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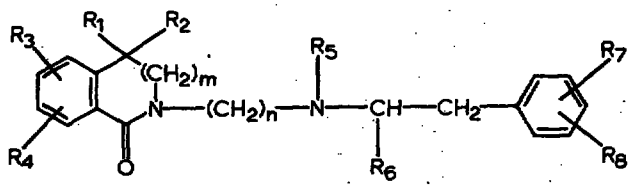


(54) PHENYLETHYLAMINES

(71) We, DR. KARL THOMAE GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a Body Corporate organised under the laws of the Federal Republic of Germany of Biberach an der Riss, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new phenylethylamines, to processes for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention there are provided compounds of general formula I,



(I)

wherein

R_1, R_2 and R_6, which may be the same or different, each represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms;

either R_3 and R_4, which may be the same or different, each represents an alkoxy group containing from 1 to 4 carbon atoms or together represent a methylenedioxy or ethylenedioxy group;

R_5 represents a hydrogen atom, an alkyl group containing from 1 to 4 carbon atoms or a benzyl group;

either R_7 represents a hydrogen atom or an alkoxy group containing from 1 to 4 carbon atoms and R_8 represents an alkoxy group containing from 1 to 4 carbon atoms, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group;

m is 1 or 2; and

n is 2 or 3;

and acid addition salts thereof.

The compounds according to the invention possess interesting pharmacological properties and, in particular, in general, a hypotensive and heart frequency decreasing activity.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible acid addition salts but other acid addition salts may find use, for example, in the preparation of compounds of general formula I and their physiologically compatible acid addition salts.

The compounds according to the invention may, for example, comprise those wherein R_1, R_2 and R_6, which may be the same or different, each represents a hydrogen

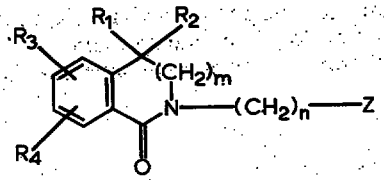
atom or an alkyl group containing from 1 to 3 carbon atoms; either R_3 and R_4, which may be the same or different, each represents an alkoxy group containing from 1 to 3 carbon atoms, or together represent a methylenedioxy or ethylenedioxy group; R_5 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or a benzyl group; and either R_7 represents a hydrogen atom or an alkoxy group containing from 1 to 3 carbon atoms and R_8 represents an alkoxy group containing from 1 to 3 carbon atoms, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group.

Preferred compounds according to the present invention are those wherein R_1 and R_2, which may be the same or different, each represents a hydrogen atom or a methyl group; either R_3 and R_4 each represents a methoxy group or together represent a methylenedioxy or ethylenedioxy group; R_5 represents a hydrogen atom, a methyl group or a benzyl group; R_6 represents a hydrogen atom; and either R_7 represents a hydrogen atom or a methoxy group and R_8 represents a methoxy group, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group, especially those wherein R_6 represents a hydrogen atom or a methyl group.

Particularly preferred compounds according to the invention are 1 - [6,7-dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl-N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane as well as acid addition salts thereof. Further compounds which should be mentioned are 1 - [4,4 - dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2-(3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and acid addition salts thereof.

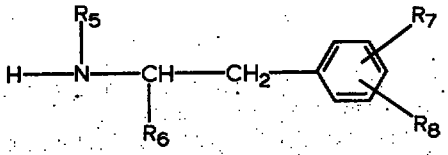
The compounds of general formula I may, for example, be prepared according to the following processes, which processes constitute further features of the present invention.

a) Reaction of a compound of formula II,



(II)

(wherein R_1, R_2, R_3, R_4, m and n are as hereinbefore defined and Z represents a leaving group e.g. a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group) with a compound of formula III,

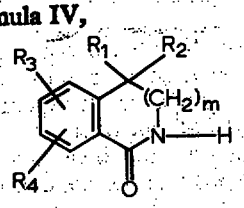


(III)

(wherein R_5, R_6, R_7 and R_8 are as hereinbefore defined).

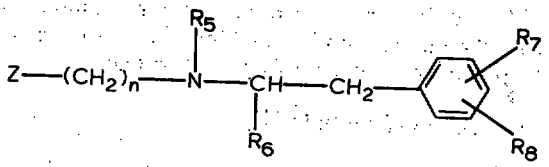
The reaction is optionally carried out in the presence of a solvent, e.g. ether, tetrahydrofuran, methylformamide, dimethylformamide, dimethylsulfoxide, chlorobenzene or benzene, and conveniently at temperatures of from −50 to 250°C depending on the reactivity of the group Z. Preferably, however, the reaction is effected at the boiling point of the reaction mixture. The presence of an acid-binding agent such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate e.g. potassium carbonate or a tertiary organic base e.g. triethylamine or pyridine and/or of an iodide as a reaction accelerator such as for example potassium iodide may also be of advantage.

b) Reaction of a compound of formula IV,



(IV)

(wherein R_1, R_2, R_3, R_4 and m are as hereinbefore defined) with a compound of formula V,

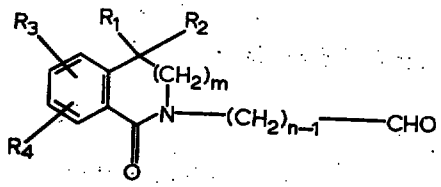


(V)

(wherein R_5, R_6, R_7, R_8 and n are as hereinbefore defined and Z represents a leaving group e.g. a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group).

The reaction is optionally carried out in the presence of a solvent, e.g. acetone, dimethylformamide, dimethylsulfoxide or chlorobenzene, and conveniently at temperatures of from 0 to 150°C depending on the reactivity of the group Z. Preferably, however, the reaction is effected at the boiling point of the reaction mixture. The presence of an acid-binding agent such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate e.g. potassium carbonate, an alkali metal amide, an alkali metal hydride e.g. sodium hydride or a tertiary organic base e.g. triethylamine or pyridine and/or of an iodide as a reaction accelerator such as, for example, potassium iodide may also be of advantage.

c) Reaction of a compound of formula VI,

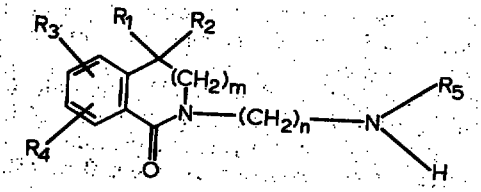


(VI)

(wherein R_1, R_2, R_3, R_4, m and n are as hereinbefore defined) or an acetal thereof with a compound of formula III as hereinbefore defined, in the presence of catalytically activated hydrogen.

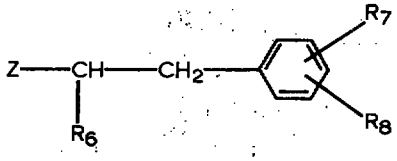
The reaction is preferably carried out in the presence of hydrogen and palladium/charcoal. Preferred hydrogen pressures are about 5 atmospheres. The reaction is preferably effected in the presence of methanol, ethanol or dioxan as solvent and preferably at temperatures of from 0 to 100°C, most preferably from 20 to 80°C.

d) Reaction of a compound of formula VII,



(VII)

(wherein R_1, R_2, R_3, R_4, R_5, m and n are as hereinbefore defined) with a compound of formula VIII,



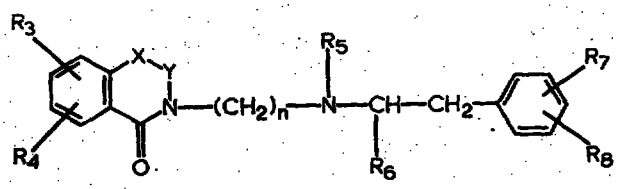
(VIII)

(wherein R_6, R_7 and R_8 are as hereinbefore defined and Z represents a leaving group e.g. a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group).

