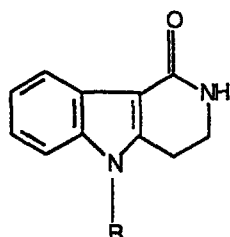


PROCESS FOR THE PREPARATION OF LACTAM DERIVATIVES

This invention relates to a process for the preparation of compounds which are useful as intermediates in the preparation of pharmaceutical compounds.

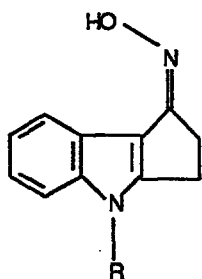
The compounds of formula (I):



(I)

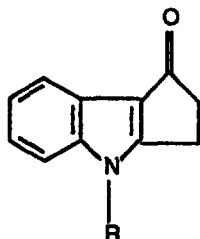
wherein R represents a hydrogen atom or a methyl group, are useful intermediates in the preparation of 2,3,4,5-tetrahydro-2-[(imidazol-4 (or 5)-yl)methyl]-1H-pyrido[4,3-b]indol-1-ones, such as those disclosed in EP-A-306323. In particular the compound of formula (I) wherein R is a methyl group is useful in the preparation of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, and its physiologically acceptable salts and solvates.

The method for the preparation of the compounds of formula (I) described in EP-A-306323 involves a Beckmann rearrangement of an oxime of formula (II):



(II)

the oxime of formula (II) being prepared by the reaction of a ketone of formula (III):



(III)

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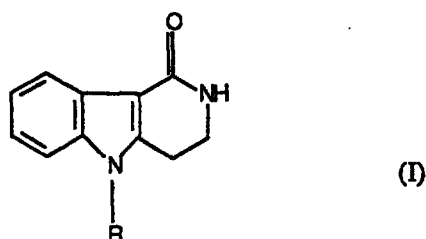
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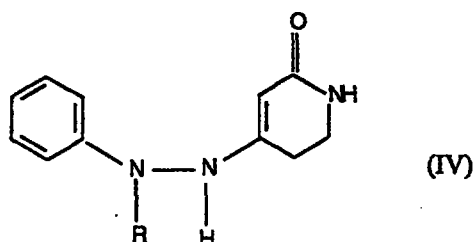
with hydroxylamine hydrochloride. The compounds of formula (III) are prepared according to the method of H. Iida *et al.*, in *J. Org. Chem.* 1980, 45, 2938, i.e. by palladium (II) acetate catalysed cyclisation of the product obtained by the reaction of an aniline with 1,3-cyclopentanedione, followed by an optional *N*-methylation reaction.

An advantageous method for the preparation of compounds of formula (I) has now been discovered, which involves fewer reaction stages and gives the desired product in a higher overall yield.

Thus the present invention provides a process for the preparation of a compound of formula (I):



wherein R represents a hydrogen atom or a methyl or ethyl group, which comprises cyclising a compound of formula (IV):



wherein R is as defined previously, and when the compound of formula (I) wherein R represents a hydrogen atom is obtained, optionally alkylating this compound to give the compound of formula (I) wherein R represents a methyl or an ethyl group.

The reaction may be effected in the presence or absence of an acid catalyst.

When the reaction is effected in the presence of an acid catalyst, suitable acids include 80-100% w/w sulphuric acid, a mixture of 100% w/w sulphuric acid and glacial acetic acid, 85% orthophosphoric acid, and hydrocarbylsulphonic acids (e.g. methanesulphonic acid). When sulphuric acid is used, the reaction may be effected

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in the presence of a suitable co-solvent such as an alcohol (e.g. ethanol) or a halogenated hydrocarbon (e.g. dichloromethane).

The acid-catalysed reaction may conveniently be effected at a temperature in the range 0 to 100°C.

Alternatively, the reaction may be effected in the presence of a Lewis acid such as zinc chloride in acetic acid at an elevated temperature (e.g. 110°C); or in the presence of polyphosphate ester in a halogenated hydrocarbon such as chloroform at the reflux temperature of the solvent.

In a yet further embodiment, the reaction may be carried out in the absence of catalyst at elevated temperature using a high boiling solvent, for example diethylene glycol at 180°C.

