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PATENT SPECIFICATION (11) 1 542 137

1 542 137

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(23) Complete Specification filed 2 June 1977
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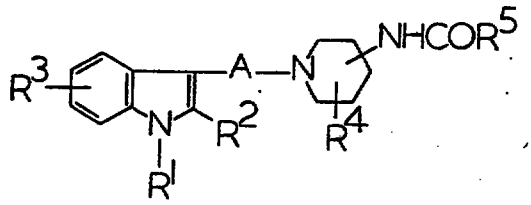
(72) Inventor GEORGE OLIVER WESTON

(54) NEW PROCESS FOR PREPARING 3(PIPERIDINOALKYL) INDOLES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, 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:—

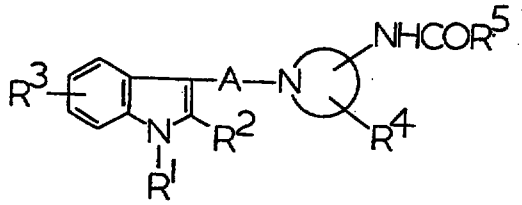
The invention relates to a novel process for preparing indole derivatives.

Accordingly the invention provides a process for preparing compounds of general formula (III)



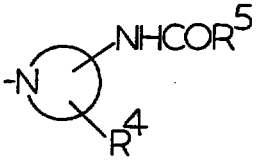
(III)

and acid addition salts thereof, wherein R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl, R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, halogen or lower alkyl, R^5 represents aryl (including heterocyclic aryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or cycloalkyl of 5 to 7 carbon atoms, and A is an alkylene radical of 1—4 carbon atoms characterised in that a compound of formula I



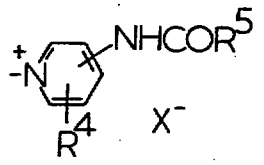
(I)

in which formula



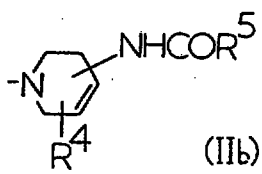
(II)

represents a ring system of general formula



(IIa)

or



(IIb)

wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined in connection with formula (III) and X is an anion, is reduced with an alkali-metal borohydride in a secondary alkanol of 3 to 5 carbon atoms to fully reduce the ring system of formula (IIa) or (IIb), and if desired converting the product to an acid addition salt.

Preferably the solvent is isopropanol (bp 82.5°C), sec-butanol or pentan-2-ol. Of these isopropanol is particularly preferred.

The reduction is preferably carried out at a temperature in the range from 80 to 120°C. Conveniently the reduction is effected in the chosen solvent at reflux temperature.

Preferably the alkali-metal borohydride is employed in a molar ratio of from 1 mol per double bond in each mol of starting material. Thus for a starting compound containing a ring system of formula (IIa) at least 3 mols of borohydride are preferred per mol of starting material, for a starting material containing a ring system of formula (IIb), at least one mol of borohydride per mol of starting material is preferred: If desired an excess of borohydride can be used.

However, it has been found for a starting material of formula (IIa) quite good yields (e.g. of the order of 75%) can be obtained with 2 mols borohydride per mol of compound with ring system IIa. Reasonable yields are obtainable with even lesser amounts. Hence the desirable amounts are at least 0.25 mol (desirable at least 0.5 mol) borohydride per double bond for compound with ring system IIa or IIb, plus in the case of compound with ring system IIa an additional 1 mol for the quaternary salt which acts in a similar manner to a Lewis acid.

The terms "lower alkyl" and "lower alkoxy" as used herein mean the radical contains from 1 to 6, preferably 1 to 4 carbon atoms and the term "lower aralkyl" means the radical contains 7 to 10, preferably 7 to 9 carbon atoms. The "lower alkylene" group may be branched or straight chain group, containing up to 4 carbon atoms. A is preferably the ethylene radical.

Examples of R^1 are hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, benzyl, benzoyl and p-chlorobenzoyl. Preferably R^1 is a hydrogen atom. R^2 can be, for example, hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or substituted or unsubstituted phenyl and is preferably hydrogen or methyl. R^3 can be, for example, hydrogen, chlorine, methoxy, ethoxy, hydroxy, methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl. Preferably R^3 is a hydrogen atom.

