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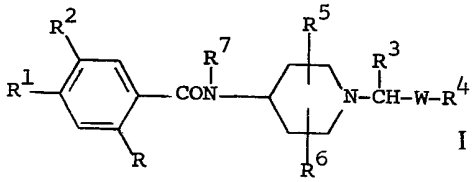
(54) PIPERIDINE DERIVATIVES

(71) We, ANPHAR S.A., a Spanish Body Corporate of Lerida Street No. 9, Madrid, Spain, 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 new therapeutically useful piperidine derivatives, to processes for their preparation and pharmaceutical compositions containing them.

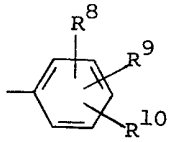
The new piperidine derivatives of the present invention are those compounds of the general formula:—



I

[wherein R represents a halogen atom or a hydroxy, lower alkoxy, lower alkenyloxy, lower alknyloxy or aralkyloxy (preferably a phenyl(lower)alkyloxy, e.g. bezyloxy) group, or a lower acyloxy group in which the acyl moiety is derived from a carboxylic acid (preferably a lower alkanoyloxy, e.g. acetoxy, group; R^1 represents a hydrogen atom or an amino, lower alkylamino, di(lower)alkylamino or a lower acylamino group in which the acyl moiety is derived from a carboxylic acid (preferably a lower alkanoylamino group); R^2 represents a nitro or trifluoromethyl group or a lower alkylthio or lower alkylsulphinyl group, or R^1 and R^2 together form a triazo group (i.e. —HN—N=N—); R^3 represents a hydrogen atom or a lower alkyl or lower alkenyl group, or a cycloalkyl or cycloalkenyl group having from 3 to 7 carbon atoms in the ring, or a phenyl group, R^4 represents a cycloalkyl group having from 3 to 7 carbon atoms in the ring, or an aroyl (e.g. benzoyl), aryl (e.g. phenyl or naphthyl) or heterocyclyl group (e.g. thienyl, pyridyl or pyrimidinyl); R^5, R^6 and R^7 each represent a hydrogen atom, a lower alkyl, lower alkenyl (e.g. $—CH_2—CH=CH_2$) or a benzyl group, and W represents a single bond or a lower alkylene (e.g. $—CH_2—$ or $—CH_2.CH_2—$) or lower alkenylene (e.g. —CH=CH— or $—CH_2—CH=CH—$) group; with the proviso that when W is a single bond R^3 is other than a cycloalkenyl group] and pharmacologically-acceptable acid addition, alkali metal, alkaline earth metal and quaternary ammonium salts thereof, or N-oxide derivatives thereof.

The aryl group represented by R^4 may be a phenyl group of the general formula:

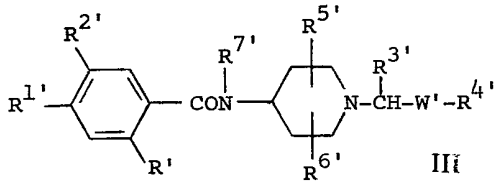


II

wherein R^8, R^9 and R^{10} each represent a hydrogen or halogen atom, or a lower alkoxy, hydroxy, nitro, amino, lower alkylamino, di(lower alkyl)amino, trifluoromethyl or lower alkyl group, or R^8 and R^9 together may form a methylenedioxy group in which case R^{10} represents a hydrogen atom.

The qualification "lower" as applied herein to alkoxy, alkenyloxy, alkynyloxy, alkyl, alkenyl, alkylene, alkenylene, alkylthio, alkylsulphinyl, acyl, acyloxy and alkanoyl groups means that the group in question contains at most 6 carbon atoms.

Preferred compounds of general formula I are those of the more specific formula:



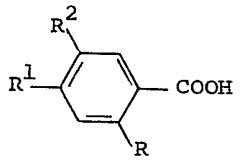
III

wherein R′ represents a halogen (preferably chlorine) atom or a hydroxy, lower alkoxy (preferably methoxy or ethoxy), allyloxy, propargyloxy, acetoxy or benzyloxy group; $R^{1'}$ represents a hydrogen atom or an amino group or a lower acylamino group in which the acyl moiety is derived from a carboxylic acid (preferably acetamido) and $R^{2'}$ represents a nitro, methylsulphinyl or methylthio group, or $R^{1'}$ and $R^{2'}$ together form a triazo group; $R^{3'}$ represents a hydrogen atom, a lower alkyl (preferably methyl) or a phenyl group; $R^{4'}$ represents a cyclohexyl group or a phenyl group optionally substituted by one or two halogen atoms, lower alkyl or lower alkoxy groups, or by a methylenedioxy or trifluoromethyl group, or by three methoxy groups, or $R^{4'}$ represents a thienyl or naphthyl (preferably β-naphthyl) group or a benzoyl group optionally substituted by a halogen atom (preferably *p*-fluorobenzoyl); $R^{5'}$, $R^{6'}$ and $R^{7'}$ each represent a hydrogen atom or a lower alkyl group (preferably methyl or ethyl), and W′ represents a single bond or a methylene, ethylene or vinylene group] and pharmacologically - acceptable acid addition salts thereof.

