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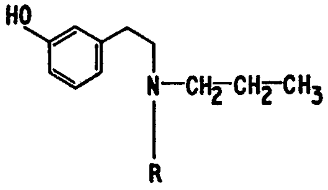
(54) Derivatives of 3-(2-aminoethyl)phenol

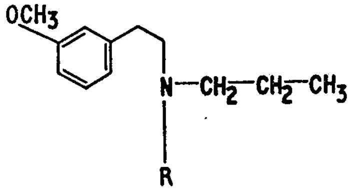
(57) Compounds of the formula:



(I)

(wherein R is a radical R′ or an alkyl radical containing from 1 to 6 carbon atom and substituted by a radical R′, the radical R′ being an aryl, a diarylmethyl, a cycloalkyl or an aromatic heterocyclic radical, always providing that R is not a 2-phenylethyl radical) and acid addition salts thereof possess dopaminergic properties and inhibit the secretion of prolactin in humans and animals.

The compounds of formula (I) may be prepared by hydrolysing corresponding compounds of the formula:



(II)

The compounds of formula II may be prepared by a variety of routes using 2-(2-methoxyphenyl)-ethylamine or 2-(2-methoxyphenyl)-acetic acid as starting material.

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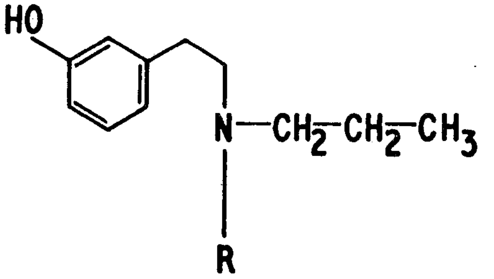
SPECIFICATION

New Derivatives of 3-(2-aminoethyl)phenol

The present invention relates to new derivatives of 3-(2-aminoethyl)phenol, which may be useful as medicaments.

Thus, in one aspect, this invention provides new derivatives of 3-(2-aminoethyl)phenols, being the compounds of general formula:

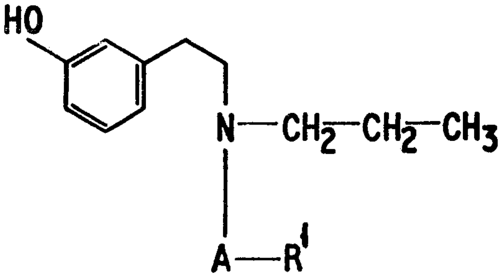


(I)

(wherein R may be a radical R′ or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms and substituted by a radical R′, the radical R′ being an aryl radical, a diaryl-methyl radical, a cycloalkyl radical or an aromatic heterocyclic radical, always providing that R may not represent a 2-phenylethyl radical) and the acid addition salts thereof formed with mineral or organic acids.

Where the radical R′ in general formula I is the aryl radical, that aryl radical will commonly be a phenyl, naphthyl or anthracenyl radical; similarly, the diarylmethyl radical will commonly be a benzhydryl radical; the cycloalkyl radical may be monocyclic or polycyclic and will commonly be a cyclopentyl, cyclohexyl or cycloheptyl radical, or an adamantyl radical; and the aromatic heterocyclic radical will commonly be a thienyl, indolyl, imidazolyl, pyrrolyl or pyridyl radical.

When R represents an alkyl radical substituted by R′, the compounds of general formula I may be defined by the general formula:



(I_A)

(wherein A represents a straight or branched chain alkylene radical containing from 1 to 6 carbon atoms and R′ represents an aryl radical, a diaryl-methyl radical, a cycloalkyl radical or an aromatic heterocyclic radical, always providing that R′ does not represent a phenyl radical when A represents an ethylene radical). The alkylene radical A in general formula I_A may be, for example, a methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene or hexamethylene radical.

A preferred group of 3-(2-aminoethyl)phenol derivatives of the invention are those wherein R′ represents a phenyl radical, a cyclopentyl radical, a cyclohexyl radical, an adamantyl radical, a thienyl radical, an indolyl radical or an imidazolyl radical.

Where the radical R in any of the derivatives falling within that preferred group represents an alkyl radical, substituted by R′, that alkyl radical is preferably an ethyl, *n*-propyl or *i*-propyl radical.

