

PATENT SPECIFICATION

(11) 1238 106

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NO DRAWINGS

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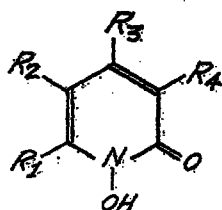
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 3A8A1 3A8A2 3A8B2 3A8C3 3A8K 719 MV



(54) 1-HYDROXY-2-PYRIDONES AND PROCESS FOR THEIR MANUFACTURE

- (71) We, FARBWERKE HOECHST AK-
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 & Brüning, a body corporate organised accord-
 ing to the laws of Germany, of 6230 Frank-
 furt (M) 80, Postfach 80 03 20, Federal
 Republic of 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 par-
 ticularly described in and by the following
 statement:—

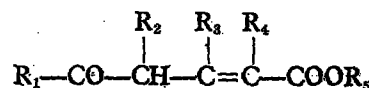
The present invention provides 1-hydroxy-
 2-pyridones of the general formula I



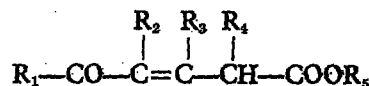
- (I)
 15 in which R₁ represents an alkyl group having
 1 to 17 carbon atoms, or a cycloalkyl group
 having from 5 to 8 carbon atoms, or a cyclo-
 hexylalkyl or phenylalkyl group having 1 to
 20 3 carbon atoms in the alkylene chain or an
 α-furyl group, which groups may be sub-
 stituted by one or more halogen atoms, R₂,
 R₃ and R₄ each represents a hydrogen atom
 or an alkyl group having up to 4 carbon
 25 atoms, an adjacent pair of substituents may
 form together a trimethylene or tetramethyl-
 ene chain, and in which the groups represented
 by R₁ to R₄ together contain at least 2 car-
 bon atoms. The groups represented by R₂, R₃
 and R₄ may be the same or different.
 30 The invention also provides a process for
 the manufacture of a 1 - hydroxy - 2 -
 pyridone of the general formula I as here-

[Price 25p]

inbefore defined, which comprises treating
 an unsaturated δ-keto-ester of the general
 formula



or of the general formula



in which formulae the groups represented by
 R₁, R₂, R₃ and R₄ are as defined above, and
 R₅ represents an alkyl group having up to
 6 carbon atoms, or a mixture of such esters,
 with hydroxylamine, or a salt thereof, or
 a functional derivative thereof, and effecting
 a cyclization of the oxime ester so obtained.
 Examples of hydroxylamine derivatives
 which may be used are hydroxylamine-sul-
 phonic acids and oximes of lower aliphatic
 aldehydes or ketones.

The process of the invention may be varied
 within wide limits. For example, the reaction
 of the unsaturated keto-ester to form the
 hydroxy - pyridone may be carried out in
 several steps, including isolation of the oxime
 ester obtained as intermediate, or the pro-
 cess may be carried out in a single step.

The oxime ester may, for example, be pre-
 pared in a buffered system by the reaction of
 hydroxylamine salt with a keto-ester and ring
 closure may subsequently be effected in a
 stronger acid or alkaline medium.

It is also possible to prepare the hydroxy-
 pyridones of the invention directly in an un-
 buffered system by reacting a keto-ester with
 a hydroxylamine salt, if desired with the
 addition of a mineral acid.

Alternatively, the formation of the oxime

ester and ring closure may be effected by heating the reactants in the presence of a lower fatty acid, for example formic acid or acetic acid: the alkoxy component of the keto-
 5 ester reacts with the fatty acid to form a readily volatile ester which is gradually removed by distillation.

The reaction temperature is not critical for any of the methods described. Conveniently,
 10 however, the reaction temperature is adapted in each case to the particular reaction conditions, for example to the necessary distillation of volatile components. As the Examples will demonstrate, the hydroxypyridones of the
 15 invention can be prepared according to the process of the invention at temperatures in the range of from 0°C to 140°C.

The reaction may be carried out in the presence or absence of solvents. Suitable solvents are, for example, water, lower alcohols,
 20 glycols, glycol ethers, glycerol, lower carboxylic acids, dimethylformamide, dimethylacetamide, N - methyl - pyrrolidone, acetonitrile or dimethylsulphoxide.