Examples of R^4 are hydrogen, chlorine, methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl, though preferably R^4 is a hydrogen atom.

R^5 can be, for example, phenyl, substituted phenyl (e.g. phenyl substituted by halogen such as chlorine, by alkoxy, such as methoxy or ethoxy or by alkyl such as methyl or ethyl), heterocyclic radicals (such as 3-indolyl, 2-thienyl, benzodioxolyl or 2-furyl), methoxy, ethoxy, phenoxy, benzyl, benzyloxy and diphenylmethyl.

X is preferably a halide ion such as a chloride or bromide. R^5 when cycloalkyl is preferably a cyclohexyl.

The products of this invention are of value as pharmaceuticals as described in our U.K. Patent Specification 1,218,570 or 1,273,563, for instance as hypotensive or antihypertensive agents or antihistamine agents.

The process of the invention provides a convenient way of preparing indoramin, a compound first described in U.K. Patent Specification 1,218,570 which is now undergoing clinical trials as a hypotensive agent.

The alkali-metal borohydride may be lithium, sodium or potassium borohydride but sodium borohydride is greatly preferred.

The starting compounds of formula I are known in the literature and are particularly described for example in U.K. Patent Specification 1,218,570 or 1,273,563.

The process of the invention is surprising since normal borohydride reductions in methanol of a compound of formula I containing ring system (IIa) stop at a compound of formula (IIb) and it is necessary to employ catalytic hydrogenation to obtain full reduction to a compound of formula I. This process has advantages in commercial production since it avoids the necessity for catalytic hydrogenation on a plant scale. The new method also does not cause reduction of the carbonyl group of an amide link or removal of groups susceptible to hydrogenolysis such as benzyloxycarbonyl.

The invention is illustrated by the following examples.

Example 1

3-[2-(4-Benzamido-1-piperidyl)ethyl]indole (indoramin)

A suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (4.2 g.) and sodium borohydride (1.14 g.) in isopropanol (50 ml.) was refluxed for 3½ hours. After cooling, the reaction mixture was diluted with water (50 ml.). The product was separated by filtration, washed with water then with acetone and dried to give the title compound in 82% yield, m.p. 203—5°C.

This sample was converted to the hydrochloride m.p. 253—6° by treatment with methanol/HCl/ethyl acetate, followed by isopropanol at reflux.

The above example is to be contrasted with Example 6 of U.K. Specification 1,218,570 where reduction of the same starting material with sodium borohydride in methanol gave 3-[2-(4-Benzamido-1,2,5,6-tetrahydropyrid-1-yl)ethyl]indole.

Repetition of the above Example using sodium borohydride in refluxing ethanol also gave the tetrahydropyridine of Example 6 of Specification 1,218,570.

Example 2

3-[2-(3-benzamido-1-piperidyl)ethyl]indole

Following the procedure of Example 1 above 3-benzamido-1-[2-(3-indolyl)ethyl]-pyridinium bromide upon reduction with sodium borohydride in isopropanol gives the title compound.

In contrast, treatment of this starting material with sodium borohydride in methanol gives the tetrahydropyridine (Example 7 of U.K. Specification 1,218,570).

Example 3

3-[2-(4-[4-chlorobenzamido]-piperid-1-yl)-ethyl]indole

4-(4-chloro)benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide is reduced with sodium borohydride in refluxing isopropanol according to the procedure of Example 1 to obtain the title compound.

In contrast treatment of the above pyridinium compound with sodium borohydride in methanol gives the 3-[2-(4-[4-benzamido]-1,2,5,6-tetrahydropyrid-1-yl)-ethyl]indole—see Example 9 of U.K. Specification 1,218,570.

Example 4

3-[2-(4-benzamido-1-piperidyl)ethyl]indole

A suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (7.3 kg.) and sodium borohydride (2.5 kg.) in isopropanol 57 kg.) was stirred and refluxed for 6 hours. The reaction mixture was cooled to 25° and diluted with water. The product was separated by filtration and washed with aqueous methanol then with water and finally with methanol, and dried to give 4.45 kg. of the crude title compound. This was purified by dissolving in dimethylformamide (21 kg.) at 50—60° and slowly adding water (22 kg.). After cooling, the product was separated by filtration, washed with water then with methanol, and dried to give 3.9 kg. of the title compound (65% yield).