Most preferably, the reaction is effected in the presence of 80-100% w/w sulphuric acid or a mixture of 100% w/w sulphuric acid and glacial acetic acid at a temperature in the range 0 to 30°C, most preferably 0 to 5°C.

The reaction of the compounds of formula (I) wherein R represents a hydrogen atom to give the compound of formula (I) wherein R represents a methyl or ethyl group may be effected with an alkylating agent (e.g. dimethyl sulphate), in an organic solvent such as acetone, in the presence of a base such as dilute aqueous sodium hydroxide at an elevated temperature (e.g. 50°C).

A preferred embodiment of the process of the invention comprises the cyclisation of the compound of formula (IV) wherein R represents a methyl group to give 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one, i.e. the compound of formula (I) wherein R represents a methyl group.

A further preferred embodiment of the process according to the invention comprises the cyclisation of the compound of formula (IV) wherein R represents a hydrogen atom to give 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one which is then methylated with a suitable methylating agent such as dimethyl sulphate to give 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one.

Compounds of formula (IV) may be prepared, for example, by the reaction of a phenylhydrazine of formula PhNRNH₂ (i.e. phenylhydrazine, 1-methyl-1-phenylhydrazine or 1-ethyl-1-phenylhydrazine) with 2,4-piperidinedione. The

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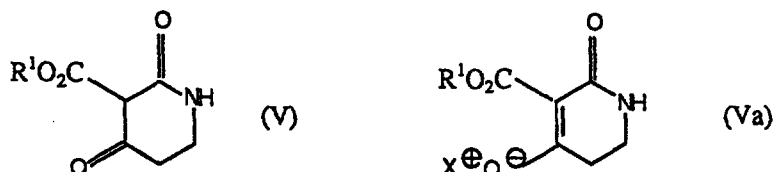


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reaction may conveniently be effected in a solvent such as an alcohol (e.g. ethanol), and at a temperature in the range 20-25°C.

The phenylhydrazine used in the above reaction may be in the form of the free base, or a salt of the phenylhydrazine (e.g. a sulphate) may be used and the free base generated in situ.

5 2,4-Piperidinedione may also conveniently be prepared in situ, from a compound of formula (V):



10

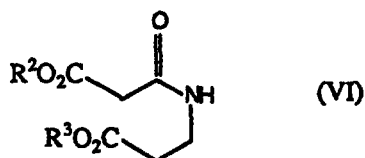
wherein R¹ represents a lower alkyl (e.g. methyl or ethyl) group, or an alkali metal (e.g. sodium) alkoxide thereof (i.e. a compound of formula (Va) wherein X⁺ represents an alkali metal ion), by hydrolysis and decarboxylation under acidic conditions (e.g. at pH2), at an elevated temperature. Where necessary, the appropriate pH may be achieved by addition of a mineral acid (e.g. hydrochloric acid).

15

Compounds of formula (IV) may also be prepared directly from a compound of formula (V) or an alkali metal alkoxide thereof without isolation of 2,4-piperidinedione. Thus compounds of formula (IV) may be prepared by treating a compound of formula (V) or (Va) under acidic conditions (which may be achieved where necessary by addition of a mineral acid e.g. dilute hydrochloric acid) at an elevated temperature, followed by reaction of the resultant cooled solution with an appropriate phenylhydrazine, or a salt thereof, in the presence of an aqueous alkali metal hydroxide (e.g. aqueous sodium hydroxide).

20

25 Compounds of formula (V) and (Va) may be prepared from a compound of formula (VI):



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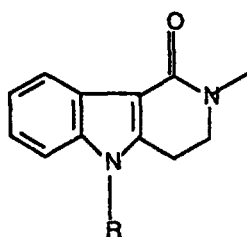
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wherein R^2 and R^3 independently represent a lower alkyl (e.g. methyl or ethyl) group, by reaction with an alkali metal alkoxide (e.g. sodium methoxide) in an alcohol (e.g. methanol) at the reflux temperature of the solvent.

Compounds of formula (VI) are either known, or may be prepared by reaction of an alkyl ester of 3-aminopropionic acid with a malonic alkyl ester.

