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- (21) Application No. 8096/77 (22) Filed 25 Feb. 1977
 (23) Complete Specification filed 24 Feb. 1978
 (44) Complete Specification published 20 Feb. 1980
 (51) INT CL³ C07D 207/08 A61K 31/40
 (52) Index at acceptance

C2C 1341 200 215 220 227 22Y 246 250 251 25Y 29X 29Y 305
 30Y 313 316 31Y 326 338 339 342 34Y 351 355 35Y 360
 361 364 366 367 368 36Y 388 38Y 401 40Y 43X 440 490
 583 623 624 625 628 62X 62Y 634 652 656 658 65X 662
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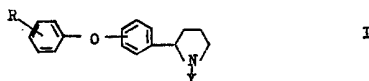
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(54) 2-PHENOXYPHENYL PYRROLIDINES AND
 PHARMACEUTICAL COMPOSITIONS CONTAINING
 THEM

(71) We, SCIENCE UNION ET CIE, SOCIETE FRANCAISE DE
 RECHERCHE MEDICALE, a French Societe en nom collectif, of 14 rue du Val
 d'Or, 92150 Suresnes, France, 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:—

This invention relates to 2-phenoxyphenyl pyrrolidine derivatives, to a process
 for their preparation and to pharmaceutical compositions containing them.

The invention provides pyrrolidine derivatives of the formula

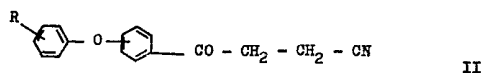


in which R is a hydrogen atom, a halogen atom, for example a chlorine or fluorine
 atom, an alkyl or alkoxy group each having from 1 to 4 carbon atoms or a
 trifluoromethyl group; and

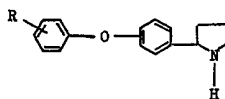
Y is a hydrogen atom, a saturated or unsaturated hydrocarbon group having up
 to 4 carbon atoms, for example a methyl, ethyl, propyl, butyl, allyl, methylallyl or
 propynyl group, or a hydroxyethyl, hydroxypropyl or carboxymethyl group.

The invention also provides acid addition salts, especially physiologically
 tolerable acid addition salts, of the compounds of the formula I. As acids which
 may be used for the formation of these salts, there may be mentioned for example,
 in the mineral series: hydrochloric, hydrobromic, sulfuric and phosphoric acids,
 and in the organic series: acetic, propionic, maleic, fumaric, tartaric, citric, oxalic,
 benzoic, methanesulfonic and isethionic acids.

The invention also provides a process for preparing compounds of the formula
 I which comprises reducing a compound of the formula



with hydrogen under pressure in the presence of a hydrogenation catalyst, in which
 R has the meaning given above to obtain a compound of the formula

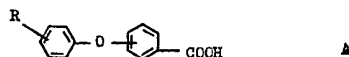


and, if desired, treating this latter compound by conventional methods to obtain a
 corresponding N-substituted pyrrolidine of the formula I in which Y is a saturated
 or unsaturated hydrocarbon radical having from 1 to 4 carbon atoms, a
 hydroxyethyl, hydroxypropyl or carboxymethyl group.

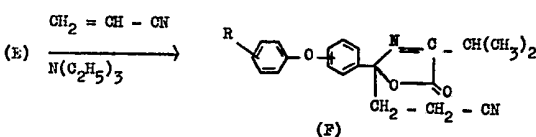
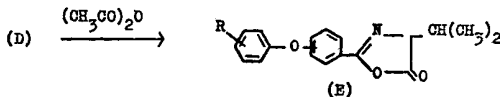
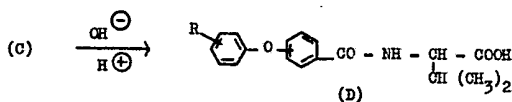
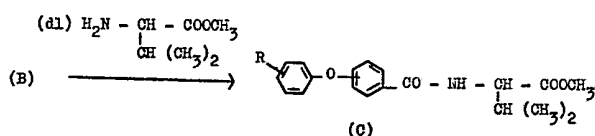
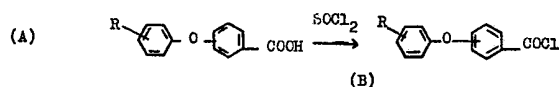
The reduction step of the process is advantageously carried out under a hydrogen pressure of about 8 kg/cm² in the presence of Raney nickel as the catalyst; the reduction is carried out in a suitable solvent, for example dimethyl formamide, at a temperature of from 50 to 80°C.