Of outstanding importance are those compounds of general formula III wherein R′ represents a lower alkoxy (methoxy or ethoxy), allyloxy or propargyloxy group, $R^{1'}$ represents an amino group, $R^{2'}$ represents a nitro group, $R^{3'}$ represents a hydrogen atom, $R^{4'}$ represents a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group (preferably in the *para*-position) $R^{5'}$, $R^{6'}$ and $R^{7'}$ each represent a hydrogen atom, and W′ represents a methylene group or, preferably, a single bond.

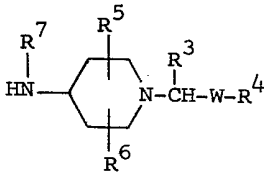
Especially preferred compounds of the present invention are N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, N - (1 - benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - amino - 5 - nitrobenzamide and N - (1 - phenethylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, and their pharmacologically - acceptable acid addition salts.

According to a feature of the present invention, the compounds of general formula I are prepared by the process which comprises reacting a reactive derivative of a benzoic acid of the general formula:



IV

(wherein R, R^1 and R^2 are as hereinbefore defined) with a piperidine derivative of the general formula:



V

wherein the various symbols are as hereinbefore defined. The reactive derivative of the said benzoic acid may be a halide (preferably chloride), an alkyl ester (preferably methyl ester), an anhydride or a mixed anhydride.

The reaction is preferably carried out in the presence of an inert organic solvent, for example benzene, toluene, chloroform, tetrahydrofuran, N,N-dimethylformamide or dioxan, at a temperature between −5° and 120°.

Halides of the benzoic acids of general formula IV can be prepared by reaction of the acid with thionyl chloride or a phosphorus halide in the presence of an inert organic solvent such as benzene, toluene or a halogenated hydrocarbon. Mixed anhydrides of the benzoic acids of general formula IV can be prepared by the reaction of the acid with, for example, an alkyl chloroformate in the presence of an organic nitrogen-containing base, e.g. triethylamine, in an inert organic solvent, e.g. tetrahydrofuran, N,N-dimethylformamide or methylene chloride, and at a temperature between −20° and +25°C. Esters and anhydrides of the benzoic acids of formula IV, which may be employed as starting materials in the aforementioned process, can be prepared from the benzoic acids by methods known *per se*.

The piperidine derivatives of general formula V wherein R^7 is a hydrogen atom can be prepared by reduction of corresponding 4-piperidone oximes with lithium aluminium hydride in the presence of diethyl ether or tetrahydrofuran, or by reductive amination of corresponding 4-

piperidones dissolved in an organic solvent, e.g. an alcohol containing from 1 to 4 carbon atoms, in the presence of platinum or Raney nickel as catalyst. The piperidine derivatives of general formula V wherein R^7 is a lower alkyl, a lower alkenyl or a benzyl group can be prepared from the corresponding N-acyl substituted compounds by reduction of the carbonyl group therein to methylene using lithium aluminium hydride.

Other piperidine derivatives of general formula V can be prepared by methods known *per se*.

The piperidine derivatives of general formula I are also prepared, according to a further feature of the invention, by the direct reaction of a benzoic acid of general formula IV with a piperidine derivative of general formula V in the presence of an appropriate dehydrating agent. Such agents are silicon tetrachloride, a mono-, di- or trialkyl-silyl chloride, titanium tetrachloride, N,N′ - dicyclohexyl - carbodiimide, thionyl chloride, sulphur trioxide in dimethyl sulphoxide, toluene - *p* - sulphonyl chloride, acetone dimethyl acetal or a polymeric dehydrating agent. The reaction is carried out in an inert organic solvent, e.g. methylene chloride, acetone, pyridine, ethyl acetate or dioxan, at a temperature between 20° and 110°C.

The piperidine derivatives of general formula I wherein R represents a hydroxy group are prepared, according to a further feature of the invention, from the corresponding O-methylated derivatives of general formula I (viz. R represents a methoxy group) by the process which comprises the reaction of such compounds with boron tribromide or aluminium trichloride using methylene chloride or benzene as solvent medium at a temperature between 20° and 80°C. The O-methylated compounds employed as starting materials in this process may be prepared by processes hereinbefore described using starting materials in which R represents a methoxy group.

The piperidine derivatives of general formula I wherein R represents a hydroxy group are also prepared, according to a still further feature of the invention, from the corresponding O-acylated derivatives of general formula I, viz. R represents an acyloxy group. In this case the O-acylated derivatives are hydrolysed with dilute hydrochloric acid or with sodium or potassium hydroxide in an aqueous-alcoholic solution at a temperature between 20° and 90°C.