5 Thus an alkyl ester of 3-aminopropionic acid may be reacted directly with a malonic acid diester; or with a more reactive derivative of malonic acid, such as an acid chloride or a mixed acid anhydride; or with a malonic acid monoalkyl ester in combination with a suitable activating agent such as dicyclohexylcarbodiimide.

10 According to a further aspect, the invention provides a process for the preparation of compounds, particularly 5-HT₃ antagonists, containing the group



15

wherein R is as defined previously, which comprises reacting a compound of formula (I) prepared as described above, with an appropriate imidazole derivative (e.g. 4-hydroxymethyl-5-methylimidazole). Thus in accordance with this aspect of the invention, 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one may be prepared from 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one by reaction with 4-hydroxymethyl-5-methylimidazole or a salt (e.g. the hydrochloride) thereof. The reaction may be carried out in the presence of an acid (e.g. p-toluenesulphonic acid) at an elevated temperature.

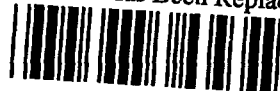
20

The invention is illustrated by the following Intermediates and Examples. All temperatures are in ⁰C. Thin layer chromatography (t.l.c.) was carried out on silica. Solvent System A as used for t.l.c. denotes dichloromethane:ethanol : 0.88 ammonia solution and solvent System B denotes dichloromethane:methanol : 0.88 ammonia solution. ¹H-N.m.r. spectra were obtained at 250MHz for dilute solutions in d₆-dimethyl sulphoxide.

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Intermediate 1

5,6-Dihydro-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone

1-Methyl-1-phenylhydrazine (21.6g) was added to a suspension of 2,4-piperidinedione (20.0g) in industrial methylated spirit (100ml) at 20-25⁰ under nitrogen. The resultant solution was stirred for 3h at room temperature. Water (300ml) was added and the resulting suspension was filtered to give the title compound (34.4g) as a solid, m.p. 180.5-182⁰.

Intermediate 2

5,6-Dihydro-4-(2-phenylhydrazino)-2(1H)-pyridinone

Phenylhydrazine (17.4ml) was added over 15min to a stirred suspension of 2,4-piperidinedione (20g) in ethanol (200ml) at ca. 20⁰. The resulting suspension was diluted with ethanol (80ml) and water (300ml) and the solid was filtered off to give the title compound (23.31g), m.p. 165-168⁰.

Intermediate 3

3-Piperidinecarboxylic acid, 2,4-dioxo-, methyl ester, ion(1-), sodium

A mixture of N-(3-ethoxy-1,3-dioxopropyl)- β -alanine, methyl ester (10.8g) and 21% w/w methanolic sodium methoxide (32ml) in methanol (16ml) was heated at reflux for ca. 3h. The resulting suspension was cooled to ca. 0⁰ and filtered to give the title compound (9.0g) as a solid.

¹H-N.m.r. (D₂O): δ 2.38(2H,t), 3.28(2H,t), 3.68(3H,s).

IR (nujol mull) : 3300, 1660, 1610 cm⁻¹.

Intermediate 4

5,6-Dihydro-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone

A suspension of 3-piperidinecarboxylic acid, 2,4-dioxo-, methyl ester, ion (1-), sodium (10.0g) in water (24ml) and 2M aqueous hydrochloric acid (26ml) was heated at reflux for 30 min. The resulting mixture was cooled to ca. 20⁰, diluted with industrial methylated spirit (25ml) and treated with 1-methyl-1-phenylhydrazine sulphate (2:1) (8.8g) and 5M aqueous sodium hydroxide (12ml).

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The resulting suspension was diluted with water (25ml), cooled to ca. 0⁰ and filtered to give the title compound (9.1g), m.p. 185⁰.

Intermediate 5

5,6-Dihydro-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone

5 A mixture of 3-piperidinecarboxylic acid, 2,4-dioxo-,methyl ester (10.0g) in industrial methylated spirits and water (1:1) (50ml) and 5M aqueous hydrochloric acid (0.4ml) was heated at 50-55⁰ for 30min, and then heated at reflux for 1.5h. The resulting mixture was cooled to room temperature and treated with 1-methyl-1-phenylhydrazine sulphate (2:1)(9.9g) and 5M aqueous sodium hydroxide (11.6ml).
10 Water (5.5ml) was added, and more water (33ml) was added slowly over 45min. The resultant solid was filtered off, washed with water (3x8ml) and dried in vacuo at 43⁰ to give the title compound (10.7g), m.p. 180-181⁰.