The methods used to prepare the N-substituted pyrrolidines of the formula I from the corresponding N-unsubstituted pyrrolidines are classical chemical methods generally used to bond an alkyl, alkenyl, hydroxyalkyl or carboxyalkyl group to the nitrogen atom of a secondary amine.

The starting compounds of the formula II are prepared according to the method of W. Steglich and P. Gruber. Angew. Chem. 83, 727 (1971) starting from the phenoxybenzoic acids of the formula



in which R has the meaning given above. This method, described in the following examples, may be illustrated schematically as follows:



The compounds of the formula I and physiologically tolerable acid addition salts thereof possess valuable pharmacological and therapeutic properties, especially lipid-metabolism regulating properties. They may, therefore, be used as medicines especially in the prevention and treatment of lipid-metabolism disorders which may be either genetic disorders or dyslipemia secondary to glucids abnormalities, contraceptive pills, diabetes and obesity. So, they may be used for preventing or treating hyperlipidemia, obesity and atherosclerosis.

Their toxicity is low and their LD₅₀ determined in mice is from 400 to 1000 mg/kg orally and from 50 to 400 mg/kg intraperitoneally.

The activity of the compounds of the present invention on the lipid metabolism can be illustrated in rats submitted to different diets. The compounds of the invention were administered to rats receiving lipid-increased food for a

period of four days at daily doses which may vary from 5 to 25 mg/kg P.O. according to the compound.

The animals were killed two hours after the last administration. There was then observed a decrease of the plasma triglycerides level of up to 76% by comparison with untreated animals.

Similarly, the compounds of the invention were administered to rats receiving a 2% cholesterol diet, for a period of four days at daily doses which may vary from 5 to 25 mg/kg P.O. according to the compound. The animals were killed two hours after the last administration and there was then observed a decrease of the plasma cholesterol level of up to 51% by comparison with untreated animals.

Due to their pharmacological activity, the most interesting compounds are those of the formula I in which R is a hydrogen atom and Y is a hydrogen atom or a saturated or unsaturated hydrocarbon group having from 1 to 4 carbon atoms, especially a methyl, ethyl or allyl group, or a carboxymethyl group.

The invention therefore also provides pharmaceutical compositions comprising as active ingredient a compound of the formula I or a physiologically tolerable acid addition salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier. The carrier may be, for example distilled water, glucose, lactose, starch, talc, magnesium stearate, ethyl cellulose or cocoa butter.

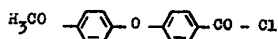
The pharmaceutical compositions are advantageous in unit dosage form and may contain from 50 to 250 mg of the active ingredient.

They may be in a form suitable for oral, rectal or parenteral administration, for example in the form of tablets, dragees, capsules, suppositories or injectable or drinkable solutions and may be administered in doses of from 50 to 250 mg of active ingredient from 1 to 3 times a day.

The following Examples illustrate the invention, the parts being by weight and the melting points being determined on the Kofler hot-plate.

EXAMPLE 1

4-(4-methoxyphenoxy)-benzoyl chloride



51 parts of 4-(4-methoxyphenoxy)-benzoic acid and 75 parts of thionyl chloride were refluxed for two hours. After the elimination of the excess thionylchloride *in vacuo*, the residue was treated twice with 100 parts of anhydrous benzene. The solvent was evaporated *in vacuo* and the remaining acid chloride was used without further purification.

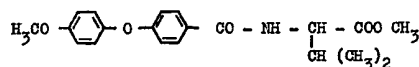
EXAMPLES 2 to 6

The following compounds were prepared according to the process described in Example 1:

2. 4-phenoxybenzoyl chloride.
3. 3-phenoxybenzoyl chloride.
4. 2-phenoxybenzoyl chloride.
5. 4-(4-methylphenoxy)-benzoyl chloride.
6. 4-(4-chlorophenoxy)-benzoyl chloride

EXAMPLE 7

dl methyl N-[4-(4-methoxyphenoxy)-benzoyl]-valinate



To a solution of 32.5 parts of *dl* methyl valinate hydrochloride in 300 parts of anhydrous dimethylformamide, there were added 42.4 parts of triethylamine. A solution of 55 parts of 4-(4-methoxyphenoxy)-benzoyl chloride in 50 parts of anhydrous tetrahydrofuran was then poured in to this reaction mixture over 20 minutes. The temperature progressively increased from 28°C to 59°C while the mixture was stirred for one hour and a half. The precipitate of triethylamine hydrochloride was filtered off and the residue concentrated *in vacuo*.