In the preparation of those compounds of general formula I wherein the symbol R^1 represents an amino group, it is sometimes advisable to use as starting material corresponding compounds in which the amino group is protected by an acyl group, the acyl protecting group preferably being acetyl, chloroacetyl, trifluoroacetyl or phthaloyl. After the reaction the N-acylated intermediate products are subjected to acid or alkaline hydrolysis to give the corresponding compounds of general formula I in which R^1 represents an amino group. Acid hydrolysis of the N-acylated compound may be carried out by heating with dilute hydrochloric acid, preferably at the boiling point of the reaction mixture, while alkaline hydrolysis is preferably carried out at a temperature between 20° and 90°C with sodium or potassium hydroxide in an aqueous-alcoholic solution.

The piperidine derivatives of general formula I have as their principal pharmacological properties the ability to antagonise the effects of dopamine or dopaminergic agents of endogenous or exogenous origin and to cause stimulation of serotoninergic mechanisms. In those circumstances where homeostatic control is a balance between dopaminergic and serotoninergic mechanisms these two actions are synergistic and the precise contribution of each one to the final biological response is difficult to determine. As a group they have exhibited activites which may be considered beneficial in the treatment of a variety of cerebral malfunctions as well as obesity and gastrointestinal disturbances in mammals, including man. Their characteristic properties in experimental animals are antagonism of the effects of dopaminergic agents such as apomorphine, induction of catatonia, production of local anaesthesia, stimulation of gastrointestinal transit and induction of both spasmogenic and spasmolytic effects on smooth muscle according to the initial resting tone.

Nevertheless, as within the series antidopaminergic, serotoninergic and local anaesthetic potency do not necessarily run in parallel, the clinical applications of the various derivatives may well be different. As a group they may be useful in the treatment of a variety of conditions affecting the central nervous system such as acute and chronic phychosis, manic psychosis, schizophrenias, serious disturbances of behaviour and non-melancholic depressive states and migraine, and be effective in the treatment of nausea and vomiting of diverse origin such as that resulting from gastrointestinal disorders, congestive heart failure, and post-operative conditions, as well as in the treatment of other gastrointestinal disorders such as dyspepsia, flatulance, bile regurgitation, hiatus hernia, peptic ulcer, reflux oesophagitis, gastritis, duodenitis and cholelithiasis. They may also

be useful in the treatment of obesity and allied conditions where the administration of an appetite suppressant is warranted.

For therapeutic purposes the compounds of general formula I may be employed in the form of biologically and pharmacologically - acceptable inorganic or organic acid addition salts such as sulphates, hydrohalides (e.g. hydrochlorides), phosphates, lower alkane-sulphonates, arylsulphonates and salts of aliphatic or aromatic acids containing from 1 to 20 carbon atoms which may contain one or more double bonds, or other functional groups such as hydroxy, lower alkoxy, amino or keto, e.g. fumarates.

The piperidine derivatives of general formula I wherein R represents a hydroxy group may also form pharmacologically - acceptable salts with alkali or alkaline earth metals, which salts are formed by reaction of the derivatives of formula I wherein R is a hydroxy group with an alkali metal or alkaline earth metal carbonate or hydroxide using water, methanol or ethanol, as solvent at a temperature between 40° and 100°C.

They may also be used for therapeutic purposes in the form of pharmacologically - acceptable quaternary ammonium salts such as those salts formed by reaction of the compounds of general formula I with lower alkyl halides or sulphates, or in the form of oxygenated derivatives in which oxygen is attached to the nitrogen atom of the piperidine nucleus, viz. the N-oxides.

The pharmacologically - acceptable acid addition salts and quaternary ammonium salts and N-oxides of the compounds of general formula I may be prepared by methods known *per se*. By the term "methods known *per se*" as used in this specification is meant methods heretofore used or described in the chemical literature.

Also included within the scope of the present invention are pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, or a pharmacologically - acceptable acid addition salt, alkali metal or alkaline earth metal salt or quaternary ammonium salt thereof or N-oxide thereof in association with a pharmaceutically acceptable carrier or diluent. Preferably the compositions are made up in a form suitable for oral, topical, percutaneous or parenteral administration.

The pharmaceutically acceptable carriers or diluents which are admixed with the active compound, or compounds, or salts or N-oxides of such compounds, to form the compositions of this invention are well known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions. Compositions of this invention are preferably adapted for administration *per os*. In this case, the compositions for oral administration may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 0.1 and 20 mg, and preferably from 0.1 to 5 mg of active ingredient or the equivalent amount of an acid addition, alkali or alkaline earth metal or quaternary ammonium salt thereof, or N-oxide thereof.