The δ - keto - ester used as the starting material can be obtained in an especially advantageous manner by condensation of a carboxylic acid chloride with a β,β - dialkyl - acrylic ester in the presence of a Friedel-
 25 Crafts catalyst.

The following compounds are examples of 1 - hydroxy - 2 - pyridones that can be prepared by the process of the invention:—

- 1-hydroxy-6-methyl-2-pyridone,
- 35 1-hydroxy-4,6-dimethyl-2-pyridone,
- 1-hydroxy-3,4,6-trimethyl-2-pyridone,
- 1-hydroxy-4-methyl-6-ethyl-2-pyridone,
- 1 - hydroxy - 4,6 - dimethyl - 5 - ethyl - 2 -
 40 pyridone,
- 1 - hydroxy - 4 - ethyl - 5,6 - dimethyl - 2 -
 pyridone,
- 1 - hydroxy - 3 - ethyl - 4 - methyl - 6 -
 isobutyl-2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - cyclohexyl -
 45 2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - cyclohexyl-
 methyl-2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - (β - cyclo-
 hexylethyl)-2-pyridone,
- 50 1 - hydroxy - 3,4 - dimethyl - 6 - cyclo-
 pentyl-2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - chloromethyl -
 2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - (β - chloro-
 ethyl)-2-pyridone,
- 55 1 - hydroxy - 4 - methyl - 6 - bromomethyl -
 2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - isopropyl - 2 -
 pyridone,
- 60 1 - hydroxy - 3,6 - dibutyl - 4 - methyl - 2 -
 pyridone,
- 1 - hydroxy - 4 - methyl - 6 - heptyl - 2 -
 pyridone,
- 1 - hydroxy - 4 - methyl - 6 - undecyl - 2 -
 65 pyridone,

- 1 - hydroxy - 3,4 - dimethyl - 6 - benzyl -
 2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - (4 - chloro-
 benzyl)-2-pyridone,
- 1 - hydroxy - 4,5 - trimethylene - 6 - methyl -
 2-pyridone,
- 1 - hydroxy - 4 - methyl - 6 - (α - furyl) -
 2-pyridone,
- 1 - hydroxy - 3,4 - dimethyl - 6 - (4 - fluoro-
 benzyl)-2-pyridone,

The compounds obtainable by the process of the invention have advantages antimycotic properties and are therefore useful medica-
 80 ments against dermatomycoses. They are effective not only against common cutaneous fungi (trichophyton and microsporum species) and against *Candida albicans*, but also against pathogenic germs, for example *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Nocardia asteroides*, *Dermatophilus congolense*,
 85 furthermore *Aspergillus fumigatus* and other moulds, for example *Mucor miechei*, *Absidia corymbifera* and *Aspergillus niger*.

Thus, the invention also provides a pharmaceutical preparation comprising a 1 - hydroxy -
 90 2-pyridone of the general formula I, or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

The compounds of the invention can be
 95 administered in the free form or in the form of salts, especially as salts with physiologically tolerable alkaline compounds. The compounds may be administered in the form of solutions, for example in alcohols or poly-
 100 glycols, creams, ointments, powders or sprays, which are applied superficially to the affected areas of the skin. The pharmaceutically suitable carrier may be, for example, a paraffin, Vaseline (Trade Mark) or lanoline for the
 105 ointments or talc for the powders.

The following Examples illustrate the invention:—

EXAMPLE 1

740 g of hydroxylamine hydrochloride, 110
 750 g of sodium formate and 1.495 g of a mixture of methyl 5 - oxo - 3 - methyl -
 hex - 2 - enoate and methyl 5 - oxo - 3 -
 methyl - hex - 3 - enoate, which mixture had
 been obtained by condensation of acetyl
 115 chloride with β,β - dimethyl - acrylic acid methyl ester, in 1,500 ml of formic acid were heated to 110 to 130°C, whereupon the methyl
 formate which was formed distilled off via
 120 a column. Subsequently, the greater part of the formic acid was distilled off, ice was added to the residue, and the precipitated 1 - hydroxy - 4,6 - dimethyl - 2 - pyridone was
 suction-filtered and washed with cold water. The yield of the compound, which melted at
 125 135°C, was 571 grams. Another 59 g was obtained from the mother liquor. The structure of the substance was confirmed by the elementary analysis: (calculated: 60.5% of C,

6.5% H, 10.0% N; found 60.8% C, 6.8% H, 10.0% N) and from its splitting by boiling it with Raney-nickel in ethanol to form 4,6-dimethyl - 2 - pyridone which is known from the literature.