There were obtained 82 parts of *dl* methyl N-[4-(4-methoxyphenoxy)-benzoyl]-valinate which was used without further purification.

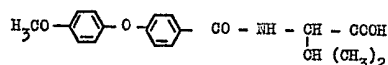
EXAMPLES 8 to 12

The following compounds were prepared according to the process described in Example 7:

8. *dl* methyl N-(4-phenoxybenzoyl)valinate.
 9. *dl* methyl N-(3-phenoxybenzoyl)-valinate.
 10. *dl* methyl N-(2-phenoxybenzoyl)-valinate.
 11. *dl* methyl N-[4-(4-methylphenoxy)-benzoyl]-valinate.
 12. *dl* methyl N-[4-(4-chlorophenoxy)-benzoyl]-valinate

EXAMPLE 13

dl N-[4-(4-methoxyphenoxy)-benzoyl]-valine



To a solution of 82 parts of *dl* methyl N-[4-(4-methoxyphenoxy)-benzoyl]-valinate in 300 parts of ethanol, there were added quickly 320 parts of a N aqueous solution of sodium hydroxide, and the reaction mixture was refluxed for two minutes.

Then, ethanol was evaporated *in vacuo*. The residue was acidified to pH 1 with 50 parts of a concentrated hydrochloric acid solution. After filtration, the precipitate was washed twice, each time with 100 parts of water, then suctioned off and dried. After recrystallization from 200 parts of benzene, there were obtained 52 parts of *dl* N-[4-(4-methoxyphenoxy)-benzoyl]-valine, M.P. 156°C.

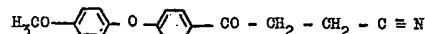
EXAMPLES 14 to 18

The following compounds were prepared according to the process described in Example 13:

14. *dl* N-(4-phenoxybenzoyl)-valine, M.P. 145°C (benzene).
 15. *dl* N-(3-phenoxybenzoyl)-valine, M.P. 145—146°C (benzene).
 16. *dl* N-(2-phenoxybenzoyl)-valine, M.P. 111°C (acetonitrile).
 17. *dl* N-[4-(4-methylphenoxy)-benzoyl]-valine, M.P. 173°C (acetonitrile).
 18. *dl* N-[4-(4-chlorophenoxy)-benzoyl]-valine, M.P. 163—164°C (acetonitrile).

EXAMPLE 19

β -[4-(4-methoxyphenoxy)-benzoyl]-propionitrile



52 parts of *dl* N-[4-(4-methoxyphenoxy)-benzoyl]-valine and 62 parts of acetic anhydride were maintained at 80—85°C for five minutes. The solution thus obtained was concentrated *in vacuo*.

The residue was treated twice, each time with 100 parts of benzene and then the solvent was evaporated *in vacuo*. The residue was a slightly yellowish oil, which was dissolved in 100 parts of anhydrous methylene chloride and chilled to -20°C.

To this solution, 16 parts of freshly distilled acrylonitrile were added and the temperature was allowed to rise slowly to 0°C. At this stage, a solution of 7.6 parts of triethylamine in 25 parts of methylene chloride was introduced while the reaction mixture was maintained at 0°C. After stirring at room temperature for 3 hours, the solvent was evaporated off *in vacuo*. The residue was treated with 200 parts of ethyl acetate and washed successively with 150 parts and 75 parts of a 0.1 N hydrochloric acid solution. The organic layer was separated off, dried over anhydrous magnesium sulphate then concentrated *in vacuo*.

The residue was treated with 45 parts of a N solution of sodium hydroxide, then with 320 parts of methanol and 120 parts of tetrahydrofuran. After stirring at room temperature for 90 minutes, the precipitate was filtered, washed with water and dried. There were obtained 29.5 g of product, M.P. 86°C, which after one recrystallization from 160 parts of isopropanol gave 23.5 parts of pure β -[4-(4-methoxyphenoxy)-benzoyl]-propionitrile, melting at 88°C.