The liquid compositions adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or an acid addition, alkali metal or alkaline earth metal, or quaternary ammonium salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

In another aspect of the invention, the compounds may be mixed with other active anti-acid and antiulcer agents (excluding anti-cholinergic agents) for oral or, in appropriate cases, for parenteral use.

Useful tranquillizing and antiemetic dosages of the most interesting compounds of the present invention appear to lie between 0.5 and 50 mg per day. Useful dosages for gastrointestinal tract indications also lie within the same range.

The following Examples illustrate the preparation of piperidine compounds of the present invention.

EXAMPLE 1

To a solution of 2 - methoxy - 4 - amino - 5 - nitrobenzoic acid (6.4 g; 0.03 moles) in N,N - dimethylformamide (175 ml) a solution of triethylamine (3 g; 0.03 moles) in N,N - dimethylformamide (5 ml) was added. The mixture was cooled to −5° to −10°C and a solution of ethyl chloroformate (3.3 g; 0.03 moles) in N,N - dimethylformamide (5 ml) was added. The reaction mixture was stirred at the same temperature for 0.5 hours and then a

solution of 1 - benzyl - 4 - amino-piperidine (5.7 g; 0.03 moles) in N,N - dimethylformamide (15 ml) was added. After stirring for 1 hour at −5° to −10°C, the temperature was allowed to reach room temperature overnight. The solvent was removed *in vacuo* and the residue was poured into an aqueous sodium bicarbonate solution. The resulting solid was exhaustively extracted with methylene chloride, the organic layers washed with an aqueous sodium bicarbonate solution and then with water, dried (Na_2SO_4) and the solvent removed *in vacuo*. N - (1 - Benzyl-piperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide (9.3 g) was obtained and converted into its hydrochloride by treatment with a saturated solution of ethanolic hydrogen chloride; the hydrochloride melted at 218°—220°C (dec).

The following compounds were prepared in a similar manner:

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 215°—217°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 235°—236°C;

N - (1 - *m* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride monohydrate of which melts at 178°—180°C;

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 202°—204°C;

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 238°—241°C (dec);

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 219°—221°C (dec);

N - [1 - (3,4,5 - trimethoxybenzyl)-piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 181°—183°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 240°—242°C (dec);

N - (1 - cinnamylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 236°—238°C (dec);

N - methyl - N - (1 - diphenylmethyl-piperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 267°—269°C (dec);

N - [1 - (2 - thienylmethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 208°—210°C (dec);

N - methyl - N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 141°—143°C;

N - (1 - benzyl - 3 - methylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 210°—212°C;

N - (1 - *m* - trifluoromethylbenzyl-piperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride monohydrate of which melts at 177°—179°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 204°—206°C;

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 199°—200°C (dec);

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 186°—188°C (dec);

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 191°—193°C;

N - [1 - (3,4,5 - trimethoxybenzyl)-piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 220°—222°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 213°—214°C;

bis [N - (1 - phenethylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide] fumarate, m.p. 209°—211°C (dec);

N - (1 - cinnamylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 201°—203°C;

N - [1 - (2 - thienylmethyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 203°—205°C;

N - methyl - N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 142°—144°C;

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 217°—219°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4,5 - azimidobenzamide, the hydrochloride of which melts at 244°—246°C (dec);

bis[N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4,5 - azimidobenzamide] fumarate, m.p. 243°—245°C (dec);

bis[N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - methoxy - 4,5 - azimidobenzamide] fumarate, m.p. 214°—216°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4,5 - azimidobenzamide, the fumarate of which melts at 203°—205°C;

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - methoxy - 4,5 - azimidobenzamide, the hydrochloride monohydrate of which melts at 239°—241°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 5 - nitrobenzamide, the fumarate of which melts at 145°—147°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - allyloxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts of 191°—193°C;

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - allyloxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 203°—205°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 213°—215°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - chloro - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 226°—228°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - nitrobenzamide, m.p. 191°—193°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - nitrobenzamide, m.p. 220°—222°C;

N - [1 - (3 - phenylpropyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 174°—176°C (dec);

N - (1 - cyclohexylmethyl - 3 - methylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 178°—180°C;

N - (1 - β - naphthylmethylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride monohydrate of which melts at 185°—187°C;

N - [1 - (3 - phenylpropyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide, the fumarate of which melts at 202°—204°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 5 - (methylthio)benzamide, the fumarate of which melts at 175°—177°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 5 - (methylthio)benzamide, the hydrochloride of which melts at 246°—248°C;

N - (1 - benzylpiperid - 4 - yl) - 2 benzyloxy - 5 - (methylthio)benzamide, the hydrochloride of which melts at 193°—195°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 5 - methylsulphinylbenzamide, the hydrochloride of which melts at 166°—168°C;

N - (1 - *p* - methoxybenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride of which melts at 220°—222°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - propargyloxy - 5 - (methylthio)benzamide, the fumarate of which melts at 196°—198°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 228°—230°C (dec);

N - [1 - (3 - *p* - fluorobenzoylpropyl)-piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the hydrochloride monohydrate of which melts at 222°—224°C (dec);

N - [1 - (3,4 - methylenedioxybenzyl)-piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, the fumarate of which melts at 231°—233°C (dec); and

N - ethyl - N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 5 - nitrobenzamide, the hydrochloride of which melts at 210°—212°C (dec);

The fumarates mentioned above were obtained by adding fumaric acid in stoichiometric amount to a hot ethanolic solution of the piperidine base. The resulting hot solution was cooled and the fumarate crystallized.

