLE 23.

1-(5-nitro-2-furyl)-2-(2-methyl-imidazo-[1,2-b]-pyridazinyl-6)-ethylene.

The hydrochloride of 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene obtained ac-

cording to Example 2 is converted into the free base by means of ammonia or sodium hydroxide solution. 1 g. of the amino compound is heated under reflux for 4 hours at a bath temperature of 100°C. with 0.5 g. chloroacetone. The crystals are then filtered off with suction, boiled out 5 times with 40 ml. amounts of chloroform, the clear filtrate evaporated and the residue recrystallised from 50 ml. 80% aqueous dioxan. For further purification of the crystals obtained (0.55 g.) m.p. 263—266°C., (decomp.), they are dissolved in hot water which contains some 2 N hydrochloric acid and, after separation of the small amount of undissolved matter, precipitated out with ammonia.

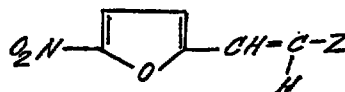
Analysis $C_{13}H_{10}N_5O_3$ (M.W. 270)

calc.: C 57.75%; H 3.70%; N 20.75%

found: 57.85%; 3.86%; 20.56%

WHAT WE CLAIM IS:—

1. Nitrofurans derivatives of the general formula:—



wherein Z is a heterocyclic ring containing two or more hetero atoms of which at least one is a tertiary nitrogen atom, which ring may also be substituted or may be fused to a further ring system; and the N-oxides, quaternary ammonium compounds and acid addition salts thereof.

2. 1-(5-nitro-2-furyl)-2-(6-acetamido-3-pyridazinyl)-ethylene.

3. 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene.

4. 1-(5-nitro-2-furyl)-2-(2-benzothiazolyl)-ethylene.

5. 1-(5-nitro-2-furyl)-2-(4-pyrimidinyl)-ethylene.

6. 1-(5-nitro-2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethylene.

7. 1-(5-nitro-2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethylene N-oxide.

8. 1-(5-nitro-2-furyl)-2-(6-methylsulphonylamido-3-pyridazinyl)-ethylene.

9. 1-(5-nitro-2-furyl)-2-(5-amino-1,3,4-thiadiazolyl)-2-ethylene.

10. 1-(5-nitro-2-furyl)-2-(4,6-diacetamido-2-s-triazinyl)-ethylene.

11. 1-(5-nitro-2-furyl)-2-(2-thiazolyl)-ethylene.

12. 1-(5-nitro-2-furyl)-2-(6-methylmercapto-3-pyridazinyl)-ethylene.

13. 1-(5-nitro-2-furyl)-2-(6-methylsulphonyl-3-pyridazinyl)-ethylene.

14. 1-(5-nitro-2-furyl)-2-(5-methylsulphonylamido-1,3,4-thiadiazolyl-2)-ethylene.



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The hydrochloride of 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene obtained ac-

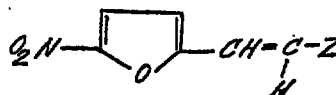
cording to Example 2 is converted into the free base by means of ammonia or sodium hydroxide solution. 1 g. of the amino compound is heated under reflux for 4 hours at a bath temperature of 100°C. with 0.5 g. chloroacetone. The crystals are then filtered off with suction, boiled out 5 times with 40 ml. amounts of chloroform, the clear filtrate evaporated and the residue recrystallised from 50 ml. 80% aqueous dioxan. For further purification of the crystals obtained (0.55 g.) m.p. 263—266°C., (decomp.), they are dissolved in hot water which contains some 2 N hydrochloric acid and, after separation of the small amount of undissolved matter, precipitated out with ammonia.

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WHAT WE CLAIM IS:—

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wherein Z is a heterocyclic ring containing two or more hetero atoms of which at least one is a tertiary nitrogen atom, which ring may also be substituted or may be fused to a further ring system; and the N-oxides, quaternary ammonium compounds and acid addition salts thereof.

2. 1 - (5 - nitro - 2 - furyl) - 2 - (6-acetamido - 3 - pyridazinyl) - ethylene.

3. 1 - (5 - nitro - 2 - furyl) - 2 - (6-amino - 3 - pyridazinyl) - ethylene.