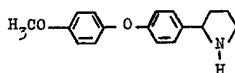
EXAMPLES 20 to 24

The following compounds were prepared according to the process described in Example 19:

20. β -(4-phenoxybenzoyl)-propionitrile, M.P. 69°C (isopropanol).
 21. β -(3-phenoxybenzoyl)-propionitrile, M.P. 80° (isopropanol).
 22. β -(2-phenoxybenzoyl)-propionitrile, M.P. 63—64°C (isopropanol).
 23. β -[4-(4-chlorophenoxy)-benzoyl]-propionitrile, M.P. 91°C (isopropanol).
 24. β -[4-(4-methylphenoxy)-benzoyl]-propionitrile, M.P. 89—90°C (isopropanol).

EXAMPLE 25

2-[4-(4-methoxyphenoxy)-phenyl]-pyrrolidine



23 parts of β -[4-(4-methoxyphenoxy)-benzoyl]-propiononitrile in solution in 200 parts of dimethylformamide were reduced with hydrogen in the presence of 10 parts of Raney nickel at a pressure of 8 kg/cm², and a temperature of 60°C. The reduction was achieved in 5 hours. After filtration and washing of the catalyst, the filtrate was distilled. There were obtained 15 parts of crude product, B.P./0.1 mm Hg: 172—174°C, which gave 12.5 parts of 2-[4-(4-methoxyphenoxy)-phenyl]pyrrolidine hydrochloride, M.P. 157°C (acetone).

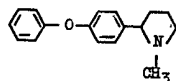
EXAMPLES 26 to 30

The following compounds were prepared according to the process described in Example 25.

26. 2-(4-phenoxyphenyl)-pyrrolidine, B.P./0.6 mm Hg: 164—165°C, M.P. of its hydrochloride: 171—172°C (acetonitrile).
27. 2-(3-phenoxyphenyl)-pyrrolidine, B.P./0.4 mm Hg: 153—155°C, M.P. of its hydrochloride: 163°C (isopropanol).
28. 2-(2-phenoxyphenyl)-pyrrolidine, B.P./0.3 mm Hg: 145—147°C, M.P. of its hydrochloride: 140°C (acetonitrile).
29. 2-[4-(4-chlorophenoxy)-phenyl]-pyrrolidine, B.P./0.3 mm Hg: 155—160°C, M.P. of its hydrochloride: 180°C (acetonitrile).
30. 2-[4-(4-methylphenoxy)-phenyl]-pyrrolidine, B.P./0.1 mm Hg: 155—157°C, M.P. of its acid fumarate: 132—133°C (isopropanol).

EXAMPLE 31

1-methyl-2-(4-phenoxyphenyl)-pyrrolidine



113.5 parts of 2-(4-phenoxyphenyl)-pyrrolidine, 115 parts of a 40% solution of formaldehyde and 145 parts of formic acid at 98% were refluxed for 10 hours. After cooling, the mixture was acidified with 600 parts of a 4N hydrochloric acid solution and then concentrated *in vacuo*.

The residue was treated with 950 parts of water, then extracted twice, each time with 300 parts of ether. The solution was dried over Mg SO₄, then the solvent was evaporated off. There were obtained 109 parts of 1-methyl-2-(4-phenoxyphenyl)-pyrrolidine, B.P./0.8 mm Hg: 157—159°C, N_D^{24.5}:1.5692, M.P. of its hydrochloride: 161—162°C (ethylacetate/isopropanol).

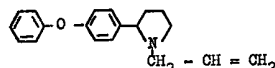
EXAMPLES 32 to 36

The following compounds were prepared according to the process described in Example 31.

32. 1-methyl-2-(3-phenoxyphenyl)-pyrrolidine, M.P. of its acid fumarate: 113—115°C (acetonitrile).
33. 1-methyl-2-(2-phenoxyphenyl)-pyrrolidine.
34. 1-methyl-2-[4-(4-methylphenoxy)-phenyl]pyrrolidine, B.P./0.9 mm Hg: 167—170°C, M.P. of its acid fumarate: 121°C (acetonitrile).
35. 1-methyl-2-[4-(4-chlorophenoxy)-phenyl]-pyrrolidine, B.P./0.2 mm Hg: 150—152°C.
36. 1-methyl-2-[4-(4-methoxyphenoxy)-phenyl]-pyrrolidine.