The reaction is optionally carried out in the presence of a solvent, e.g. acetone, methylene chloride, dimethylformamide, dimethylsulfoxide or chlorobenzene and con-

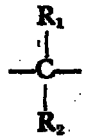
veniently at temperatures of from 0 to 150°C depending on the reactivity of the group Z. Preferably, however, the reaction is effected at the boiling point of the reaction mixture. The presence of an acid-binding agent such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate e.g. potassium carbonate or a tertiary organic base e.g. triethylamine or pyridine and/or of an iodide as a reaction accelerator such as, for example, potassium iodide may be of advantage.

e) Reduction of a compound of formula IX,

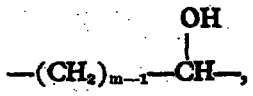


(IX)

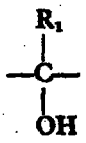
(wherein R_3, R_4, R_5, R_6, R_7, R_8 and n are as hereinbefore defined and either X represents a group of formula



and Y represents a group of formula



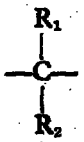
the moiety $-(CH_2)_{m-1}-$ in Y being attached to the group X or X represents a group of formula



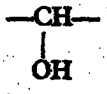
and Y represents a group of formula $-(CH_2)_m-$, R_1, R_2 and m being as hereinbefore defined) whereby the desired compound of formula I is obtained.

The reduction is preferably carried out in the presence of a solvent such as, for example, glacial acetic acid, water, ethanol or ethyl acetate. Reduction may, for example, be effected by means of nascent hydrogen, e.g. by means of zinc in glacial acetic acid, tin in hydrochloric acid or tin(II) chloride in hydrochloric acid or by means of catalytically activated hydrogen, e.g. by means of hydrogen in the presence of palladium/charcoal, preferably at a hydrogen pressure of from 1 to 7 atmospheres. Preferred temperatures for the reduction are from 0 to 150°C, most preferably from 25 to 110°C.

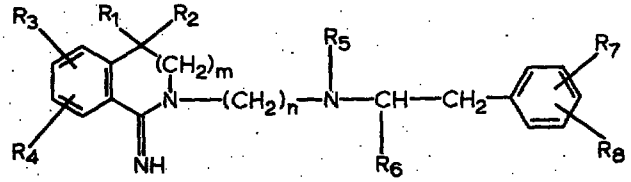
In one embodiment of this process, for example, X in the compound of formula IX represents a group of formula



or of formula



f) Hydrolysis of compound of formula Xa,

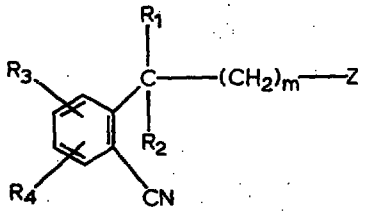


(Xa)

(wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, n and m are as hereinbefore defined) whereby the desired compound of formula I is obtained.

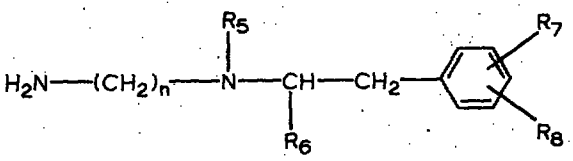
The hydrolysis may, for example, be carried out in the presence of a base such as, e.g. potassium carbonate or in the presence of an acid such as, e.g. hydrochloric acid. An aqueous medium such as aqueous ethanol or aqueous dioxan is preferred. Preferred temperatures for the hydrolysis are from 50°C to the boiling point of the reaction mixture.

The compound of formula Xa may, for example, be obtained, preferably *in situ*, by reaction of a compound of formula X,



(X)

(wherein R_1, R_2, R_3, R_4 and m are as hereinbefore defined and Z represents a leaving group, e.g. a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group) with a compound of formula XI,

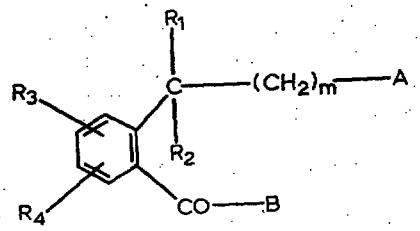


(XI)

(wherein R_5, R_6, R_7, R_8 and n are as hereinbefore defined).

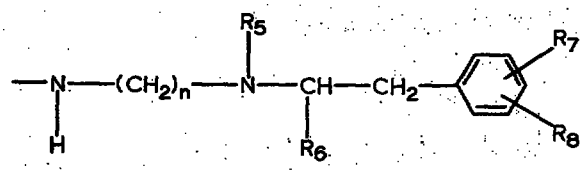
The reaction of the compound of formula X with the compound of formula XI is optionally carried out in the presence of a solvent, e.g. acetone, ethanol, dimethylformamide, dimethylsulfoxide or methylene chloride and conveniently at elevated temperatures, e.g. at temperatures of from 50 to 150°C. The presence of an acid-binding agent such as, for example, an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base e.g. triethylamine or pyridine and/or of an iodide as a reaction accelerator such as, for example, potassium iodide may be of advantage.

g) Cyclisation of a compound of formula XII,



(XII)

(wherein R_1, R_2, R_3, R_4 and m are as hereinbefore defined, one of A and B represents a leaving group and the other of A and B represents a group of formula:

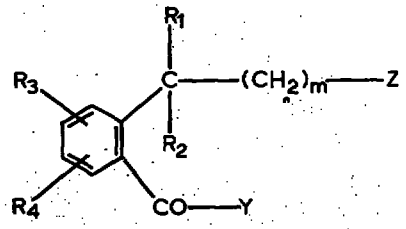


in which R_5, R_6, R_7, R_8 and n are as hereinbefore defined) whereby the desired compound of formula I is obtained.

In the compound of formula XII, preferably A represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group or B represents a chlorine, bromine or iodine atom or an alkoxy or aryloxy group.

The cyclisation is optionally carried out in the presence of a solvent, e.g. acetone, dimethylformamide, dimethylsulfoxide or methylene chloride and conveniently at elevated temperatures, e.g. at temperatures of from 50 to 150°C. The presence of an acid-binding agent such as, for example, an alcoholate, an alkali metal hydroxide, e.g. potassium hydroxide, an alkali metal carbonate or a tertiary organic base e.g. triethylamine or pyridine and/or of an iodide as a reaction accelerator such as, for example, potassium iodide may be of advantage.

The compound of formula XII may, for example, be obtained, preferably *in situ*, by reaction of a compound of formula XIII,

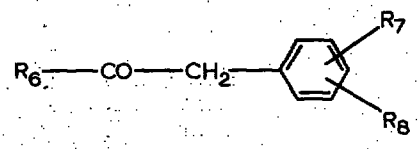


(XIII)

(wherein R_1, R_2, R_3, R_4 and m are as hereinbefore defined and Z and Y, which may be the same or different, each represents a leaving group) with a compound of formula XI as hereinbefore defined. In the compound of formula XIII preferably Z represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group and Y represents a chlorine, bromine or iodine atom or an alkoxy or aryloxy group.

Preferred conditions for the reaction of the compound of formula XIII with the compound of formula XI are generally those described for the cyclisation above except that preferred temperatures are from 0 to 80°C, most preferred being ambient temperature,

h) Reaction of a compound of formula XIV,



(XIV)

(wherein R_6, R_7 and R_8 are as hereinbefore defined) or an acetal or ketal thereof with a compound of formula VII as hereinbefore defined, in the presence of catalytically activated hydrogen.