EXAMPLE 2

A mixture of N - (1 - benzylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - nitrobenzamide (1.4 g; 0.0031 moles) [prepared by the procedure described in Example 1], sodium hydroxide (0.3 g; 0.0062 moles), water (25 ml) and ethanol (12.5 ml) was boiled under reflux for 3 hours. Then the mixture was diluted with water, neutralized with diluted hydrochloric acid and the solid filtered off, washed with water and diethyl ether to give 1.1 g of N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - nitrobenzamide, m.p. 220°—222°C.

EXAMPLE 3

A mixture of N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 -

nitrobenzamide (1 g; 0.0024 moles) [prepared as described in Example 2], sodium hydroxide (0.2 g; 0.0048 moles), water (25 ml) and ethanol (12.5 ml) was boiled under reflux for 3 hours. Then the mixture was diluted with water, neutralized with diluted hydrochloric acid and the precipitate collected by filtration. This precipitate was washed with water and then with diethyl ether to give 0.9 g of N - (1 - Benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - nitrobenzamide. This compound was treated with a saturated solution of hydrogen chloride in methanol to give the hydrochloride which was recrystallized from ethanol. N - (1 - Benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - nitrobenzamide hydrochloride was obtained, m.p. 248°—250°C (dec).

EXAMPLE 4

A mixture of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide (4.26 g; 0.01 mol) [prepared by the procedure described in Example 1], concentrated hydrochloric acid (5 ml), methanol (40 ml) and water (40 ml) was boiled under reflux for 2 hours. The solvent was removed *in vacuo* and the solid recrystallized from ethanol to give 3.4 g of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride, m.p. 218°—220°C (dec).

EXAMPLE 5

A suspension of N - (1 - benzylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - nitrobenzamide (4.5 g; 0.01 mol) [prepared by the procedure described in Example 1] in ethanol (25 ml), concentrated hydrochloric acid (4.5 ml) and water (50 ml) was boiled under reflux for 2 hours. The mixture was diluted with water, made alkaline with sodium bicarbonate and extracted with chloroform. The organic solution was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue triturated with diethyl ether to give a solid which was treated with a saturated solution of hydrogen chloride in ethanol. After crystallization from ethanol 3 g of N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - nitrobenzamide hydrochloride were obtained, m.p. 248°—250°C (dec).

EXAMPLE 6

A solution of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide (3.8 g; 0.01 mol) [prepared as described in Example 1] in methylene chloride (70 ml) was added to another solution of boron tribromide (2.84 ml; 0.03 moles) in methylene chloride (20 ml). The mixture was stirred at room temperature for 24 hours and then poured into a mixture of a saturated solution of sodium bicarbonate in water (250 ml) and methylene chloride (100 ml). The decanted organic solution was dried and the solvent removed *in vacuo* to give a paste which was triturated with petroleum ether. The residue obtained was treated with a saturated solution of ethanolic hydrogen chloride to give 3 g of N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - nitrobenzamide hydrochloride, m.p. 248°—250°C (dec).

EXAMPLE 7

N,N' - Dicyclohexylcarbodiimide (4.12 g; 0.02 moles) and 1 - benzyl - 4 - aminopiperidine (3.8 g; 0.02 moles) were added successively to a solution of 2 - methoxy - 4 - acetamido - 5 - nitrobenzoic acid (5.1 g; 0.02 moles) in methylene chloride (125 ml). After stirring overnight at room temperature, the insoluble N,N' - dicyclohexylurea was filtered off, the solution was washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to give a solid. It was suspended in hot methanol and treated with the stoichiometric amount of fumaric acid to give a solution from which the N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide fumarate (6.2 g) crystallized. After recrystallization from methanol this compound melted at 204°—206°C.

EXAMPLE 8

A solution of 2 - methoxy - 4 - acetamido - 5 - nitrobenzoyl chloride (8.2 g; 0.03 moles) dissolved in anhydrous tetrahydrofuran (45 ml) was added little by little to another solution of 1 - benzyl - 4 - aminopiperidine (5.25 g; 0.028 moles) and triethylamine (3.87 ml; 0.028 moles) in anhydrous tetrahydrofuran (45 ml) at room temperature. On completion of the addition, the mixture was left at room temperature with stirring overnight and then the mixture was concentrated *in vacuo*, poured into water and extracted with chloroform. The organic solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was suspended in hot methanol and treated with the stoichiometric amount of fumaric acid to give a solution from which the N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide fumarate (13.1 g) crystallized, m.p. 204°—206°C.