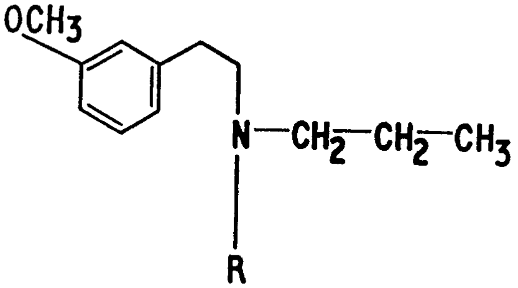
A still more preferred group of 3-(2-aminoethyl)phenol derivatives of the invention are those wherein R represents a phenylpropyl radical, a cyclohexyl-ethyl radical, a cyclopentyl radical, an adamantyl radical, a 2-(2-thienyl)-ethyl radical, a 2-[(1H)-indol-3-yl]-ethyl radical or a 2-[(1H)-imidazol-4-yl]-ethyl radical.

The addition salts of the compounds of general formula I may be formed with mineral acids such as hydrochloric, hydrobromic, hydriodic, nitric, sulphuric or phosphoric acid, or with organic acids. The organic acids may be aliphatic carboxylic acids such as acetic, formic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic or aspartic acid, arylcarboxylic acids such as benzoic acid, alkanesulphonic acids such as methane or ethane sulphonic acid, or arylsulphonic acids such as benzene- or *p*-toluene-sulphonic acid.

The following salts are specifically preferred derivatives of this invention:
3-(2-[N-(3-phenylpropyl)-N-propylamino]ethyl-phenol oxalate;
3-(2-[N-(2[2-thienyl]ethyl)-N-propylamino]ethyl)phenol hydrochloride;

3-(2-[N-(2-cyclohexylethyl)-N-propylamino]ethyl)phenol hydrochloride; and
3-(2-[N-cyclopentyl-N-propylamino]ethyl)phenol hydrochloride.

The invention also provides a process for preparing the compounds of general formula I above, in which process a compound of general formula:



(II)

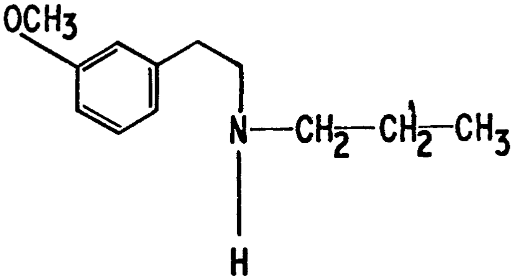
(wherein R is as defined hereinbefore) is hydrolysed to obtain the desired product of general formula I.

The hydrolysis of the compound of formula II is preferably carried out with a concentrated solution of hydrobromic acid or with pyridine hydrochloride, at the reflux temperature of the reaction mixture.

The hydrolysis may be followed by treatment of the product with ammonium hydroxide, which enables the compound produced to be obtained in non-salified form.

The starting materials of general formula II may be prepared by a variety of routes, depending on which particular compound of general formula II it is desired to obtain.

The compounds of general formula II wherein R is the radical R′ or a straight or branched chain alkyl radical containing from 1 to 3 carbon atoms and substituted by the radical R′ may be prepared by reacting a compound of the structural formula:



(III)

with a halide of general formula:

$$\mathrm{Hal—R_1} \qquad \text{(IV)}$$

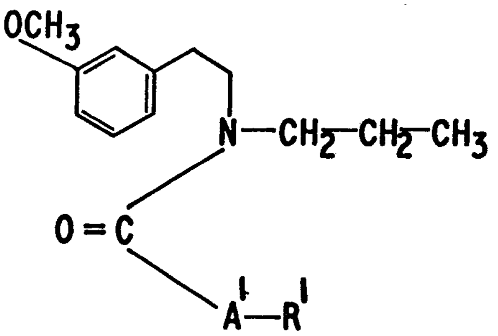
(in which Hal represents a chlorine, bromine or iodine atom and R_1 is the radical R′ or a straight or branched chain alkyl radical containing from 1 to 3 carbon atoms and substituted by the radical R′) to obtain the desired compound of general formula II.

The reaction of the compound of formula III with the halide of general formula IV is advantageously carried out in an alkanol such as ethanol and in the presence of an alkaline agent. The alkaline agent may be a mineral base such as sodium or potassium carbonate, or an organic base such as tertiaryamine — for instance triethylamine. The reaction should preferably be performed at the reflux temperature of the reaction mixture.