The reaction is preferably carried out in the presence of hydrogen and palladium/charcoal. Preferred hydrogen pressures are about 5 atmospheres. The reaction is preferably effected in the presence of methanol, ethanol or dioxan as solvent and preferably at temperatures of from 0 to 100°C, most preferably 20 to 80°C.

i) for the preparation of compounds of general formula I wherein R_5 represents a hydrogen atom:

Debenzylation of a compound of formula I as hereinbefore defined wherein R_5 represents a benzyl group.

Debenzylation is preferably effected by means of catalytically activated hydrogen, e.g. with hydrogen in the presence of palladium/charcoal. Preferred hydrogen pressures are from 1 to 7 atmospheres. The debenzylation is preferably effected in the presence

of a solvent such as e.g. ethanol or ethyl acetate and conveniently at temperatures of from 25 to 75°C.

j) for the preparation of compounds of general formula I wherein R_8 represents an alkyl group containing from 1 to 4 carbon atoms:

Alkylation of a compound of formula I as hereinbefore defined wherein R_8 represents a hydrogen atom with an appropriate alkylating agent.

Suitable alkylating agents include, for example, alkyl halides e.g. iodides and bromides, and dialkyl sulphates. Thus, for example the alkylating agent may be methyl iodide, ethyl iodide, isopropyl bromide or dimethyl sulfate. It is preferred to effect the alkylation in the presence of acetone, dimethylformamide or dioxan as solvent. The alkylation may also be optionally carried out in the presence of a base. Preferred alkylation temperatures are from 0 to 50°C.

When it is desired to prepare a compound of formula I wherein R_8 represents a methyl group then the alkylating agent may, for example comprise a mixture of formaldehyde and formic acid in which case the alkylation is preferably effected at the boiling point of the reaction mixture.

k) for the preparation of compounds of general formula I wherein R_8 represents a benzyl group;

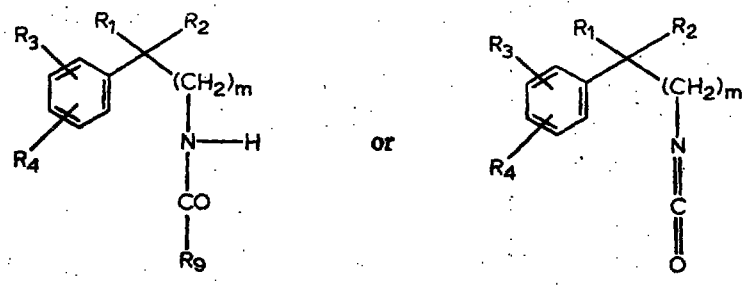
Benzylation of a compound of formula I as hereinbefore defined wherein R_8 represents a hydrogen atom.

Benzylation may, for example, be effected by means of a benzyl halide. Preferred solvents and temperatures are those described for the alkylation in process (j) above. The benzylation may also optionally be effected in the presence of a base.

The compounds of general formula I may, if desired, be converted into their physiologically compatible acid addition salts by reaction with an appropriate acid. Suitable acids include, for example hydrochloric, phosphoric, hydrobromic, sulfuric, lactic, tartaric and maleic acid.

The compounds of general formulae II, III, IV, V, VI, VII, VIII, IX, X, XI, XIII and XIV are either known from the literature or may be prepared by processes analogous to those known from the literature.

For example a compound of formula IV may be obtained by cyclization of a compound of formula:



(wherein R_1, R_2, R_3, R_4 and m are as hereinbefore defined and R_9 represents an alkoxy or alkylthio group) in the presence of an acidic condensation agent e.g. polyphosphoric acid [see S. Karady *et al.* in J. Org. Chem. *27*, 3720 (1962)]. A compound of formula IV thus obtained may be converted into a compound of formula II, VI or VII by means of alkylation.

A compound of formula IX may be obtained by selective reduction of a corresponding carbonyl derivative (see Belgian Patent Specification No. 819.651) with a complex metal hydride.

As already mentioned above, the compounds according to the invention possess interesting pharmacological properties. Those compounds which we have tested exhibit a selective heart frequency decreasing activity as well as a mild hypotensive effect. The compounds of general formula I and their physiologically compatible acid addition salts are thus useful in the treatment of pectanginose complaints, especially chronic coronary insufficiency.

For example the following compounds were tested with regard to their biological activities:

A = 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino]propane hydrochloride,

B = 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino]propane hydrochloride,

C = 1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one-2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino]-propane hydrochloride,

D = 1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one-2 - yl] - 3 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride and

E = 1 - [7,8 - Dimethoxy - 1,2,3,4 - tetrahydro - 5H - 2 - benzazepine - 1 - one - 2-yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino]-propane hydrochloride.

The activity on heart frequency of the test compounds was tested on cats using groups of 2 to 4 cats of both sexes with a body weight of 2.5 to 3.5 kg per dosage. The cats were narcotized with " Nembutal " [registered Trade Mark] (30 mg/kg i.p.) and chloralose-urethane (40 mg/ml of chloralose + 200 mg/ml of urethane as required). The test compound was injected into the *vena saphena* or duodenum as an aqueous solution.

The heart frequency was recorded on a Grass polygraph before and after administration of the test compound by means of a Grass tachograph from an electrocardiogram (precordial lead).

The following table contains the results:

Test compound	Dosage mg/kg	Decrease of heart frequency 1/minute	Duration of activity in minutes
A	0.1 i.v.	- 14	> 30
A	0.3 i.v.	- 31	> 30
A	1.0 i.v.	- 53	> 50
A	10.0 i.v.	- 116	> 70
A	3.0 i.d.	- 44	> 60
A	30.0 i.d.	- 28	> 60
B	0.3 i.v.	- 11	22
B	1.0 i.v.	- 14	17
B	2.0 i.v.	- 24	43
C	0.3 i.v.	- 7	8
C	1.0 i.v.	- 18	11
C	3.0 i.v.	- 32	18
D	1.0 i.v.	- 2	6
D	3.0 i.v.	- 28	16
E	1.0 i.v.	- 15	30
E	2.0 i.v.	- 28	> 20

All dosages of the test compound applied were tolerated without toxic side-effects. The LD_{50} in the mouse for test compound A was 53 mg/kg i.v. (observation time 14 days).

According to a yet further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as hereinbefore defined or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible salts may be incorporated into the conventional pharmaceutical preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Preferred forms include, for example, tablets, coated tablets, powders, suspensions, suppositories and solutions e.g. for injection.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 50 to 250 mg of active ingredient.

The following non-limiting examples serve to illustrate the present invention.

Example 1.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

a) 1 - (6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl) - 3-chloro - propane

2.1 g (44 mmol) of sodium hydride were added to a solution of 8.0 g (41 mmol) of 6,7-dimethoxy-3,4-dihydro-2H-isoquinoline-1-one in 100 ml of dimethylformamide and the mixture obtained was heated up to 80°C for 30 minutes. 20 ml of 1-bromo-3-chloro-propane were then added dropwise thereto and the resultant mixture was heated up to 100°C for 3 hours. The solvent was then removed *in vacuo*. The solid residue was digested in water and the solution obtained was extracted several times with chloroform. The combined organic layers were dried over sodium sulfate and evaporated to dryness. 3.2 g (27.6% of theory) of the desired compound were obtained as a viscous oil by chromatography on silica gel (chloroform/methanol = 150:1).

R_f value (ethyl acetate): 0.8

b) 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

A solution of 1.4 g (4.95 mmol) of 1-(6,7-dimethoxy-3,4-dihydro-2H-isoquinoline-1-one-2-yl)-3-chloro-propane in 50 ml of chlorobenzene was refluxed for 30 hours together with 0.97 g (5.0 mmol) or 3,4-dimethoxyphenylethyl-N-methylamine, 3.0 g of potassium carbonate and a peaked spatula-full of potassium iodide. After cooling the resultant mixture the solid residue was filtered off and the filtrate was evaporated. The residue was purified by chromatography on silica gel (chloroform/methanol = 50:1 to 30:1). The major fractions were evaporated and the base was precipitated as its hydrochloride with ethereal hydrochloric acid.