EXAMPLE 37

1-allyl-2-(4-phenoxyphenyl) pyrrolidine



8 parts of 2-(4-phenoxyphenyl)-pyrrolidine, 3.3 parts of triethylamine, 4 parts

of allyl bromide and 70 parts of toluene were refluxed for 5 hours. After cooling and filtration, there were obtained by distillation 7.7 parts of 1-allyl-2-(4-phenoxyphenyl)-pyrrolidine, B.P./0.2 mm Hg: 148—150°C, $n_D^{26}=1.5695$, M.P. of its acid fumarate: 115—116°C (isopropanol/ether).

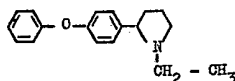
EXAMPLES 38 to 42

The following compounds were prepared according to the process described in Example 37.

38. 1-allyl-2-(3-phenoxyphenyl)-pyrrolidine.
39. 1-allyl-2-(2-phenoxyphenyl)-pyrrolidine.
40. 1-allyl-2-[4-(4-chlorophenoxy)-phenyl]-pyrrolidine.
41. 1-allyl-2-[4-(4-methylphenoxy)-phenyl]-pyrrolidine.
42. 1-allyl-2-[4-(4-methoxyphenoxy)-phenyl]-pyrrolidine.

EXAMPLE 43

1-ethyl-2-(4-phenoxyphenyl)-pyrrolidine



To a solution of 10 parts of 2-(4-phenoxyphenyl)-pyrrolidine in 200 parts of anhydrous ether and 4.2 parts of triethylamine, there was added a solution of 3.3 parts of acetyl chloride in 30 parts of ether. The mixture was refluxed for one hour, then the reaction mixture was filtered when cool and the filtrate was distilled. There were obtained 13 parts of 1-acetyl-2-(4-phenoxyphenyl)-pyrrolidine.

These 13 parts were dissolved in 150 parts of anhydrous ether, and added over 90 minutes to a suspension of 3.5 parts of lithium aluminium hydride in 80 parts of ether. The mixture was refluxed for 4 further hours. After hydrolysis of the mixture, the precipitate was filtered off. There were obtained 9 parts of 1-ethyl-2-(4-phenoxyphenyl)-pyrrolidine, B.P./0.9 mm Hg: 146—148°C, n_D^{24} : 1.5620, M.P. of its acid fumarate: 142—143°C (ethyl acetate).

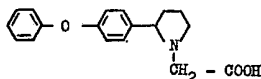
EXAMPLES 44 to 48

The following compounds were prepared according to the process described in Example 43:

44. 1-ethyl-2-(3-phenoxyphenyl)-pyrrolidine.
45. 1-ethyl-2-(2-phenoxyphenyl)-pyrrolidine.
46. 1-ethyl-2-[4-(4-chlorophenoxy)-phenyl]-pyrrolidine.
47. 1-ethyl-2-[4-(4-methylphenoxy)-phenyl]-pyrrolidine.
48. 1-ethyl-2-[4-(4-methoxyphenoxy)phenyl]-pyrrolidine.

EXAMPLE 49

1-carboxymethyl-2-(4-phenoxyphenyl)-pyrrolidine



To a solution of 23.9 parts of 2-(4-phenoxyphenyl)-pyrrolidine in 80 parts of anhydrous benzene, there were quickly added 8.35 parts of ethyl bromoacetate. The reaction mixture was then refluxed for 4 hours. After cooling and filtration, the residue was treated with 50 parts of water and 100 parts of ether. After decantation, then distillation, there were obtained 11.3 parts of 1-ethoxycarbonylmethyl-2-(4-phenoxyphenyl)-pyrrolidine, B.P./0.1 mm Hg: 165°C, n_D^{23} : 1.5524.

11 parts of the 1-ethoxycarbonylmethyl-2-(4-phenoxyphenyl)pyrrolidine, 50 parts of a N solution of sodium hydroxide and 40 parts of ethanol were refluxed for one hour. The reaction mixture was concentrated *in vacuo*, acidified with 50 parts of a N solution of hydrochloric acid, treated with 80 parts of anhydrous isopropanol, then concentrated again.

After treatment with hydrochloric acid and recrystallization from acetone, there were obtained 1-carboxymethyl-2-(4-phenoxyphenyl)-pyrrolidine hydrochloride, melting at 114°C.