The compounds of general formula II, wherein R represents a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and substituted at any position but the 1-position by the radical R′ may be prepared by a process in which the compound of formula III (as defined hereinbefore) is reacted with an acid of general formula:

$$\mathrm{R'—A'—COOH} \qquad \text{(V)}$$

(wherein A′ represents a straight or branched alkylene radical containing from 1 to 5 carbon atoms and R′ is as defined hereinbefore) to obtain a compound of general formula:



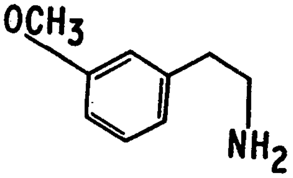
(VI)

(wherein A′ and R′ are as defined hereinbefore) which compound of general formula VI is reduced to obtain the desired compound of general formula II.

The reaction of the compound of formula III with the acid of general formula V is advantageously carried out at the reflux temperature of the reaction mixture and in the presence of dicyclohexylcarbodiimide.

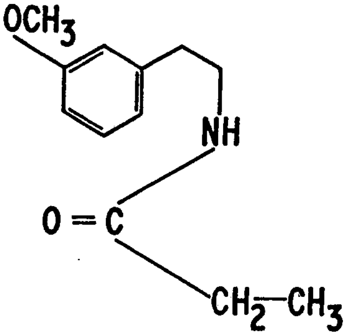
The reduction of the compound of general formula VI may advantageously be carried out using lithium aluminium hydride, diborane or the complex of diborane with dimethylsulphide as the reducing agent. The reduction is preferably carried out in an organic solvent such as tetrahydrofuran.

The compound of formula III used as starting materials in the above processes may be prepared by reacting a compound of structural formula:—



(VII)

with propionic acid to obtain an amide of structural formula:



(VIII)

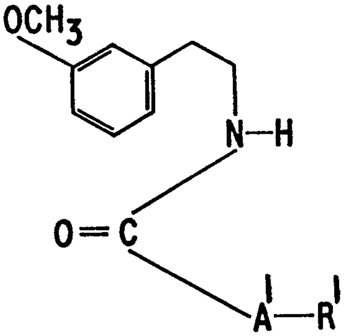
which amide is reduced to obtain the compound of formula III.

Alternatively, the compound of formula III may be prepared by reacting the compound of formula VII (as defined hereinbefore) with a propyl halide of general formula:

$$\text{Hal—CH}_2\text{—CH}_2\text{—CH}_3 \qquad \text{(IX)}$$

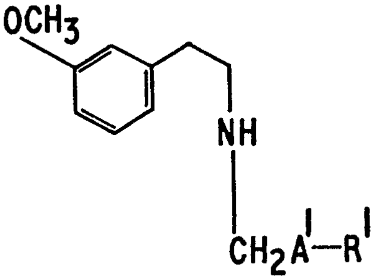
(wherein Hal represents a chlorine, bromine or iodine atom). The reaction between the compounds of formulae VII and IX is preferably effected in the presence of a basic agent such as a tertiary amine, for instance triethylamine, and at the reflux temperature of the reaction medium.

The compounds of general formula II wherein R represents a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and substituted at any position but the 1-position by the radical R′ may alternatively be prepared by a process in which the compound of formula VII (as defined hereinbefore) is reacted with an acid of general formula V (as defined hereinbefore) to obtain a compound of general formula:



(X)

(wherein A′ and R′ are as defined hereinbefore) which compound of general formula X is reduced to obtain a compound of general formula:



(XI)

(wherein A′ and R′ are as defined hereinbefore) which compound of general formula XI is then reacted with a propyl halide of general formula IX (as defined hereinbefore) to obtain the desired product of general formula II.

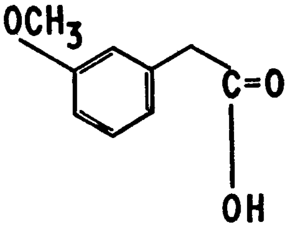
The reaction of the compound of general formula VII with the acid of general formula V is carried out in the same manner as that of the compound of general formula III with the acid of general formula V.

Similarly, the reduction of the compound of general formula X is performed in the same manner as that of the compound of general formula VI.

The reaction of the compound of general formula XI with the propyl halide of formula IX is preferably carried out in a polar organic solvent such as a carbonyl compound, for instance acetone or methylethyl ketone, or an alkanol, for instance ethanol.