Yield: 0.4 g (21% of theory).

m.p.: 178—179°C.

Example 2.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-{2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

a) 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - benzyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane

Prepared analogously to Example 1b by reaction of 1 - (6,7 - dimethoxy - 3,4-dihydro - 2H - isoquinoline - 1 - one - 2 - yl) - 3 - chloro - propane with 3,4 - dimethoxyphenylethyl - N - benzylamine in chlorobenzene in the presence of potassium carbonate.

Yield: 2.2 g (69.8% of theory),

R_f value (chloroform/methanol = 19:1): 0.8.

b) 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

Hydrogen was introduced over a period of 4 hours into a solution of 2.17 g (4.2 mmol) 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl]-

3 - [N - benzyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane in 50 ml of methanol and containing 1 g of palladium/charcoal (30%) at room temperature. After absorption of the hydrogen, the catalyst was filtered off and the solution was evaporated *in vacuo*. The residue was dissolved in acetone and the hydrochloride was precipitated by addition of ethereal hydrochloric acid.

Yield: 0.62 g (32% of theory),
m.p.: 132—134°C.

Example 3.

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

a) 1 - [3 - Hydroxy - 4,4 - dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane

0.49 g (13.0 mmol) of sodium borohydride were added at 0°C to a solution of 4.0 g (8.2 mmol) of 1 - [4,4 - dimethyl - 6,7 - dimethoxy - 1,3 - dioxo - (2H,4H) - isoquinoline - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane in 100 ml of dioxan and 20 ml of water. The mixture obtained was stirred at room temperature for 8 hours and subsequently mixed with 100 ml of 2 N hydrochloric acid. After extraction of the resultant mixture with chloroform, the organic layer was dried over sodium sulfate and evaporated *in vacuo*.

Yield: 3.25 g (80% of theory).

b) 1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

2.3 g of zinc dust were added to 3.25 g (6.7 mmol) of 1 - [3 - hydroxy - 4,4 - dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane dissolved in 80 ml of glacial acetic acid. The mixture obtained was refluxed for 4 hours. In order to separate the zinc dust the hot solution was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was subsequently dissolved in chloroform and the solution obtained was extracted with saturated aqueous sodium hydrogen carbonate solution and water, dried over sodium sulfate and evaporated. The crude product was purified by chromatography on silica gel (chloroform/methanol = 19:1). The hydrochloride was obtained by precipitation with ethereal hydrochloric acid.

Yield: 2.2 g (70% of theory),
m.p.: 70°C (decomp.).
R_f value (chloroform/methanol = 9:1): 0.45.

Example 4.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

5.0 g (10.7 mmol) of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride were heated up to 100°C in a mixture of 1.38 g (30 mmol) of formic acid and 1.5 g (20 mmol) of formalin for 1 hour. After cooling, the resultant mixture was made alkaline by the addition of 2N sodium hydroxide solution and the mixture thus obtained was extracted with chloroform. The combined organic phases were washed with water, dried and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (chloroform/methanol = 50:1). The major fractions were evaporated and the base was precipitated as its hydrochloride with ethereal hydrochloric acid.

Yield: 2.7 g (52% of theory),
m.p.: 178—179°C.

Example 5.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

0.5 g of sodium hydride were added to a solution of 3.0 g (14.5 mmol) of 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one in 100 ml of dimethyl-

formamide and the mixture obtained was subsequently heated up to 90°C for 1 hour. 8.5 g (30 mmol) of 1 - [2 - (3,4 - dimethoxyphenyl) - ethyl - methylamino] - 3-chloro - propane dissolved in 100 ml of dimethylformamide were then added dropwise thereto and the resultant mixture was heated up to 140°C for 7 hours. After cooling the mixture was diluted with water and the mixture obtained was extracted several times with chloroform. The organic layers were dried and evaporated to dryness *in vacuo*. The crude product was purified by chromatography on silica gel. The hydrochloride was obtained by precipitation with ethereal hydrochloric acid.

Yield: 0.62 g (10% of theory),
m.p.: 178—179°C.

Example 6.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-{2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

Hydrogen was introduced at a temperature of 50°C and at 5 atm. pressure for 4 hours into a solution of 4.2 g (15.9 mmol) of 3 - [6,7 - dimethoxy - 3,4 - dihydro-2H - isoquinoline - 1 - one - 2 - yl] - propionaldehyde and 2.9 g (16 mmol) of 3,4-dimethoxyphenylethylamine in 100 ml of ethanol also containing 0.3 g of palladium/charcoal (10%). After absorption of the hydrogen, the catalyst was filtered off and the solution was evaporated *in vacuo*. The hydrochloride was obtained by precipitation with ethereal hydrochloric acid.

Yield: 2.17 g (42% of theory),
m.p.: 132—134°C.

Example 7.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-{2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

Hydrogen was introduced at a temperature of 50°C and at 5 atm. pressure within 4 hours into a solution of 2.6 g (10 mmol) of 1 - [6,7 - dimethoxy - 3,4 - dihydro-2H - isoquinoline - 1 - one - 2 - yl] - 3 - amino - propane and 1.8 g (10 mmol) of 2 - (3,4 - dimethoxyphenyl) - acetaldehyde in 100 ml of ethanol also containing 0.5 g of palladium/charcoal (10%). After absorption of the hydrogen, the catalyst was filtered off and the solution was evaporated *in vacuo*. The hydrochloride was obtained by precipitation with ethereal hydrochloric acid.

Yield: 1.0 g (22% of theory),
m.p.: 132—134°C.

Example 8.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

a) 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - imino - 2 - yl] - 3-[N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane

6.7 g (25 mmol) of 2 - cyano - 4,5 - dimethoxyphenylethyl bromide and 6.3 g (25 mmol) of 1 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino]-3 - amino - propane were refluxed together in 80 ml of ethanol for 6 hours. After cooling the mixture obtained, the solvent was removed *in vacuo* and the crude product was used in stage (b) without further purification, R_f value (chloroform/methanol = 19:1): 0.6.

b) 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

5.2 g (10.8 mmol) of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline-1 - imino - 2 - yl] - 3 -[N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl}-amino] - propane and 10 g of potassium carbonate were refluxed together in a mixture of 50 ml of ethanol and 80 ml of water for 8 hours. The mixture obtained was evaporated *in vacuo* and the residue was purified by chromatography on silica gel (chloroform/methanol = 50:1 to 30:1). The major fractions were evaporated and the hydrochloride was precipitated with ethereal hydrochloric acid.

Yield: 1.07 g (9% of theory),
m.p.: 178—179°C.

Example 9.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

A solution of 6.6 g (25 mmol) of 2 - (2 - chloroethyl) - 4,5 - dimethoxy - benzoyl chloride in 20 ml of acetone was added dropwise at room temperature to a mixture of 6.3 g (25 mmol) of 1 - [N - methyl - N - {2 - (3,4 - dimethoxy - phenyl) - ethyl}-amino] - 3 - amino - propane and 7.0 g of potassium hydroxide in 100 ml of acetone. The mixture obtained was subsequently refluxed for 4 hours. After cooling the insoluble matter was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (chloroform/methanol = 19:1). The hydrochloride was obtained by precipitation with ethereal hydrochloric acid.

Yield: 2.6 g (22% of theory).

m.p.: 178—179°C.

Example 10.