EXAMPLE 9

To a solution of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide (3.8 g; 0.01 mole) [prepared as described in Example 1 or 4], in acetone (100 ml) and chloroform (100 ml), methyl

iodide (1.25 ml; 0.02 moles) was added. After stirring at room temperature for 8 hours, an additional amount of methyl iodide (1.25 ml; 0.02 moles) was added and the mixture was left at room temperature for another 15 hours and then filtered. A solid was collected which was washed with diethyl ether to give 4.8 g of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide methyl iodide. After recrystallization from a mixture of water-methanol, it melted at 232°—234°C (dec).

EXAMPLE 10

To a solution of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide (3.7 g; 0.0087 moles) [prepared by the procedure described in Example 1] in glacial acetic acid (25 ml) a 30% hydrogen peroxide solution (2.0 ml) was added. The mixture was heated for 12 hours at a temperature between 70° and 75°C, the solvent removed *in vacuo* and the residue was treated with water, made alkaline with diluted sodium hydroxide aqueous solution and extracted with methylene chloride. The organic solution was washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to give a residue which was triturated with diethyl ether to give N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide N' - oxide (1.6 g), m.p. 184—186°C (dec).

The following Examples illustrate pharmaceutical compositions according to the present invention.

EXAMPLE 11

50,000 capsules each containing 0.5 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride were prepared from the following formulation:

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride	25 g
citric acid	50 g
magnesium stearate	5000 g
lactose spray dried	11175 g
Pluronic F-68 ("Pluronic" is a registered Trade Mark)	2000 g
sodium lauryl sulphate	1750 g

Procedure:

The N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, citric acid, sodium lauryl sulphate, lactose and Pluronic F-68 were mixed together and passed through a screen with an opening of 0.6 mm. The magnesium stearate was added and the mixture encapsulated into gelatine capsules of appropriate size.

EXAMPLE 12

100,000 tablets each containing 1 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride were prepared from the following formulation:

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride	100 g
microcrystalline cellulose	1850 g
lactose spray dried	9820 g
carboxymethyl starch	570 g
sodium stearyl fumarate	80 g
colloidal silicon dioxide	80 g

Procedure:

All the powders were passed through a screen with an opening of 0.6 mm. They were then all mixed in a suitable mixer for 30 minutes and compressed into 125 mg. tablets using 6 mm discs and flat bevelled punches. The disingegration time of the tablets was about 60 seconds.

EXAMPLE 13

10,000 suppositories each containing 1 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride were prepared as follows:

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride	10 g
theobroma oil	19990 g

Procedure:

The theobroma oil was melted and the active compound suspended in it. The mixture was then poured into appropriate suppository moulds to make 2.0 g suppositories.

EXAMPLE 14

50,000 ampoules each containing 0.5 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride were prepared from the following formulation:

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride	25 g
sodium chloride	500 g
water injectable grade q.s.	100 litres

Procedure:

The N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride and the sodium chloride were dissolved in approximately 80 litres of water with slight heating. The solution was diluted with water to 100 litres passed through a bacteria-retaining filter and filled into 2 ml glass ampoules in known manner. The

production of the injectable solution can take place under sterile conditions. It is also possible to work under normal conditions and then to heat-sterilize the filled ampoules.

EXAMPLE 15

1,000 bottles (capacity 150 ml) each containing 15 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride were prepared as follows:

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride	15 g
sorbitol	70000 g
sorbic acid	125 g
citric acid	125 g
distilled water q.s.	150 litres
flavouring agent	q.s.

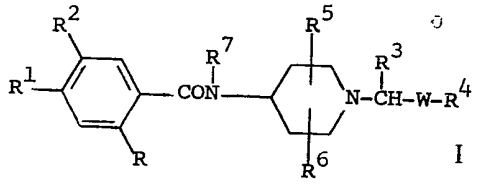
Procedure:

The N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide hydrochloride and the sorbic acid were dissolved in 100 litres of water and then the sorbitol, citric acid and flavouring agent were added with stirring until dissolution. The mixture was diluted to 150 litres and divided amongst the bottles.

Similar compositions to those described in Examples 11 to 15 can be prepared having as the active ingredient piperidine derivatives of general formula I other than N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide, for example other products conforming to that formula mentioned in or at the end of Examples 1 to 10.