The presence of an alkaline agent such as potassium carbonate is advantageous, and the reaction is preferably conducted at the reflux temperature of the mixture.

Finally, any of the compounds of general formula II may be prepared by a process in which an acid of structural formula:

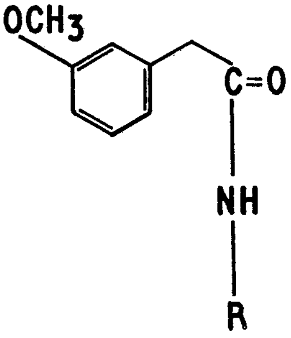


(XII)

is reacted with an amine of general formula:

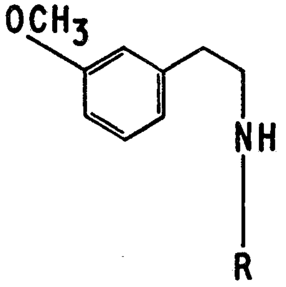
$$R—NH_2 \qquad (XIII)$$

(wherein R is defined hereinbefore) to obtain a compound of general formula:



(XIV)

(wherein R is as defined hereinbefore), which compound of general formula XIV is reduced to obtain a compound of general formula:



(XI$_A$)

(wherein R is as defined hereinbefore) which compound of general formula XI$_A$ is reacted with a propyl halide of general formula IX (as defined hereinbefore) finally to obtain the desired compound of general formula II.

The reaction between the acid of formula XII and the amine of general formula XIII is preferably carried out at about 200°C, or in the presence of a dehydrating agent.

The reduction of the compound of general formula XIV may advantageously be carried out using lithium aluminium hydride, diborane or the complex of diborane with dimethylsulphide in a solvent such as tetrahydrofuran.

The reaction between the compound of general formula XI$_A$ and the propyl halide of general formula IX may be conducted under the preferred conditions described above in relation to the reaction between the compound of general formula XI and the propyl halide of general formula IX.

The acid addition salts of the compounds of general formula I may be prepared simply by reacting, in substantially stoichiometric proportions, a mineral or organic acid with a compound of general formula I to form the desired acid addition salt.

The 3-(2-aminoethyl)phenol derivatives of the invention possess very interesting pharmacological properties. In particular they display remarkable dopaminergic properties and may be capable of being used in the treatment of neurological syndromes of extrapyramidal origin. They also tend to inhibit the secretion of prolactin.

These properties are illustrated in the Pharmacological Study set out hereinafter. Thus the derivatives of the invention may be useful in human or veterinary medicine and especially in the treatment of Parkinson's disease, of postencephalitic parkinsonian syndromes, of parkinsonian syndromes of arteriosclerotic origin or of toxic etiology, as well as in the treatment of disorders connected with hyperprolactinaemia.

But before using them in medicine, it is preferred to form the derivatives of the invention into pharmaceutical compositions, by association with suitable pharmaceutical vehicles.

Accordingly, this invention further provides pharmaceutical compositions containing as active ingredient one or more compounds of general formula I and/or acid addition salts thereof with pharmaceutically acceptable mineral or organic acids, in association with a pharmaceutically acceptable vehicle.

The compositions of the invention preferably contain those derivatives mentioned hereinbefore as being preferred.

The description "pharmaceutically acceptable" is used herein to exclude any possibility that the nature of the vehicle or the acid, considered of course in relation to the route by which the composition is to be administered, could be harmful to the patient to be treated. The choice of a suitable vehicle or acid is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

The compositions are preferably administered via the digestive or parenteral route, and in respect of those routes the pharmaceutical vehicle is preferably:

a) the ingestible excipient of a pill, such as a sublingual or coated compressed tablet; the ingestible container of a capsule or cachet, such as a gelatin capsule; the ingestible pulverulent solid carrier of a powder or granules; or the ingestible liquid medium of a syrup, solution, suspension or elixir;

b) a sterile injectable liquid solution or suspension medium; or

c) a base material of a suppository.

Whilst the pharmaceutical forms just listed represent those most likely to be employed, they do not necessarily exhaust the possibilities.

The vehicles employed will generally be those excipients commonly employed in the formulation of pharmaceutical compositions. Such excipients may be solid or liquid as appropriate to the pharmaceutical form chosen, and may include a wide range of organic and inorganic solids, and aqueous and non-aqueous liquids; examples include talc, gum arabic, starch, lactose, magnesium stearate or fatty substances of animal or vegetable origin such as cocoa butter, paraffin derivatives or glycols. These excipients may be compounded with one or more wetting, dispersing or emulsifying agents and/or one or more preservatives.