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N-methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

6.3 g (22.6 mmol) of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline-1 - one - 2 - yl] - 3 - amino - propane and 4.6 g (23 mmol) of 3,4 - dimethoxyphenyl ethyl chloride, together with 5.0 g of potassium carbonate, were refluxed for 5 hours in 100 ml of chlorobenzene. After cooling, the solution obtained was filtered and the filtrate was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (chloroform/methanol = 19:1). The fractions were evaporated and the residue was dissolved in acetone. The hydrochloride was precipitated by addition of ethereal hydrochloric acid.

Yield: 2.9 g (27% of theory),

m.p.: 178—179°C.

The following compounds were prepared analogously to the foregoing examples:

1 - [6,7 - Ethylenedioxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl]-3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.40 (chloroform/methanol = 19:1)

1 - [6,7 - Methylenedioxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl]-3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl} - amino] - propane hydrochloride

R_f value: 0.25 (chloroform/methanol = 19:1)

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 2-[N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - ethane hydrochloride

R_f value: 0.25 (chloroform/methanol = 19:1)

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 2-[N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - ethane hydrochloride

R_f value: 0.15 (chloroform/methanol = 19:1)

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - methyl - N - {2 - (4 - methoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.35 (chloroform/methanol = 19:1)

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - methyl - N - {2 - (3 - methoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.30 (chloroform/methanol = 19:1)

1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3-[N - methyl - N - {2 - (3,4 - methylenedioxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.40 (chloroform/methanol = 19:1)

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one-2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.25 (chloroform/methanol = 19:1)

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one-2 - yl] - 3 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.20 (chloroform/methanol = 19:1)

Calculated: C 62.20 H 7.63 N 5.58
Found: 62.80 7.95 5.31

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1-one - 2 - yl] - 2 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino]-ethane hydrochloride

R_f value: 0.40 (chloroform/methanol = 9:1)

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1-one - 2 - yl] - 2 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - ethane hydrochloride

R_f value: 0.20 (chloroform/methanol = 9:1)

1 - [7,8 - Dimethoxy - 1,2,3,4 - tetrahydro - 5H - 2 - benzazepine - 1 - one - 2-yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.20 (chloroform/methanol = 9:1)

IR spectrum (potassium bromide): $>CO$ at 1640 cm^{-1}

1 - [7,8 - Dimethoxy - 1,2,3,4 - tetrahydro - 5H - 2 - benzazepine - 1 - one - 2-yl] - 3 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

R_f value: 0.10 (chloroform/methanol = 3:1)

Example A.

Tablets containing 100 mg of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl)-ethyl} - amino] - propane hydrochloride

Composition:	
Active ingredient	100.0 mg
lactose	50.0 mg
polyvinylpyrrolidone	5.0 mg
carboxymethylcellulose	19.0 mg
magnesium stearate	1.0 mg
	175.0 mg

Method of preparation:

The active ingredient and lactose were homogeneously moistened with an aqueous solution of the polyvinylpyrrolidone and passed through a screen. After drying, the granulate thus obtained was mixed with the remaining ingredients and the resultant mixture was pressed into tablets in the conventional manner.

Example B.

Coated tablets containing 50 mg of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl)-ethyl} - amino] - propane hydrochloride

1 coated tablet core contains:	
Active ingredient	50.0 mg
dried corn starch	20.0 mg
soluble starch	2.0 mg
carboxymethylcellulose	7.0 mg
magnesium stearate	1.0 mg
	80.0 mg

Method of preparation:

The ingredients were processed to coated tablet cores as described in Example A. The cores were then coated with sugar and gum aarbic according to conventional methods.

Example C.

Suppositories containing 150 mg of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl)-ethyl} - amino] - propane hydrochloride

Composition:	
Active ingredient	150.0 mg
suppository mass	1 550.0 mg
	1 700.0 mg

Method of preparation:

The active ingredient was stirred into the molten suppository mass and the liquid suspension thus formed was poured into cooled suppository moulds.

Example D.

Suspension containing 50 mg/ml of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H-isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

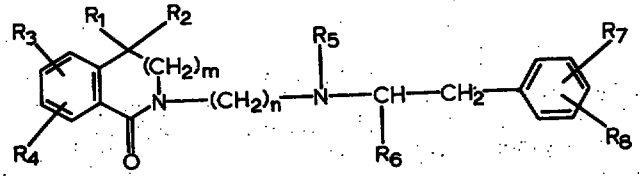
100 ml of suspension contain	
Active ingredient	5.0 g
carboxymethylcellulose	0.1 g
methyl *p*-hydroxybenzoate	0.05 g
propyl *p*-hydroxybenzoate	0.01 g
sugar	10.0 g
glycerine	5.0 g
70% sorbitol solution	20.0 g
flavouring	0.3 g
distilled water ad	100.0 ml

Method of preparation:

The benzoic acid esters, as well as the glycerine and carboxymethylcellulose, were dissolved whilst stirring in the water heated up to 70°C. The solution obtained was cooled to room temperature and the active ingredient was then added whilst stirring and homogeneously dispersed. After adding and dissolving the sugar, the sorbitol solution and the flavouring, the suspension obtained was deaerated under vacuum whilst stirring.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

R_1, R_2 and R_6, which may be the same or different, each represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms;

either R_3 and R_4, which may be the same or different, each represents an alkoxy group containing from 1 to 4 carbon atoms or together represent a methylenedioxy or ethylenedioxy group;

R_5 represents a hydrogen atom, an alkyl group containing from 1 to 4 carbon atoms or a benzyl group;

either R_7 represents a hydrogen atom or an alkoxy group containing from 1 to 4 carbon atoms and R_8 represents an alkoxy group containing from 1 to 4 carbon atoms, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group;

m is 1 or 2; and

n is 2 or 3;

and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R_1, R_2 and R_6, which may be the

Example C.

Suppositories containing 150 mg of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl)-ethyl} - amino] - propane hydrochloride

Composition:	
Active ingredient	150.0 mg
suppository mass	1 550.0 mg
	1 700.0 mg

Method of preparation:

The active ingredient was stirred into the molten suppository mass and the liquid suspension thus formed was poured into cooled suppository moulds.

Example D.

Suspension containing 50 mg/ml of 1 - [6,7 - dimethoxy - 3,4 - dihydro - 2H-isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane hydrochloride

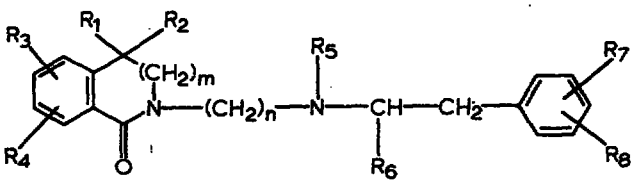
100 ml of suspension contain	
Active ingredient	5.0 g
carboxymethylcellulose	0.1 g
methyl *p*-hydroxybenzoate	0.05 g
propyl *p*-hydroxybenzoate	0.01 g
sugar	10.0 g
glycerine	5.0 g
70% sorbitol solution	20.0 g
flavouring	0.3 g
distilled water ad	100.0 ml

Method of preparation:

The benzoic acid esters, as well as the glycerine and carboxymethylcellulose, were dissolved whilst stirring in the water heated up to 70°C. The solution obtained was cooled to room temperature and the active ingredient was then added whilst stirring and homogeneously dispersed. After adding and dissolving the sugar, the sorbitol solution and the flavouring, the suspension obtained was deaerated under vacuum whilst stirring.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

R_1, R_2 and R_6, which may be the same or different, each represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms;

either R_3 and R_4, which may be the same or different, each represents an alkoxy group containing from 1 to 4 carbon atoms or together represent a methylenedioxy or ethylenedioxy group;

R_5 represents a hydrogen atom, an alkyl group containing from 1 to 4 carbon atoms or a benzyl group;

either R_7 represents a hydrogen atom or an alkoxy group containing from 1 to 4 carbon atoms and R_8 represents an alkoxy group containing from 1 to 4 carbon atoms, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group;

m is 1 or 2; and

n is 2 or 3;

and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R_1, R_2 and R_6, which may be the

same or different, each represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms; either R_3 and R_4, which may be the same or different, each represents an alkoxy group containing from 1 to 3 carbon atoms, or together represent a methylenedioxy or ethylenedioxy group; R_5 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or a benzyl group; and either R_7 represents a hydrogen atom or an alkoxy group containing from 1 to 3 carbon atoms and R_8 represents an alkoxy group containing from 1 to 3 carbon atoms, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group.