Example 1

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one

5,6-Dihydro-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone (337g) was added portionwise over 1.5h to a stirred mixture of concentrated sulphuric acid (675ml) and water (236ml) at 13-15⁰. The mixture was allowed to warm to ambient temperature over 2h, then cooled to 13⁰ and added dropwise to 2N sodium
20 hydroxide (6.07l) at 10⁰. The resultant suspension was cooled to 8⁰ and filtered. The solid product was triturated with water (2l), then ethanol (0.85l) at reflux, to provide the title compound (270g), t.l.c. (System A, 100:8:1) Rf 0.41.
¹H-N.m.r: δ 3.04 (2H,t), 3.52 (2H,dt), 3.75 (3H,s), 7.08 (1H,br.t), 7.20 (2H,m), 7.53 (1H,dd), 7.96 (1H,dd).

25

Example 2

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one

A solution of 5,6-dihydro-4-(2-methyl-2-phenylhydrazino)- 2(1H)-pyridinone (100g) in glacial acetic acid (200ml) was added dropwise to concentrated sulphuric
30 acid (200ml) at 10-20⁰. The mixture was stirred at ambient temperature for 1h, then

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cooled to 10⁰ and added slowly to 2N sodium hydroxide (1.8l) at 5⁰. The resultant suspension was cooled to 2⁰ and filtered. The solid product was triturated with water (0.6l), then ethanol (250ml) at reflux, to provide the title compound (72g), m.p. 240-245⁰, t.l.c. (System A, 100:8:1) Rf 0.41.

5 Example 3

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one

A solution of 5,6-dihydro-4-(2-phenylhydrazino)-2(1H)-pyridinone (8.0g) in acetic acid (16ml) was added over 30 min to concentrated sulphuric acid (16ml) at 10-20⁰. The reaction mixture was stirred for 2h, then added over 10 min to 2N sodium
10 hydroxide (150ml) at 15-25⁰. The solid product was filtered off, triturated with water (50ml), then recrystallised from ethanol (20ml) and dried in vacuo to give the title compound (3.79g), m.p. 255⁰, t.l.c. (System B, 100:8:1) Rf 0.2.

Example 4

15 2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one

5,6-Dihydro-4-(2-phenylhydrazino)-2(1H)-pyridinone (5.0g) was added portionwise over 1h to a mixture of concentrated sulphuric acid (10ml) and water (3.5ml) at ca. 20⁰, and the resulting mixture was aged for 18h at ambient temperature. The solution was then added to a mixture of 2N sodium hydroxide (94ml) and
20 dichloromethane (20ml). The solid product was filtered off and dried in vacuo at 45⁰ to give the title compound (2.99g), m.p. 255⁰, t.l.c. (System B, 100:8:1) Rf 0.2.

Example 5

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one

25 Dimethylsulphate (2.28ml) was added over 5 min to a stirred mixture of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (3g), acetone (12ml) and 20% w/v aqueous sodium hydroxide (9ml) at ca. 50⁰. The mixture was heated at reflux for 10 min. Further sodium hydroxide (6ml) was added and the mixture was heated at reflux for 5 min. On cooling a solid crystallised. Water (10ml) was added and the mixture was
30 filtered. The solid was washed with water (2x20ml), and dried in vacuo 45⁰ to give

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the title compound (3.16g). The t.l.c. data for this material were consistent with those obtained for the product of Example 1.

Analysis	Found:	C,71.8; H,6.2; N,14.0;
$C_{12}H_{12}N_2O$	requires	C,72.0; H,6.0; N,14.0%.