WHAT WE CLAIM IS:—

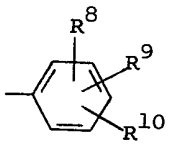
1. Piperidine derivatives of the general formula:—



I

[wherein R represents a halogen atom or a hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy or aralkyloxy group, or a lower acyloxy group in which the acyl moiety is derived from a carboxylic acid; R^1 represents a hydrogen atom or an amino, lower alkylamino, di(lower)alkylamino or a lower acylamino group in which the acyl moiety is derieved from a carboxylic acid; R^2 represents a nitro or trifluoromethyl group or a lower alkylthio or lower alkylsulphinyl group, or R^1 and R^2 together form a triazo group; R^3 represents a hydrogen atom or a lower alkyl or lower alkenyl group, or a cycloalkyl or cycloalkenyl group having from 3 to 7 carbon atoms in the ring, or a phenyl group, R^4 represents a cycloalkyl group having from 3 to 7 carbon atoms in the ring, or an aroyl, aryl or heterocyclyl group; R^5, R^6 and R^7 each represent a hydrogen atom, a lower alkyl, lower alkenyl or a benzyl group, and W represents a single bond or a lower alkylene or lower alkenylene group, with the proviso that when W is a single bond R^3 is other than a cycloalkenyl group] and pharmacologically - acceptable acid addition, alkali metal, alkaline earth metal and quaternary ammonium salts thereof, or N-oxide derivatives thereof.

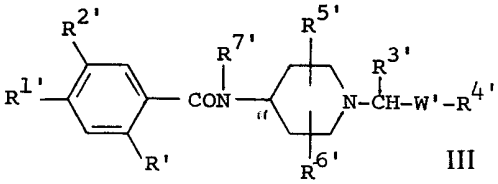
2. Piperidine derivatives according to claim 1 wherein R^4 represents a phenyl group of the general formula:



II

wherein R^8, R^9 and R^{10} each represent a hydrogen or halogen atom, or a lower alkoxy, hydroxy, nitro, amino, lower alkylamino, di(lower alkyl)amino, trifluoromethyl or lower alkyl group, or R^8 and R^9 together form a methylenedioxy group in which case R^{10} represents a hydrogen atom.

3. Piperidine derivatives according to claim 1 of the general formula:



III

[wherein R' represents a halogen atom or a hydroxy, lower alkoxy, allyloxy, propargyloxy, acetoxy or benzyloxy group; $R^{1'}$ represents a hydrogen atom or an amino group or a lower acylamino group in which the acyl moiety is derived from a carboxylic acid and $R^{2'}$ represents a nitro, methylsulphinyl or methylthio group, or $R^{1'}$ and $R^{2'}$ together form a triazo group; $R^{3'}$ represents a hydrogen atom, a lower alkyl or a phenyl group; $R^{4'}$ represents a cyclohexyl group or a phenyl group optionally substituted by one or two halogen atoms, lower alkyl or lower alkoxy groups, or by a methylenedioxy or trifluoromethyl group, or by three methoxy groups, or $R^{4'}$ represents a thienyl or naphthyl group or a

benzoyl group optionally substituted by a halogen atom; $R^{5'}$, $R^{6'}$ and $R^{7'}$ each represent a hydrogen atom or a lower alkyl group, and W' represents a single bond or a methylene, ethylene or vinylene group] and pharmacologically - acceptable acid addition salts thereof.

4. Piperidine derivatives according to claim 1, 2 or 3 wherein W or W' represents a single bond; and pharmacologically - acceptable acid addition salts thereof.

5. Piperidine derivatives according to claim 3 wherein R' represents a lower alkoxy, allyloxy or propargyloxy group, $R^{1'}$ represents an amino group, $R^{2'}$ represents a nitro group, $R^{3'}$ represents a hydrogen atom, $R^{4'}$ represents a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, $R^{5'}$, $R^{6'}$ and $R^{7'}$ each represent a hydrogen atom, and W' represents a single bond or the methylene group, and pharmacologically - acceptable acid addition salts thereof.

6. Piperidine derivatives according to claim 5 wherein R' represents the methoxy or ethoxy group.

7. Piperidine derivatives according to claim 5 or 6 wherein W' represents a single bond.

8. N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide.

9. N - (1 - *p* - Methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide.

10. N - (1 - *p* - Chlorobenzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide.

11. N - (1 - Benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - amino - 5 - nitrobenzamide.

12. N - (1 - phenethylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide.

13. A piperidine derivative conforming to the general formula specified in claim 1 mentioned at the end of Example 1 and other than a compound claimed in claims 8 to 12.

14. The piperidine derivative conforming to the general formula specified in claim 1 obtained as the product of Example 3.

15. Pharmacologically - acceptable acid addition salts of a piperidine derivative as claimed in any one of claims 8 to 14.

16. Pharmacologically - acceptable quaternary salts of a piperidine derivative as claimed in any one of claims 8 to 14.

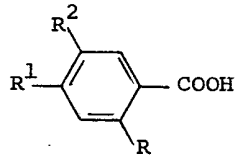
17. The N-oxide derivative of a piperidine derivative as claimed in any one of claims 8 to 14.