3. Compounds as claimed in claim 2 wherein R_1 and R_2, which may be the same or different, each represents a hydrogen atom or a methyl group; either R_3 and R_4 each represents a methoxy group or together represent a methylenedioxy or ethylenedioxy group; R_5 represents a hydrogen atom, a methyl group or a benzyl group; R_6 represents a hydrogen atom; and either R_7 represents a hydrogen atom or a methoxy group and R_8 represents a methoxy group, or R_7 and R_8 together represent a methylenedioxy or ethylenedioxy group.

4. Compounds as claimed in claim 3 wherein R_6 represents a hydrogen atom or a methyl group.

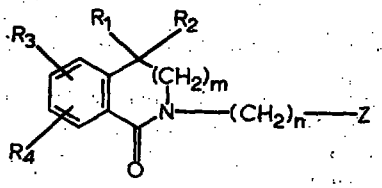
5. 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and acid addition salts thereof.

6. 1 - [6,7 - Dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and acid addition salts thereof.

7. 1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 3,4 - dihydro - 2H - isoquinoline - 1 - one - 2 - yl] - 3 - [N - methyl - N - {2 - (3,4 - dimethoxyphenyl) - ethyl} - amino] - propane and acid addition salts thereof.

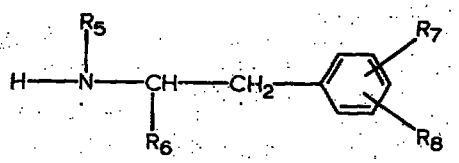
8. Compounds as claimed in any of the preceding claims in the form of physiologically compatible acid addition salts.

9. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula II,



(II)

(wherein R_1, R_2, R_3, R_4, m and n are as defined in claim 1 and Z represents a leaving group) with a compound of formula III,



(III)

(wherein R_5, R_6, R_7 and R_8 are as defined in claim 1).

10. A process as claimed in claim 9 wherein, in the compound of formula II, Z represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group.

11. A process as claimed in claim 9 or claim 10 wherein the reaction is effected in the presence of a solvent.

12. A process as claimed in claim 11 wherein the solvent comprises ether, tetrahydrofuran, methylformamide, dimethylformamide, dimethylsulfoxide, chlorobenzene or benzene.

13. A process as claimed in any of claims 9 to 12 wherein the reaction is effected at temperatures of from −50 to 250°C.

14. A process as claimed in any of claims 9 to 12 wherein the reaction is effected at the boiling point of the reaction mixture.

15. A process as claimed in any of claims 9 to 14 wherein the reaction is effected in the presence of an acid-binding agent.

16. A process as claimed in claim 15 wherein the acid-binding agent comprises

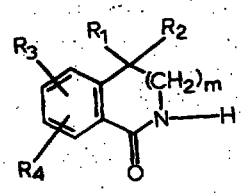
an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base.

17. A process as claimed in claim 16 wherein the acid-binding agent comprises potassium carbonate, triethylamine or pyridine.

18. A process as claimed in any of claims 9 to 17 wherein the reaction is effected in the presence of an iodide as a reaction accelerator.

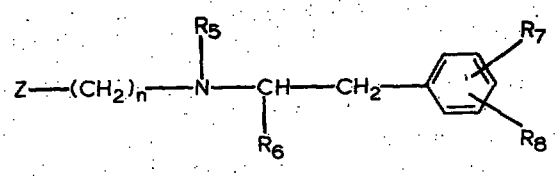
19. A process as claimed in claim 18 wherein the reaction accelerator comprises potassium iodide.

20. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula IV,



(IV)

(wherein R_1, R_2, R_3, R_4 and m are as defined in claim 1) with a compound of formula V,



(V)

(wherein R_5, R_6, R_7, R_8 and n are as defined in claim 1 and Z represents a leaving group).

21. A process as claimed in claim 20 wherein, in the compound of formula V, Z is as defined in claim 10.

22. A process as claimed in claim 20 or claim 21 wherein the reaction is effected in the presence of a solvent.

23. A process as claimed in claim 22 wherein the solvent comprises acetone, dimethylformamide, dimethylsulfoxide or chlorobenzene.

24. A process as claimed in any of claims 20 to 23 wherein the reaction is effected at temperatures of from 0 to 150°C.

25. A process as claimed in any of claims 20 to 23 wherein the reaction is effected at the boiling point of the reaction mixture.

26. A process as claimed in any of claims 20 to 25 wherein the reaction is effected in the presence of an acid-binding agent.

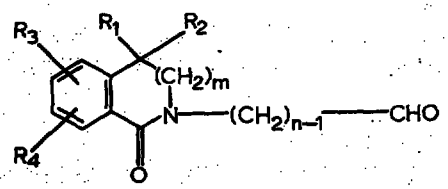
27. A process as claimed in claim 26 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate, an alkali metal amide, an alkali metal hydride or a tertiary organic base.

28. A process as claimed in claim 27 wherein the acid-binding agent comprises potassium carbonate, sodium hydride, triethylamine or pyridine.

29. A process as claimed in any of claims 20 to 28 wherein the reaction is effected in the presence of an iodide as a reaction accelerator.

30. A process as claimed in claim 29 wherein the reaction accelerator comprises potassium iodide.

31. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula VI,



(VI)

(wherein R_1, R_2, R_3, R_4, m and n are as defined in claim 1), or an acetal thereof, with

a compound of formula III as defined in claim 9 in the presence of catalytically activated hydrogen.

32. A process as claimed in claim 31 wherein the hydrogen is at a pressure of about 5 atmospheres.

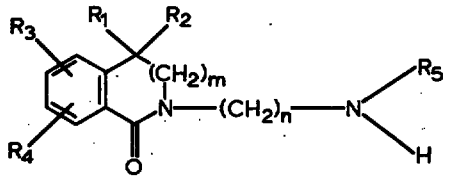
33. A process as claimed in claim 31 or claim 32 wherein the reaction is effected in the presence of hydrogen and palladium/charcoal.

34. A process as claimed in any of claims 31 to 33 wherein the reaction is effected in the presence of methanol, ethanol or dioxan as solvent.

35. A process as claimed in any of claims 31 to 34 wherein the reaction is effected at temperatures of from 0 to 100°C.

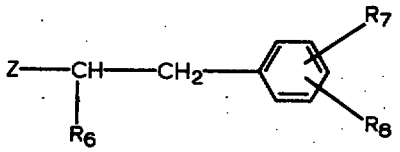
36. A process as claimed in claim 35 wherein the reaction is effected at temperatures of from 20 to 80°C.

37. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula VII,



(VII)

(wherein R_1, R_2, R_3, R_4, R_5, m and n are as defined in claim 1) with a compound of formula VIII,



(VIII)

(wherein R_6, R_7 and R_8 are as defined in claim 1 and Z represents a leaving group).