EXAMPLE 2

19.8 g of isobutyl 5 - oxo - 3 - methyl - hex - 3 - enoate in a solution of 9 g of hydroxylamine sulphate and 3 ml of concentrated sulphuric acid in 30 ml of water were heated to 100°C for 2 hours. After cooling, the pH of the solution was adjusted to 4 by means of sodium carbonate, whereupon 5.15 g of 1 - hydroxy - 4,6 - dimethyl - 2 - pyridone crystallised. Another 1.7 g of the same product was obtained by extraction of the solution by means of methylene chloride.

EXAMPLE 3

78 g of the ester mixture used in Example 1 and 50 ml of methanol were added to a solution of 40 g of hydroxylamine hydrochloride and 26 g of sodium carbonate in 150 ml of water and the mixture was stirred for 5 hours at room temperature. The mixture was then shaken with methylene chloride, the organic phase was washed with water and distilled. 76.5 g of the mixture of isomeric oxime esters were obtained having a boiling point of from 90 to 110°C under a pressure of 0.1 torr. (Calculated: 56.2% C, 7.7% H, 8.2% N, 18.1% OCH₃; found: 56.2% C, 7.8% H, 8.3% N, 17.7% OCH₃). 17.1 g of the distillate and 15 ml of glacial acetic acid were heated for 1 hour at a bath temperature of 140°C and the methyl acetate which formed was distilled off. The residue was placed on ice, whereupon 5.8 g of 1-hydroxy-4,6-dimethyl-2-pyridone crystallised.

EXAMPLE 4

15.6 g of the ester mixture used in Example 1, 8 g of hydroxylamine hydrochloride and 9.4 g of sodium acetate were stirred for 24 hours at 0°C in a mixture of 15 ml of methanol and 15 ml of water. At the same temperature, a solution of 6 g of sodium hydroxide in 12 ml of water was then added, the whole was stirred for 1 hour, acidified to pH 4 and the methanol was distilled off *in vacuo*. 3.5 g of 1 - hydroxy - 4,6 - dimethyl-2-pyridone crystallised from the residue.

EXAMPLE 5

a) 15.6 g of the ester mixture used in Example 1 and a solution of 8 g of hydroxylamine hydrochloride in 25 ml of water were shaken at 25°C, whereupon, after about 4 hours, a homogeneous solution was obtained. After 48 hours the pH-value of the solution was adjusted to 4 by means of sodium carbonate and the precipitated 1 - hydroxy - 4,6 - dimethyl - 2 - pyridone was suction-filtered. The yield was 4.6 grams.

b) 1 - hydroxy - 4 - methyl - 6 - chloromethyl - 2 - pyridone, melting point 196°C, was obtained, under the same reaction conditions, from methyl 5 - oxo - 6 - chloro - 3 - methyl - hex - 2 - enoate. (Calculated: 48.5% C, 4.6% H, 8.1% N, 20.4% Cl; found: 48.7% C, 4.7% H, 8.2% N, 20.2% Cl) and

c) 1 - hydroxy - 3,4,6 - trimethyl - 2 - pyridone, melting point 130°C, was obtained, under the same reaction conditions, from ethyl 5 - oxo - 2,3 - dimethyl - hex - 2 - enoate. (Calculated: 62.7% C, 7.2% H, 9.2% N; found: 62.7% C, 7.1% H, 9.3% N).

EXAMPLE 6

a) 11.2 g of a mixture of methyl 5 - oxo - 3 - methyl - 5 - cyclohexylpent - 2 - enoate and methyl 5 - oxo - 3 - methyl - cyclohexylpent - 3 - enoate which mixture had been obtained by condensation of hexahydrobenzoyl - chloride with β,β - dimethyl - acrylic acid methyl ester, and a solution of 4.6 g of sodium acetate and 4 g of hydroxylamine hydrochloride were shaken for 20 hours at 25°C with a mixture of 8 ml of water and 15 ml of methanol. Subsequently, a solution of 4 g of sodium hydroxide in 8 ml of water was added, while cooling, the reaction mixture was shaken for another hour at room temperature, extracted by means of benzene and the aqueous phase was acidified to reach a pH-value of 6. 3.5 g of 1 - hydroxy - 4 - methyl - cyclohexyl - 2 - pyridone, melting point 144°C, were obtained. (Calculated: 69.5% C, 8.3% H, 6.8% N; found 69.2% C, 8.3% H, 6.8% N).