Example 5

3-[2-(4-benzamido-1-piperidyl)ethyl]indole

A suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (48.7 kg.) and sodium borohydride (17.4 kg.) in isopropanol (424 kg.) was stirred and refluxed for 6 hours. The reaction mixture was cooled to 25° and diluted with water. The product was separated by filtration and washed with aqueous methanol then with water and finally with methanol, and dried to give 40.7 kg. of the crude title compound. This was purified by dissolving in dimethylformamide (193 kg.) at 50—60° and slowly adding water (220 kg.) to the filtered solution. After cooling, the product was separated by filtration, washed with water then with methanol, and dried to give 30.3 kg. of the title compound (75.5% yield).

Example 6

3-[2-(4-benzamido-1-piperidyl)ethyl]indole

A suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (10.5 g.) and sodium borohydride (2.8 g.) in sec-butanol (100 ml.) was stirred and refluxed for 6 hours. The reaction mixture was cooled to 25° and diluted with aqueous methanol. The product was separated by filtration and washed with aqueous methanol then with water and finally with methanol, and dried to give the crude title compound. This was purified as described in Example 5 to give the title compound mp 203—5°C.

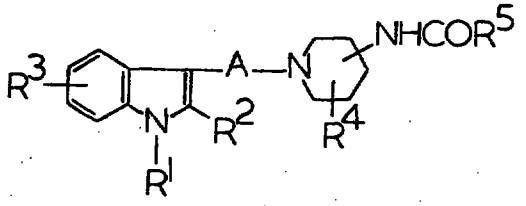
Example 7

3-[2-(4-Benzamido-1-piperidyl)ethyl]indole

A suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (10.5 g.) and sodium borohydride (2.9 g.) in pentan-2-ol (100 ml.) was stirred at 95—100° for 5 hours. The reaction mixture was cooled and diluted with water (200 ml.) and methanol (300 ml.). The product was separated by filtration, washed with water then with methanol and dried to give 3.7 g. of the title compound (42.5% yield).

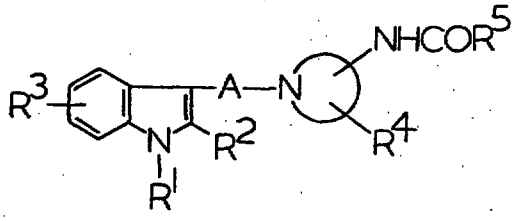
WHAT WE CLAIM IS:—

1. A process for preparing compounds of general formula (III)



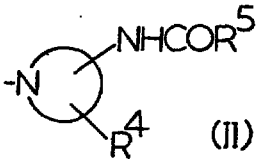
(III)

and acid addition salts thereof wherein R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl, R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, halogen or lower alkyl, R^5 represents aryl (including heterocyclic aryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or cycloalkyl of 5 to 7 carbon atoms, and A is an alkylene radical of 1—4 carbon atoms in which a compound of formula I



(I)

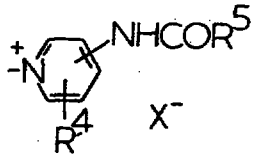
in which formula



(II)

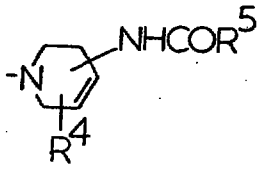
(II)

represents a ring system of general formula



(IIa)

or



(IIb)

wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined in connection with formula (III) and X is an anion, is reduced with an alkali-metal borohydride in a secondary alkanol of 3 to 5 carbon atoms to fully reduce the ring system of formula (IIa) or (IIb), and if desired converting the product to an acid addition salt.

2. A process as claimed in Claim 1, wherein the solvent is a secondary alkanol of 3—4 carbon atoms.

3. A process as claimed in Claim 2, wherein the solvent is isopropanol.

4. A process as claimed in any one of Claims 1 to 3, wherein the reduction is carried out at a temperature from 80 to 120°C.