5 Example 6

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one

A solution of 5,6-dihydro-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone (250g) in glacial acetic acid (500ml) was added over ca. 2h to concentrated sulphuric acid (500ml) at 0-5⁰. The mixture was stirred at 0-5⁰ for a further ca. 1h then added over ca. 30min. to 2N aqueous sodium hydroxide (4.5l) at 20-30⁰. The solid product was isolated by filtration, washed by displacement with water (4.5l) and triturated with ethanol (625ml) at reflux to provide the title compound (185g), m.p. 240-244⁰, t.l.c. (System A, 100:8:1) Rf 0.4

Example 7

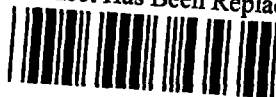
15 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (49.97g), p-toluenesulphonic acid monohydrate (9.50g) and 4-hydroxymethyl-5-methylimidazole hydrochloride (20.25g) in N-methylpyrrolidinone (250ml) was stirred and heated to 125⁰ (over 1h) The reaction was then heated at 125-130⁰ for 4.5h, during which time two further portions of 4-hydroxymethyl-5-methylimidazole hydrochloride (17.51g and 6.88g) were added. The reaction mixture was cooled, diluted with water (100ml), and the stirred mixture was treated slowly with 8% aqueous sodium bicarbonate (750ml). The resultant suspension was stirred in an ice bath for 1h and then filtered to give a solid (57.64g). A portion of this solid (11.09g) was dissolved in dichloromethane (307ml) and ethanol (166ml), boiled with decolourising charcoal for 10min and then filtered. The dichloromethane was distilled off at atmospheric pressure until the temperature of the mixture was at 65⁰.

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The stirred mixture was cooled and the resulting precipitate was filtered off to give the title compound (9.28g), t.l.c. (System A, 50:8:1) Rf 0.55.

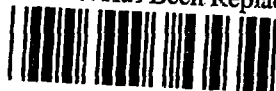
¹H-N.m.r: δ 2.20(3H,s), 3.03(2H,t), 3.64(2H,m), 3.71(3H,s), 4.50(2H,s), 7.19(2H,m), 7.44(1H,s), 7.50(1H,d), 7.99(1H,d), 11.76(1H,s).

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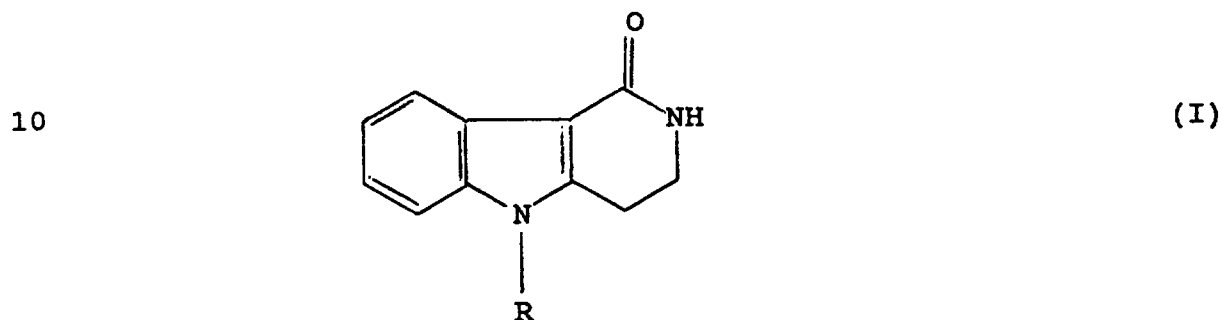
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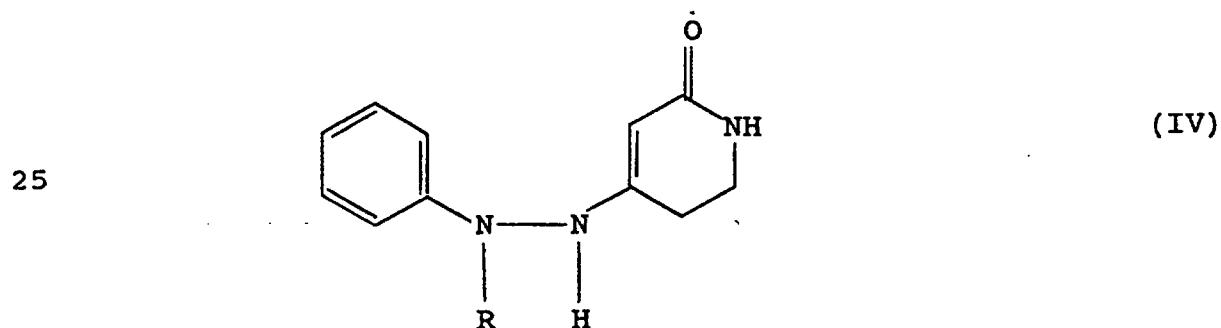
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**CLAIMS**