Under the same conditions there were obtained

b) from methyl 5 - oxo - 3 - methyl - dodec - 2 - enoate, 1 - hydroxy - 4 - methyl - 6 - n - heptyl - 2 - pyridone, melting point 48°C, (calculated 69.9% C, 9.5% H, 6.3% N; found: 70.0% C, 9.5% H, 6.2% N),

c) from methyl 5 - oxo - 3 - ethyl - 4 - methyl - hex - 3 - enoate, 1 - hydroxy - 4 - methyl - 5,6 - dimethyl - 2 - pyridone, melting point 138°C, (calculated: 64.7% C, 7.8% H, 8.4% N; found: 64.9% C, 7.8% H, 8.6% N),

d) from methyl 5 - oxo - 3,4 - trimethylen - hex - 3 - enoate, 1 - hydroxy - 4,5 - trimethylene - 6 - methyl - 2 - pyridone, melting point 178°C (calculated: 65.4% C, 6.7% H, 8.5% N; found: 65.3% C, 6.9% H, 8.4% N),

e) from methyl 5 - oxo - 3 - methyl - 6 - (4 - chlorophenyl) - hex - 2 - enoate, 1 - hydroxy - 4 - methyl - 6 - (4 - chlorobenzyl) - 2 - pyridone, melting point 141°C (calculated: 62.5% C, 4.9% H, 5.6% N; 4.2% Cl; found: 62.3% C, 5.0% H, 5.9% N, 14.4% Cl),

f) from methyl 5 - oxo - 3 - methyl - 6 -

cyclohexyl - hex - 2 - enoate, 1 - hydroxy - 4 - methyl - 6 - cyclohexylmethyl - 2 - pyridone, melting point 131°C (calculated: 70.5% C, 8.7% H, 6.3% N; found: 70.2% C, 8.7% H, 6.5% N) and

5 g) from methyl 5 - oxo - 3 - methyl - 7 - cyclohexyl - hept - 2 - enoate, 1 - hydroxy - 4 - methyl - 6 - (β - cyclohexyl - ethyl) - 2 - pyridone, melting point 90°C (calculated: 71.4% C, 9.0% H, 6.0% N; found: 71.6% C, 8.7% H, 5.8% N).

EXAMPLE 7

8.5 g of methyl 5 - oxo - 3 - methyl - hept - 2 - enoate and a solution of 3.85 g of hydroxylamine hydrochloride and 4.5 g of sodium acetate in 12 ml of water were shaken for 15 hours at room temperature. Subsequently a solution of 4 g of sodium hydroxide in 8 ml of water was added thereto, the mixture was cooled to 0°C after standing for 30 minutes at room temperature, the precipitated sodium salt of the hydroxypyridone was suction-filtered, dissolved in water and free 1 - hydroxy - 4 - methyl - 6 - ethyl - 2 - pyridone was precipitated by acidification to pH 5. The yield was 2.9 g of a compound that melted at 110°C. Calculated: 62.7% C, 7.2% H, 9.2% N; found: 62.7% C, 7.2% H, 9.4% N.

EXAMPLE 8

To a solution of 9.85 g of hydroxylamine hydrochloride and 8 g of tertiary sodium phosphate in 30 ml of water, there were added 20 ml of methanol and 20 g of a mixture of methyl 5 - oxo - 3, 6 - dimethyl - hept - 2 - enoate and methyl 5 - oxo - 3, 6 - dimethyl - hept - 3 - enoate, which mixture had been obtained by condensation of isobutyric acid chloride with β, β - dimethylacrylic acid methyl ester, and the whole was shaken for 15 hours at room temperature. Subsequently a solution of 14 g of sodium hydroxide in 30 ml of water was added thereto, and after having been shaken for 1 hour at room temperature the pH-value of the solution was adjusted to 5 by acidification and the 1-hydroxy - 4 - methyl - 6 - isopropyl - 2 - pyridone was shaken with methylene chloride. 5.6 g of a substance melting at 110°C was obtained. Calculated: 64.6% C, 7.9% H, 8.4% N; found: 64.6% C, 8.0% H, 8.2% N.