4. 1 - (5 - nitro - 2 - furyl) - 2 - (2-benzothiazolyl) - ethylene.

5. 1 - (5 - nitro - 2 - furyl) - 2 - (4-pyrimidinyl) - ethylene.

6. 1 - (5 - nitro - 2 - furyl) - 2 - (6-methoxy - 3 - pyridazinyl) - ethylene.

7. 1 - (5 - nitro - 2 - furyl) - 2 - (6-methoxy - 3 - pyridazinyl) - ethylene N-oxide.

8. 1 - (5 - nitro - 2 - furyl) - 2 - (6-methylsulphonylamido - 3 - pyridazinyl)-ethylene.

9. 1 - (5 - nitro - 2 - furyl) - 2 - (5-amino - 1,3,4 - thiadiazolyl) - 2 - ethylene.

10. 1 - (5 - nitro - 2 - furyl) - 2 - (4,6-diacetamido - 2 - s - triazinyl) - ethylene.

11. 1 - (5 - nitro - 2 - furyl) - 2 - (2-thiazolyl) - ethylene.

12. 1 - (5 - nitro - 2 - furyl) - 2 - (6-methylmercapto - 3 - pyridazinyl) - ethylene.

13. 1 - (5 - nitro - 2 - furyl) - 2 - (6-methylsulphonyl - 3 - pyridazinyl) - ethylene.

14. 1 - (5 - nitro - 2 - furyl) - 2 - (5-methylsulphonylamido - 1,3,4 - thiadiazolyl-2) - ethylene.

15. 1 - (5 - nitro - 2 - furyl) - 2 - (6-dimethylolmethylamino - 3 - pyridazinyl)-ethylene.
- 5 16. Quaternary ammonium salt from 1 - (5-nitro - 2 - furyl) - 2 - (6 - amino - 3-pyridazinyl) - ethylene and ethylene chlorohydrin.
- 10 17. 1 - (5 - nitro - 2 - furyl) - 2 - (5-methylureido - 1,3,4 - thiadiazolyl - 2)-ethylene.
18. 1 - (5 - nitro - 2 - furyl) - 2 - (pyrazinyl - 2) - ethylene.
19. 1 - (5 - nitro - 2 - furyl) - 2 - (5-amino - 1,3,4 - oxadiazolyl - 2) - ethylene.
- 15 20. 1 - (5 - nitro - 2 - furyl) - 2 - (5-methylol - 1,2,4 - triazolyl - 3) - ethylene.
21. The N-oxide of 1-(5-nitro-2-furyl)-2-(6-amino-3-pyridazinyl)-ethylene.
- 20 22. 1 - (5 - nitro - 2 - furyl) - 2 - [6-(β,γ - dihydroxy - *n* - propoxy) - 3 - pyridazinyl] - ethylene.
23. The N-oxide of 1 - (5 - nitro - 2-furyl) - 2 - [6 - (β,γ - dihydroxy - *n* - propoxy) - 3 - pyridazinyl] - ethylene.
- 25 24. 1 - (5 - nitro - 2 - furyl) - 2 - (5-formamido - 1,3,4 - thiadiazolyl - 2) - ethylene.
25. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - β -hydroxyethoxy - 3 - pyridazinyl) - ethylene.
- 30 26. 1 - (5 - nitro - 2 - furyl) - 2 - (6 - β -hydroxyethylamino - 3 - pyridazinyl) - ethylene.
27. 1 - (5 - nitro - 2 - furyl) - 2 - (2-methyl - imidazo - [1,2-b] - pyridazinyl - 6)-ethylene.
28. Process for the production of nitrofurans compounds of the general formula given in claim 1, wherein 5-nitrofurfural is condensed with an alkyl-substituted heterocyclic compound of the general formula H_2C-Z , in which Z has the meaning given in claim 1.
29. Process according to claim 28, wherein a substituent in the heterocyclic ring is first introduced or liberated after termination of the reaction.
30. Process according to claim 28 or 29, wherein the product obtained is converted by methods in actual use or described in the literature into its N-oxide or into a quaternary ammonium compound.
31. Process for the preparation of nitrofurans compounds of the general formula given in claim 1, substantially as hereinbefore described and with reference to any of the specific Examples.
32. Nitrofurans compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 28 to 31.

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