18. Pharmacologically - acceptable alkali metal and alkaline earth metal salts of a piperidine derivative as claimed in claim 13 when the piperidine derivative has a hydroxy group present, or claim 14.

19. N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - nitrobenzamide methyl iodide.

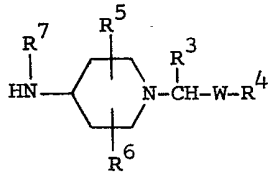
20. N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - nitrobenzamide N'-oxide.

21. Process for the preparation of a piperidine derivative as claimed in claim 1 which comprises reacting a reactive derivative of a benzoic acid of the general formula:



IV

(wherein R, R^1 and R^2 are as defined in claim 1) with a piperidine derivative of the general formula:



V

wherein the various symbols are as defined in claim 1.

22. Process according to claim 21 in which a halide, alkyl ester, anhydride or a mixed anhydride of the benzoic acid is used.

23. Process according to claim 21 or 22 in which the reaction is carried out in the presence of an inert organic solvent at a temperature between −5° and 120°C.

24. Process for the preparation of a piperidine derivative as claimed in claim 1 which comprises reacting a benzoic acid of general formula IV depicted in claim 21 with a piperidine derivative of general formula V depicted in claim 21 in the presence of a dehydrating agent in an inert organic solvent at a temperature between 20° and 110°C.

25. Process for the preparation of a piperidine derivative of the general formula depicted in claim 1 wherein R represents a hydroxy group which comprises reacting a corresponding compound of that formula but wherein R represents a methoxy group with boron tribromide or aluminium trichloride using methylene chloride or benzene as solvent medium at a temperature between 20° and 80°C to convert the methoxy group to hydroxy.

26. Process for the preparation of a piperidine derivative of the general formula depicted in claim 1 wherein R represents a hydroxy group which comprises subjecting a corresponding compound of that formula wherein R represents an acyloxy group to acid or alkaline hydrolysis with hydrochloric acid or sodium or potassium

hydroxide, in an aqueous-alcoholic solution at a temperature between 20° and 90°C.

27. Process according to any one of claims 21 to 24 for the preparation of a piperidine derivative of the general formula depicted in claim 1 wherein R^1 represents an amino group in which the amino group of the benzoic acid reactant of general formula IV depicted in claim 21 is protected by an acyl group, and after the reaction with the piperidine derivative of general formula V depicted in claim 21 the protecting acyl group of the N-acylated intermediate product is removed by acid or alkaline hydrolysis to give a corresponding compound of the general formula depicted in claim 1 wherein R^1 represents an amino group.

28. Process according to any one of claims 21 to 27 followed by the step of converting by a method known *per se* a piperidine derivative of the general formula depicted in claim 1 thus obtained into a pharmacologically - acceptable acid addition salt.

29. Process according to any one of claims 21 to 27 followed by the step of converting by a method known *per se* a piperidine derivative of the general formula depicted in claim 1 wherein R represents a hydroxy group into a pharmacologically - acceptable alkali metal or alkaline earth metal salt.

30. Process according to any one of claims 21 to 27 followed by the step of converting by a method known *per se* a piperidine derivative of the general formula depicted in claim 1 thus obtained into a pharmacologically - acceptable quaternary ammonium salt.

31. Process according to any one of claims 21 to 27 followed by the step of converting by a method known *per se* a piperidine derivative of the general formula depicted in claim 1 thus obtained into an N-oxide derivative.

32. Process for the preparation of a piperidine derivative of the general formula depicted in claim 1, and acid addition, alkali metal, alkaline earth metal and quaternary ammonium salts and N-oxides thereof, substantially as hereinbefore described with especial reference to Example 1.

33. Process for the preparation of a piperidine derivative of the general formula depicted in claim 1 and acid addition salts, quaternary ammonium salts and N-oxide derivatives thereof substantially as hereinbefore described in any one of Examples 2 to 10.

34. Piperidine derivatives of the general formula depicted in claim 1, and acid addition salts, alkali metal or alkaline earth metal salts, quaternary ammonium salts and N-oxide derivatives thereof, when prepared by a process claimed in any one of claims 21 to 33.

35. A pharmaceutical composition which comprises, as active ingredient, a piperidine derivative as claimed in any one of claims 1 to 14, or a pharmacologically - acceptable acid addition, alkali metal, alkaline earth metal or quaternary ammonium salt thereof or N-oxide thereof, in association with a pharmaceutically - acceptable carrier or diluent.

36. A pharmaceutical composition according to claim 35 substantially as hereinbefore described.

37. A pharmaceutical composition according to claim 35 substantially as hereinbefore described in any one of Examples 11 to 15.

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