EXAMPLE 9

A solution of 260 g of the ester mixture used in Example 1 in 220 ml of methylene chloride was added dropwise within 30 minutes to a boiling solution of 139 g of hydroxylamine hydrochloride in a mixture of 500 ml of water and 50 ml of concentrated hydrochloric acid, whereupon the methylene chloride distilled off. The mixture was heated to 100°C for another hour, subsequently ad-

justed to pH 4 by means of a sodium hydroxide solution, cooled to 0°C, and the precipitate was suction-filtered and washed free from salt with cold water. 110 g of 1-hydroxy - 4, 6 - dimethyl - 2 - pyridone were obtained.

EXAMPLE 10

A solution of 260 g of the ester mixture used in Example 1 in 250 ml of chlorobenzene and 115 g of pulverized hydroxylamine hydrochloride were heated while stirring to 100°C for 4 hours. Subsequently the mixture was cooled to room temperature and the precipitated 1 - hydroxy - 4, 6 - dimethyl - 2 - pyridone was suction-filtered. The yield was 101 g. By dissolution in water and adjusting to a pH of 4, the free hydroxypyridone was obtained.

EXAMPLE 11

18.3 g of acetone-oxime were dissolved in 39 g of the ester mixture used in Example 1, 5 ml of 1N-hydrochloric acid were added thereto and the whole was heated to 150°C in an oil bath. Via a column, the methanol and acetone which were set free were distilled off, heating at 150°C was continued for another 2 hours and the solution was then distilled *in vacuo*.

From the fraction that passed over at 120—150°C under a pressure of 7 torr, 13.4 g of 1 - hydroxy - 4, 6 - dimethyl - 2 - pyridone, melting point 135°C, crystallised upon cooling.

EXAMPLE 12

8 g of hydroxylamine hydrochloride were dissolved in 100 ml of methanol, 10 g of anhydrous sodium acetate and 22.4 g of a mixture of methyl 5 - oxo - 3 - methyl - 5 - cyclohexyl - pent - 2 - enoate and methyl 5 - oxo - 3 - methyl - 5 - cyclohexyl - pent - 3 - enoate were added thereto and the whole was stirred for 20 hours at 0°C. Subsequently a solution of 10 g of sodium hydroxide in 15 ml of water was added and stirring was continued for another 10 hours at 0°C. Most of the methanol was distilled off *in vacuo*, the residue was taken up in 100 ml of water, extracted with methylene chloride, the pH of the solution was adjusted to 2 by acidification, the solution was shaken once more with methylene chloride, the acid extract obtained was concentrated *in vacuo* and 50 ml of concentrated hydrochloric acid were added thereto. The hydrochloride of 1 - hydroxy - 4 - methyl - 6 - cyclohexyl - 2 - pyridone which crystallised was suction filtered, washed with concentrated hydrochloric acid and converted into the free hydroxy-pyridone by trituration with 100 ml of water.

EXAMPLE 13

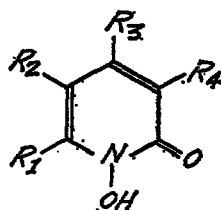
52 g of a mixture of methyl 5 - oxo - 3 -

- methyl - 5 - (α - furyl) - pent - 2 - enoate and methyl 5 - oxo - 3 - methyl - 5 - (α - furyl) - pent - 3 - enoate which mixture had been obtained by condensation of pyromucic acid chloride with β,β -dimethylacrylic acid methyl ester, were heated to 80°C for 6 hours with 20 g of hydroxylamine hydrochloride, 20 g of sodium formate and 75 ml of formic acid. Subsequently the formic acid was distilled off *in vacuo*, water was added to the residue and the mixture was shaken three times with 25 ml each of methylene chloride. The combined organic phases were washed with 25 ml of water, then shaken with a solution of 5 g of sodium carbonate in 30 ml of water and finally cooled to 0°C. 3.2 g of the sodium salt crystallized, were dissolved in water and acidified to form the free 1 - hydroxy - 4 - methyl - 6 - (α - furyl) - 2 - pyridone having a melting point of 146°C.