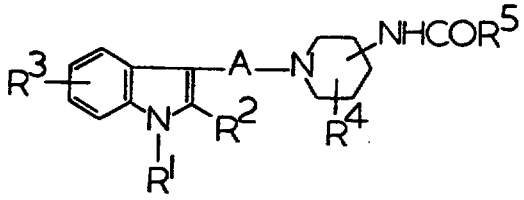
Example 7

3-[2-(4-Benzamido-1-piperidyl)ethyl]indole

A suspension of 4-benzamido-1-[2-(3-indolyl)ethyl]pyridinium bromide (10.5 g.) and sodium borohydride (2.9 g.) in pentan-2-ol (100 ml.) was stirred at 95—100° for 5 hours. The reaction mixture was cooled and diluted with water (200 ml.) and methanol (300 ml.). The product was separated by filtration, washed with water then with methanol and dried to give 3.7 g. of the title compound (42.5% yield).

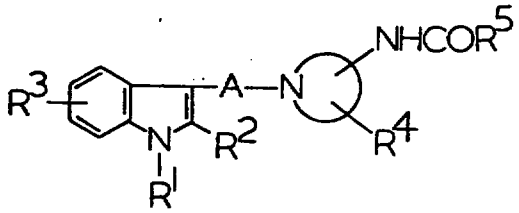
WHAT WE CLAIM IS:—

1. A process for preparing compounds of general formula (III)



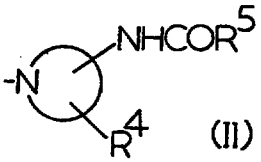
(III)

and acid addition salts thereof wherein R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl, R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, halogen or lower alkyl, R^5 represents aryl (including heterocyclic aryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or cycloalkyl of 5 to 7 carbon atoms, and A is an alkylene radical of 1—4 carbon atoms in which a compound of formula I



(I)

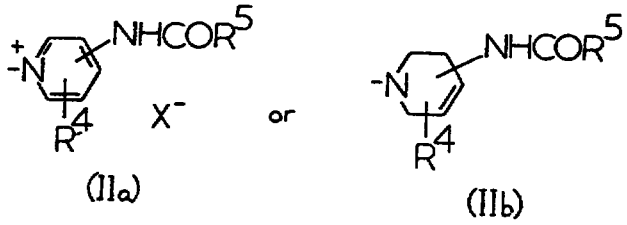
in which formula



(II)

(II)

represents a ring system of general formula



(IIa) (IIb)

wherein A, R^1, R^2, R^3, R^4 and R^5 are as defined in connection with formula (III) and X is an anion, is reduced with an alkali-metal borohydride in a secondary alkanol of 3 to 5 carbon atoms to fully reduce the ring system of formula (IIa) or (IIb), and if desired converting the product to an acid addition salt.

2. A process as claimed in Claim 1, wherein the solvent is a secondary alkanol of 3—4 carbon atoms.

3. A process as claimed in Claim 2, wherein the solvent is isopropanol.

4. A process as claimed in any one of Claims 1 to 3, wherein the reduction is carried out at a temperature from 80 to 120°C.

* C L M S *

5. A process as claimed in any one of Claims 1 to 3 wherein a compound of formula III wherein R^1, R^2, R^3 and R^4 are hydrogen and R^5 is phenyl, substituted phenyl or cyclohexyl is reduced to a corresponding compound of formula I.

6. A process as claimed in Claim 5, wherein a 4-benzamido-1-[2-(3-indolyl)-ethyl]pyridinium halide is reduced to give 3-[2-(4-benzamido-1-piperidyl)ethyl]-indole.

7. A process as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1—4.

8. A process as claimed in Claim 1, substantially as hereinbefore described in Example 5.

9. A process as claimed in Claim 1, substantially as hereinbefore described in Example 6.

10. A process as claimed in Claim 1, substantially as hereinbefore described in Example 7.

11. An indole derivative whenever prepared by a process as claimed in any one of Claims 1 to 7.

12. An indole derivative whenever prepared by a process as claimed in Claim 9.

13. An indole derivative whenever prepared by a process as claimed in Claim 10.

G. R. PORTER
Chartered Patent Agent

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PATENTS ACT 1949

SPECIFICATION NO 1542137

The following corrections were allowed under Section 76 on 22 March 1979:

Page 2, line 56, *for* formula I. *read* formula III.

Page 4, line 29, *after* in *delete* any one of Claims 1 to 3, *insert* Claim 1,

Page 5, line 2, *for* formula III *read* formula I

Page 5, line 3, *for* formula I. *read* formula III.

THE PATENT OFFICE
8 May 1979

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