38. A process as claimed in claim 37 wherein, in the compound of formula VIII, Z is as defined in claim 10.

39. A process as claimed in claim 37 or claim 38 wherein the reaction is effected in the presence of a solvent.

40. A process as claimed in claim 39 wherein the solvent comprises acetone, methylene chloride, dimethylformamide, dimethylsulfoxide or chlorobenzene.

41. A process as claimed in any of claims 37 to 40 wherein the reaction is effected at temperatures of from 0 to 150°C.

42. A process as claimed in any of claims 37 to 40 wherein the reaction is effected at the boiling point of the reaction mixture.

43. A process as claimed in any of claims 37 to 42 wherein the reaction is effected in the presence of an acid-binding agent.

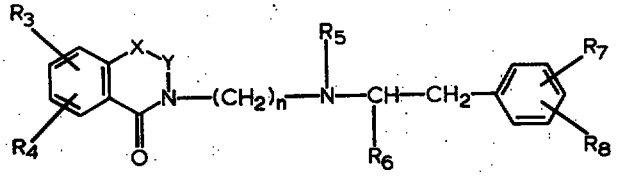
44. A process as claimed in claim 43 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base.

45. A process as claimed in claim 44 wherein the acid-binding agent comprises potassium carbonate, triethylamine or pyridine.

46. A process as claimed in any of claims 37 to 45 wherein the reaction is effected in the presence of an iodide as a reaction accelerator.

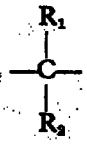
47. A process as claimed in claim 46 wherein the reaction accelerator comprises potassium iodide.

48. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reducing a compound of formula IX,

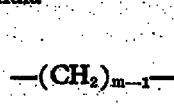


(IX)

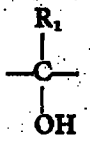
(wherein R_3, R_4, R_5, R_6, R_7 and R_8 are as defined in claim 1 and either X represents a group of formula



and Y represents a group of formula



the moiety $-(CH_2)_{m-1}-$ in Y being attached to the group X, or X represents a group of formula



and Y represents a group of formula $-(CH_2)_m-$, R_1, R_2 and m being as defined in claim 1) whereby the desired compound of formula I is obtained.

49. A process as claimed in claim 48 wherein reduction is effected by means of nascent hydrogen.

50. A process as claimed in claim 49 wherein reduction is effected by means of zinc in glacial acetic acid, tin in hydrochloric acid or tin(II) chloride in hydrochloric acid.

51. A process as claimed in claim 48 wherein reduction is effected by means of catalytically activated hydrogen.

52. A process as claimed in claim 51 wherein reduction is effected by means of hydrogen in the presence of palladium/charcoal.

53. A process as claimed in claim 51 or claim 52 wherein the hydrogen is at a pressure of from 1 to 7 atmospheres.

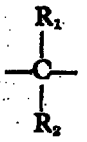
54. A process as claimed in any of claims 48 to 53 wherein the reduction is effected in the presence of a solvent.

55. A process as claimed in claim 54 wherein the solvent comprises glacial acetic acid, water, ethanol or ethyl acetate.

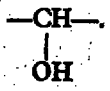
56. A process as claimed in any of claims 48 to 55 wherein the reduction is effected at temperatures of from 0 to 150°C.

57. A process as claimed in claim 56 wherein the reduction is effected at temperatures of from 25 to 110°C.

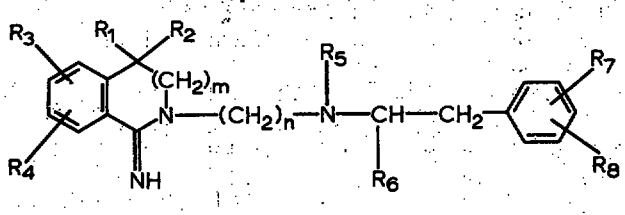
58. A process as claimed in any of claims 48 to 55 wherein, in the compound of formula IX, X represents a group of formula



or of formula



59. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises hydrolysing a compound of formula Xa,



(Xa)

(wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, n and m are as defined in claim 1) whereby the desired compound of formula I is obtained.

60. A process as claimed in claim 59 wherein hydrolysis is effected in the presence of a base.

61. A process as claimed in claim 60 wherein the base comprises potassium carbonate.

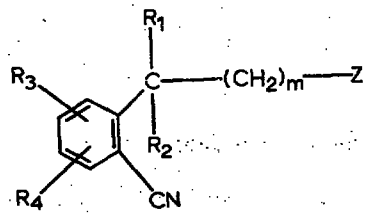
62. A process as claimed in claim 59 wherein hydrolysis is effected in the presence of an acid.

63. A process as claimed in claim 62 wherein the acid comprises hydrochloric acid.

64. A process as claimed in any of claims 59 to 63 wherein the hydrolysis is effected in the presence of aqueous ethanol or aqueous dioxan as solvent.

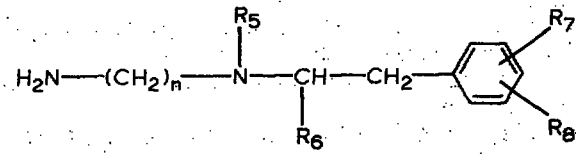
65. A process as claimed in any of claims 59 to 64 wherein the hydrolysis is effected at temperatures of from 50°C to the boiling point of the reaction mixture.

66. A process as claimed in any of claims 59 to 65 wherein the compound of formula Xa is obtained by reaction of a compound of formula X,



(X)

(wherein R_1, R_2, R_3, R_4 and m are as defined in claim 1 and Z represents a leaving group) with a compound of formula XI,



(XI)

(wherein R_5, R_6, R_7, R_8 and n are as defined in claim 1).

67. A process as claimed in claim 66 wherein, in the compound of formula X, Z is as defined in claim 10.

68. A process as claimed in claim 66 or claim 67 (wherein the reaction of the compound of formula X with the compound of formula XI is effected in the presence of a solvent.

69. A process as claimed in claim 68 wherein the solvent comprises acetone, ethanol, dimethylformamide, dimethylsulfoxide or methylene chloride.

70. A process as claimed in any of claims 66 to 69 wherein the reaction of the compound of formula X with the compound of formula XI is effected at elevated temperatures.

71. A process as claimed in claim 70 wherein the reaction of the compound of formula X with the compound of formula XI is effected at temperatures of from 50 to 150°C.

72. A process as claimed in any of claims 66 to 71 wherein the reaction of the compound of formula X with the compound of formula XI is effected in the presence of an acid-binding agent.

73. A process as claimed in claim 72 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base.

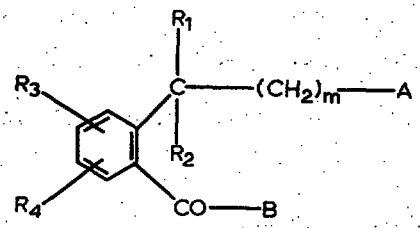
74. A process as claimed in claim 73 wherein the acid-binding agent comprises triethylamine or pyridine.

75. A process as claimed in any of claims 66 to 74 wherein the reaction of the compound of formula X with the compound of formula XI is effected in the presence of an iodide as a reaction accelerator.

76. A process as claimed in claim 75 wherein the reaction accelerator comprises potassium iodide.

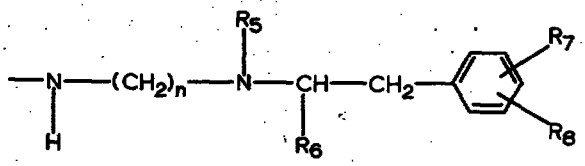
77. A process as claimed in any of claims 66 to 76 wherein the compound of formula Xa is formed *in situ*.

78. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises cyclising a compound of formula XII,



(XII)

(wherein R_1, R_2, R_3, R_4 and m are as defined in claim 1, one of A and B represents a leaving group and the other of A and B represents a group of formula:



in which R_5, R_6, R_7, R_8 and n are as defined in claim 1) whereby the desired compound of formula I is obtained.

79. A process as claimed in claim 78 wherein, in the compound of formula XII, A represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group, or B represents a chlorine, bromine or iodine atom or an alkoxy or aryloxy group.

80. A process as claimed in claim 78 or claim 79 wherein the cyclisation is effected in the presence of a solvent.

81. A process as claimed in claim 80 wherein the solvent comprises acetone, dimethylformamide, dimethylsulfoxide or methylene chloride.

82. A process as claimed in any of claims 78 to 81 wherein the cyclisation is effected at elevated temperatures.

83. A process as claimed in claim 82 wherein cyclisation is effected at temperatures of from 50 to 150°C.

84. A process as claimed in any of claims 78 to 83 wherein the cyclisation is effected in the presence of an acid-binding agent.

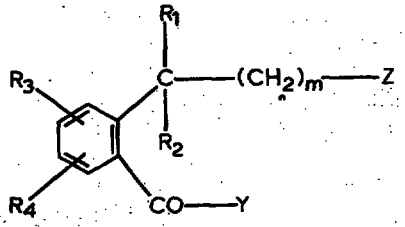
85. A process as claimed in claim 84 wherein the acid-binding agent comprises an alcoholate, an alkali metal hydroxide, an alkali metal carbonate or a tertiary organic base.

86. A process as claimed in claim 85 wherein the acid-binding agent comprises potassium hydroxide, triethylamine or pyridine.

87. A process as claimed in any of claims 78 to 86 wherein the cyclisation is effected in the presence of an iodide as a reaction accelerator.

88. A process as claimed in claim 87 wherein the reaction accelerator comprises potassium iodide.

89. A process as claimed in any of claims 78 to 88 wherein the compound of formula XII is obtained by reaction of a compound of formula XIII,



(XIII)

(wherein R_1, R_2, R_3, R_4 and m are as defined in claim 1 and Z and Y, which may be the same or different, each represents a leaving group) with a compound of formula XI as defined in claim 66.

90. A process as claimed in claim 89 wherein, in the compound of formula XIII, Z represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group and Y represents a chlorine, bromine or iodine atom or an alkoxy or aryloxy group.

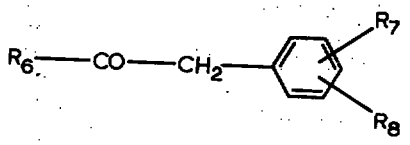
91. A process as claimed in claim 89 or claim 90 wherein the reaction of the compound of formula XIII with the compound of formula XI is effected under the conditions defined for the cyclisation in any of claims 80, 81 and 84 to 88.

92. A process as claimed in any of claims 89 to 91 wherein the reaction of the compound of formula XIII with the compound of formula XI is effected at temperatures of from 0 to 80°C.

93. A process as claimed in claim 92 wherein the reaction of the compound of formula XIII with the compound of formula XI is effected at ambient temperature.

94. A process as claimed in any of claims 89 to 93 wherein the compound of formula XII is formed *in situ*.

95. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula XIV,



(XIV)

(wherein R_6, R_7 and R_8 are as defined in claim 1) or an acetal or ketal thereof, with a compound of formula VII as defined in claim 37, in the presence of catalytically activated hydrogen.

96. A process as claimed in claim 95 wherein the reaction is effected in the presence of hydrogen and palladium/charcoal.

97. A process as claimed in claim 95 or claim 96 wherein the reaction is effected with a hydrogen pressure of about 5 atmospheres.

98. A process as claimed in any of claims 95 to 97 wherein the reaction is effected in the presence of methanol, ethanol or dioxan as solvent.

99. A process as claimed in any of claims 95 to 98 wherein the reaction is effected at temperatures of from 0 to 100°C.

100. A process as claimed in claim 99 wherein the reaction is effected at temperatures of from 20 to 80°C.

101. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_5 represents a hydrogen atom which comprises debenzylating a compound of formula I as defined in claim 1 wherein R_5 represents a benzyl group.

102. A process as claimed in claim 101 wherein debenzylation is effected by means of catalytically activated hydrogen.

103. A process as claimed in claim 102 wherein debenzylation is effected at a hydrogen pressure of from 1 to 7 atmospheres.

104. A process as claimed in claim 102 or claim 103 wherein debenzylation is effected by means of hydrogen in the presence of palladium/charcoal.

105. A process as claimed in any of claims 101 to 104 wherein the reaction is effected in the presence of a solvent.

106. A process as claimed in claim 105 wherein the solvent comprises ethanol or ethyl acetate.

107. A process as claimed in any of claims 101 to 106 wherein the debenzylation is effected at temperatures of from 25 to 75°C.

108. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_5 represents an alkyl group containing from 1 to 4 carbon atoms which comprises alkylating a compound of formula I as defined in claim 1 wherein R_5 represents a hydrogen atom with an appropriate alkylating agent.

109. A process as claimed in claim 108 wherein the alkylating agent comprises an alkyl halide or dialkyl sulphate.

110. A process as claimed in claim 109 wherein the alkylating agent comprises an alkyl iodide or bromide.

111. A process as claimed in any of claims 108 to 110 wherein the alkylation is effected in the presence of acetone, dimethylformamide or dioxan as solvent.

112. A process as claimed in any of claims 108 to 111 wherein the alkylation is effected in the presence of a base.

113. A process as claimed in any of claims 108 to 112 wherein the reaction is effected at temperatures of from 0 to 50°C.

114. A process as claimed in claim 108, for the preparation of compounds of general formula I wherein R_5 represents a methyl group, wherein the alkylating agent comprises a mixture of formaldehyde and formic acid.

115. A process as claimed in claim 114 wherein the alkylation is effected at the boiling point of the reaction mixture.

116. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_5 represents a benzyl group which comprises benzylating a compound of formula I as defined in claim 1 wherein R_5 represents a hydrogen atom.

117. A process as claimed in claim 116 wherein benzylation is effected by means of a benzyl halide.

118. A process as claimed in claim 116 or claim 117 wherein the benzylation is effected under the conditions defined for the alkylation in any of claims 111 to 113.

119. A process for the preparation of physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an appropriate acid.

120. A process as claimed in claim 119 wherein the acid comprises hydrochloric, phosphoric, hydrobromic, sulfuric, lactic, tartaric or maleic acid.

121. A process for the preparation of compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts substantially as herein described.

122. A process for the preparation of compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts substantially as herein described in any of Examples 1 to 10.

123. Compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts when prepared by a process as claimed in any of claims 9 to 122.

124. Compounds of general formula I as defined in claim 1 and their physiologically compatible acid addition salts when prepared by a process as claimed in any of claims 9 to 47, 58 to 115, 119, 120 and 122.

125. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

126. Compositions as claimed in claim 125 in a form suitable for oral, rectal or parenteral administration.

127. Compositions as claimed in claim 125 or claim 126 in the form of tablets, coated tablets, powders, suspensions, suppositories and solutions.

128. Compositions as claimed in any of claims 125 to 127 in the form of dosage units.

129. Composition as claimed in claim 128 wherein each dosage unit contains from 50 to 250 mg of active ingredient.

130. Compositions as claimed in any of claims 125 to 129 wherein the active ingredient comprises a compound as claimed in any of claims 5 to 7.

131. Pharmaceutical compositions as claimed in claim 125 substantially as herein described.

132. Pharmaceutical compositions substantially as herein described in any of Examples A to D.

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