Calculated: 62.8% C, 4.8% H, 7.3% N
Found: 63.0% C, 4.7% H, 7.4% N.

WHAT WE CLAIM IS:—

1. 1 - Hydroxy - 2 - pyridones of the general formula I



(I)

- in which R_1 represents an alkyl group having 1 to 17 carbon atoms, or a cycloalkyl group having from 5 to 8 carbon atoms, or a cyclohexylalkyl or phenylalkyl group having 1 to 3 carbon atoms in the alkylene chain or an α -furyl group, which groups may be substituted by one or more halogen atoms, R_2 , R_3 and R_4 each represents a hydrogen atom or an alkyl group having up to 4 carbon atoms, an adjacent pair of substituents may form together a trimethylene or tetramethylene chain, and in which the groups represented by R_1 to R_4 together contain at least 2 carbon atoms.

2. 1-Hydroxy-4,6-dimethyl-2-pyridone.
3. 1-Hydroxy-4-methyl-6-ethyl-2-pyridone.
4. 1 - Hydroxy - 4 - methyl - 6 - isopropyl-2-pyridone.
5. 1 - Hydroxy - 4 - methyl - 6 - heptyl - 2-pyridone.
6. 1 - Hydroxy - 4 - methyl - 6 - chloromethyl-2-pyridone.
7. 1 - Hydroxy - 4 - methyl - 6 - cyclohexyl-2-pyridone.

8. 1 - Hydroxy - 3,4,6 - trimethyl - 2 - pyridone.

9. 1 - Hydroxy - 4 - ethyl - 5,6 - dimethyl - 2-pyridone.

10. 1 - Hydroxy - 4,5 - trimethylene - 6 - methyl-2-pyridone. 55

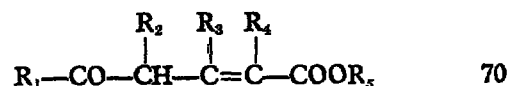
11. 1 - Hydroxy - 4 - methyl - 6 - cyclohexylmethyl-2-pyridone.

12. 1 - Hydroxy - 4 - methyl - 6 - (β - cyclohexylethyl)-2-pyridone. 60

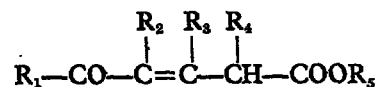
13. 1 - Hydroxy - 4 - methyl - 6 - (4 - chlorobenzyl)-2-pyridone.

14. 1 - Hydroxy - 4 - methyl - 6 - (α - furyl)-2-pyridone.

15. A process for the manufacture of a 1-hydroxy - 2 - pyridone of the general formula I as defined in claim 1, which comprises treating an unsaturated δ -keto-ester of the general formula



or of the general formula



in which formulae the groups represented by R_1 , R_2 , R_3 and R_4 are as defined in claim 1, and R_5 represents an alkyl group having up to 6 carbon atoms, or a mixture of two or more of such esters, with hydroxylamine, or a salt thereof, or a functional derivative thereof, and effecting a cyclisation of the oxime ester so obtained. 75

16. A process as claimed in claim 15, wherein the cyclisation is effected under acid conditions. 80

17. A process as claimed in claim 15, wherein the cyclisation is effected under alkaline conditions. 85

18. A process as claimed in claim 15, conducted substantially as described in any one of the Examples herein.

19. A compound of the general formula I as defined in claim 1, whenever prepared by a process as claimed in any one of claims 15 to 18. 90

20. A salt of a compound as claimed in any one of claims 1 to 14. 95

21. A physiologically tolerable salt of a compound as claimed in any one of claims 1 to 14.

22. A pharmaceutical preparation compris-

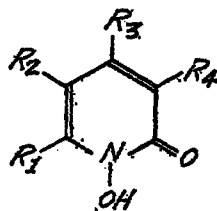


5 methyl - 5 - (α - furyl) - pent - 2 - enoate and methyl 5 - oxo - 3 - methyl - 5 - (α - furyl) - pent - 3 - enoate which mixture had been obtained by condensation of pyromucic acid chloride with β,β -dimethylacrylic acid methyl ester, were heated to 80°C for 6 hours with 20 g of hydroxylamine hydrochloride, 20 g of sodium formate and 75 ml of formic acid. Subsequently the formic acid was distilled off *in vacuo*, water was added to the residue and the mixture was shaken three times with 25 ml each of methylene chloride. The combined organic phases were washed with 25 ml of water, then shaken with a solution of 15 5 g of sodium carbonate in 30 ml of water and finally cooled to 0°C. 3.2 g of the sodium salt crystallized, were dissolved in water and acidified to form the free 1 - hydroxy - 4 - methyl - 6 - (α - furyl) - 2 - pyridone having a melting point of 146°C.