1. A process for the preparation of a compound of
5 formula (I)



wherein R represents a hydrogen atom or a methyl or ethyl
group, which comprises cyclising a compound of formula
20 (IV)



and where R represents a hydrogen atom, optionally
alkylating the compound of formula (I) produced to give
the compound of formula (I) in which R is methyl or ethyl.

- 35 2. A process as claimed in claim 1, wherein the
cyclisation is carried out in the presence of an acid

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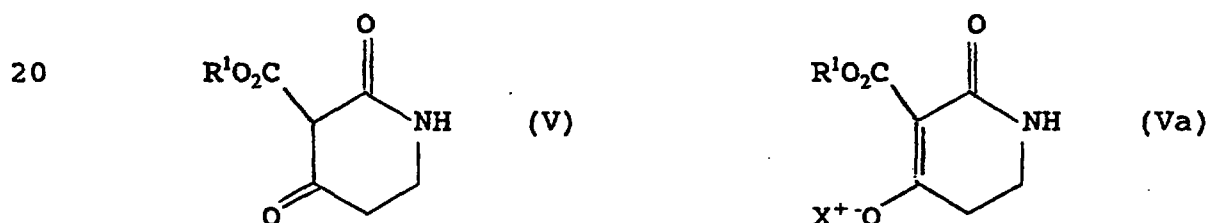


catalyst at a temperature of 0 to 100°C.

3. A process as claimed in claim 2, carried out in the presence of 80 to 100% w/w sulphuric acid or a mixture of 100% w/w sulphuric acid and glacial acetic acid at a temperature in the range 0 to 30°C.

4. A process as claimed in any of claims 1 to 3, wherein the compound of formula (IV) is prepared by reaction of 2,4-piperidinedione with a compound of formula PhNRNH_2 where R is a hydrogen atom or a methyl or ethyl group, or a salt thereof.

5. A process as claimed in claim 4, wherein the 2,4-piperidinedione is prepared from a compound of formula (V) or an alkali metal alkoxide thereof (Va)



25 wherein R' represents a lower alkyl group and X represents an alkali metal, by hydrolysis and decarboxylation under acidic conditions at elevated temperature.

30 6. A process as claimed in claim 5, wherein the compound of formula (IV) is prepared directly by treating the compound of formula (V) or (Va) under acidic conditions at elevated temperature and subsequent reaction of the resultant cooled solution with a phenylhydrazine of formula PhNRNH_2 , or a salt thereof without isolation of the 2,4-piperidinedione.

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7. A process as claimed in claim 5 or 6, wherein the compound of formula (V) or (Va) is prepared from a compound of formula (VI)

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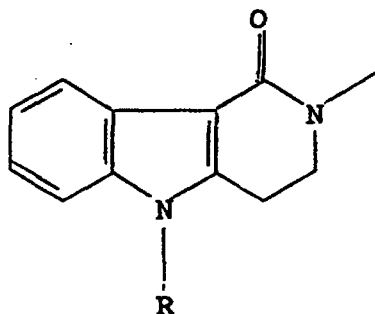


15 wherein R^2 and R^3 each independently represent lower alkyl groups, by reaction with an alkali metal alkoxide.

20 8. A process as claimed in any of claims 1 to 7, for the preparation of a compound of formula (I) in which R represents a methyl group.

25 9. A process as claimed in any of claims 1 to 8, wherein the compound of formula (I) is subsequently used for the preparation of a compound containing a

30



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group.

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10. A process as claimed in claim 9, wherein the compound of formula (I) is reacted with an imidazole derivative.

5 11. A process as claimed in Claim 10, wherein the compound of formula (I) in which R is methyl is reacted with 4-hydroxymethyl-5-methylimidazole or a salt thereof to produce 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

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