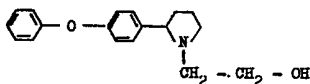
EXAMPLES 50 to 54

The following compounds were prepared according to the process described in Example 49:

50. 1-carboxymethyl-2-(3-phenoxyphenyl)-pyrrolidine.
 51. 1-carboxymethyl-2-(2-phenoxyphenyl)-pyrrolidine.
 52. 1-carboxymethyl-2-[4-(4-chlorophenoxy)-phenyl]-pyrrolidine.
 53. 1-carboxymethyl-2-[4-(4-methylphenoxy)-phenyl]-pyrrolidine.
 54. 1-carboxymethyl-2-[4-(4-methoxyphenoxy)-phenyl]-pyrrolidine.

EXAMPLE 55

- 10 1- β -hydroxyethyl-2-(4-phenoxyphenyl)-pyrrolidine 10



- 15 12 parts of 2-(4-phenoxyphenyl)-pyrrolidine, 2.2 parts of ethylene oxide and 1 part of water were heated at 80°C for 5 hours. After cooling, there were obtained 8 parts of 1- β -hydroxyethyl-2-(4-phenoxyphenyl)-pyrrolidine, B.P./0.3 mm Hg: 179—180°C. 15

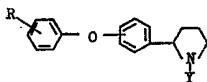
EXAMPLES 56 to 60

The following compounds were prepared according to the process described in Example 55:

56. 1- β -hydroxyethyl-2-(3-phenoxyphenyl)-pyrrolidine.
 57. 1- β -hydroxyethyl-2-(2-phenoxyphenyl)-pyrrolidine.
 58. 1- β -hydroxyethyl-2-[4-(4-chlorophenoxy)-phenyl]-pyrrolidine.
 59. 1- β -hydroxyethyl-2-[4-(4-methylphenoxy)-phenyl]-pyrrolidine.
 60. 1- β -hydroxyethyl-2-[4-(4-methoxyphenoxy)-phenyl]-pyrrolidine.

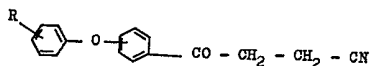
WHAT WE CLAIM IS:—

- 25 1. A compound of the formula 25

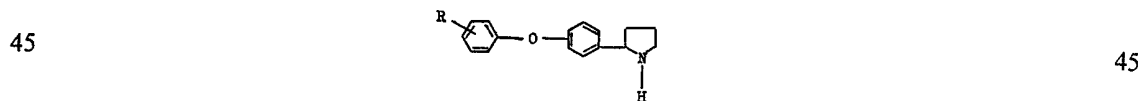


- in which R is a hydrogen atom, a halogen atom, an alkyl or alkoxy group each having from 1 to 4 carbon atoms or a trifluoromethyl group; and
 Y is a hydrogen atom, a saturated or unsaturated hydrocarbon group having up to 4 carbon atoms or a hydroxyethyl, hydroxypropyl or carboxymethyl group.
 2. An addition salt of a compound as claimed in Claim 1 with a mineral or organic acid.
 3. An acid addition salt as claimed in Claim 2 which is physiologically tolerable.

4. 2-(2-Phenoxyphenyl)-pyrrolidine.
 5. 1-Methyl-2-(4-phenoxyphenyl)-pyrrolidine.
 6. 1-Allyl-2-(4-phenoxyphenyl)-pyrrolidine.
 7. 1-Ethyl-2-(4-phenoxyphenyl)-pyrrolidine.
 8. 1-Carboxymethyl-2-(4-phenoxyphenyl)-pyrrolidine.
 9. A process for preparing a compound as claimed in Claim 1, which comprises reducing a compound of the formula



in which R has the meaning specified in Claim 1, with hydrogen under pressure in the presence of a hydrogenation catalyst, to obtain a compound of the formula



and, if desired, treating the latter by conventional methods to obtain a corresponding N-substituted pyrrolidine as claimed in Claim 1.

10. A process as claimed in Claim 9, carried out substantially as described in any one of Examples 25 to 60 herein.

5 11. A compound as claimed in Claim 1 whenever prepared by a process as claimed in Claim 9 or Claim 10. 5

12. A pharmaceutical composition which comprises as active ingredient a compound as claimed in Claim 1 or a physiologically tolerable acid addition salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

10 13. A pharmaceutical composition as claimed in Claim 12 which is in unit dosage form and contains from 50 to 250 mg of the active ingredient. 10

14. A pharmaceutical composition as claimed in Claim 12 or Claim 13 which is in a form suitable for oral, rectal or parenteral administration.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
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