Calculated: 62.8% C, 4.8% H, 7.3% N
Found: 63.0% C, 4.7% H, 7.4% N.

WHAT WE CLAIM IS:—

25 1. 1 - Hydroxy - 2 - pyridones of the general formula I



in which R_1 represents an alkyl group having 1 to 17 carbon atoms, or a cycloalkyl group having from 5 to 8 carbon atoms, or a cyclohexylalkyl or phenylalkyl group having 1 to 30 3 carbon atoms in the alkylene chain or an α -furyl group, which groups may be substituted by one or more halogen atoms, R_2 , R_3 and R_4 each represents a hydrogen atom or an alkyl group having up to 4 carbon atoms, an adjacent pair of substituents may form together a trimethylene or tetramethylene chain, and in which the groups represented by R_1 to R_4 together contain at least 40 2 carbon atoms.

2. 1-Hydroxy-4,6-dimethyl-2-pyridone.
3. 1-Hydroxy-4-methyl-6-ethyl-2-pyridone.
4. 1 - Hydroxy - 4 - methyl - 6 - isopropyl-2-pyridone.
- 45 5. 1 - Hydroxy - 4 - methyl - 6 - heptyl - 2-pyridone.
6. 1 - Hydroxy - 4 - methyl - 6 - chloromethyl-2-pyridone.
7. 1 - Hydroxy - 4 - methyl - 6 - cyclohexyl-2-pyridone.

8. 1 - Hydroxy - 3,4,6 - trimethyl - 2 - pyridone.

9. 1 - Hydroxy - 4 - ethyl - 5,6 - dimethyl - 2-pyridone.

10. 1 - Hydroxy - 4,5 - trimethylene - 6 - methyl-2-pyridone. 55

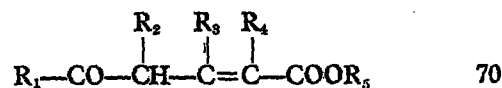
11. 1 - Hydroxy - 4 - methyl - 6 - cyclohexylmethyl-2-pyridone.

12. 1 - Hydroxy - 4 - methyl - 6 - (β - cyclohexylethyl)-2-pyridone. 60

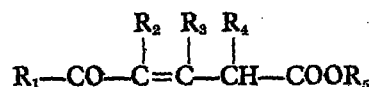
13. 1 - Hydroxy - 4 - methyl - 6 - (4 - chlorobenzyl)-2-pyridone.

14. 1 - Hydroxy - 4 - methyl - 6 - (α - furyl)-2-pyridone.

15. A process for the manufacture of a 1-hydroxy - 2 - pyridone of the general formula I as defined in claim 1, which comprises treating an unsaturated δ -keto-ester of the general formula 65



or of the general formula



in which formulae the groups represented by R_1 , R_2 , R_3 and R_4 are as defined in claim 1, and R_5 represents an alkyl group having up to 6 carbon atoms, or a mixture of two or more of such esters, with hydroxylamine, or a salt thereof, or a functional derivative thereof, and effecting a cyclisation of the oxime ester so obtained. 75

16. A process as claimed in claim 15, wherein the cyclisation is effected under acid conditions. 80

17. A process as claimed in claim 15, wherein the cyclisation is effected under alkaline conditions. 85

18. A process as claimed in claim 15, conducted substantially as described in any one of the Examples herein.

19. A compound of the general formula I as defined in claim 1, whenever prepared by a process as claimed in any one of claims 15 to 18. 90

20. A salt of a compound as claimed in any one of claims 1 to 14. 95

21. A physiologically tolerable salt of a compound as claimed in any one of claims 1 to 14.

22. A pharmaceutical preparation compris-



ing a compound as claimed in claim 1 or claim 21 in admixture or conjunction with a pharmaceutically suitable carrier.

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