The dosage of the active ingredient to be administered to a patient will of course vary with the compound concerned, the complaint and the patient being treated and the route of administration chosen. By way of illustration it may be said that a desirable dosage in an adult would be from 10 mg to 500 mg per day, administered by the oral route.

Finally, this invention provides the compounds of general formula II (as defined hereinbefore), which are useful as intermediates in the preparation of the derivatives of the invention.

The following Examples and Formulations are given, though only by way of illustration, to show certain aspects of this invention.

Example 1
3-(2-[N-(3-phenylpropyl)-N-propylamino]ethyl)-phenol Oxalate
Stage A: 3-methoxy-N-propyl-benzene-ethanamine

Under an inert atmosphere and with agitation, a mixture of 10 g of 3-methoxy-benzene-ethanamine, 11.25 g of 1-iodopropane and 66 ml of triethylamine were heated to reflux for 1 hour 30 minutes. The reaction mixture was then distilled to dryness under reduced pressure, and 250 ml of 0.5 N ammonia were added. After extracting with ethyl acetate, washing with water, drying and distilling to dryness under reduced pressure, 12.1 g of an oil were obtained. The oil was chromatographed on silica, eluting with a mixture of chloroform (7) and methanol (3), to recover 8 g of the expected product.

For analysis, 8 g of the product obtained were dissolved in 20 cm^3 of ethyl acetate and to the resulting solution was added, drop by drop, a saturated solution of HCl gas in ethyl acetate until a pH of 1 was reached. After crystallisation and vacuum-filtering, 7.2 g of 3-methoxy-N-propyl-benzene-ethanamine hydrochloride were obtained as a product melting at 182°C.

Stage B: N-[2-(3-methoxy-phenyl)-ethyl]-N-propyl-benzene-propanamine

With agitation and under an atmosphere of nitrogen, 6 g of 3-methoxy-N-propyl-benzene-ethanamine, 12 g of 3-phenylpropyl bromide and 12 g of potassium carbonate were suspended in 100 ml of acetone. The suspension was heated to reflux for 40 hours, cooled to ambient temperature and poured on to 500 ml of water. After extracting with methylene chloride, drying and distilling to dryness under reduced pressure, 12 g of a yellow oil were obtained. This oil was taken up with N hydrochloric acid, washed with diethyl ether and at about 10°C rendered alkaline with a sodium hydroxide solution. The precipitate formed was extracted with methylene chloride and after drying and distilling to dryness under reduced pressure, 9.5 g of a yellow oil were obtained. This was used without purification in the following stage.

Stage C: 3-(2-[N-(3-phenylpropyl)-N-propylamino]ethyl)phenol Oxalate

9.5 g of N-[2-(3-methoxy-phenyl)-ethyl]-N-propyl-benzene-propanamine in 50 ml of 48% hydrobromic acid were agitated under inert atmosphere, and the mixture was heated to reflux for 1 hour 30 minutes.

After cooling to 20°C, rendering alkaline with concentrated ammonia, extracting with methylene chloride, drying and distilling to dryness under reduced pressure, 9 g of a yellow oil were obtained. This oil was dissolved in 10 ml of methanol, and 1.9 g of crystalline hydrated oxalic acid (containing 2 molecules of water for each one of acid) were added. The whole was heated to 40°C until dissolution. 50 ml of ethyl acetate were added, and after concentrating to 50 ml, the crystalline product obtained was vacuum-filtered to give 6.5 g of expected oxalate M.Pt.=145°C.

The oxalate was recrystallised by dissolving it in 60 ml of methanol, filtering, adding 100 ml of ethyl acetate and concentrating to 60 ml. The concentrate was vacuum-filtered to obtain 5.5 g of crystalline salt. M.Pt.=145°C.

Analysis: $(C_{20}H_{27}NO)_2$ HOOC—COOH: 684.88

Calculated:	C%=73.65	H%=8.24	N%=4.09
Found:	C%=73.5	H%=8.4	N%=3.8

UV Spectrum

EtOH

infl: 215 nm	E_1^1 367	
infl: 223 nm	E_1^1 184	
infl: 268 nm	E_1^1 51	
max: 273 nm	E_1^1 61	ε 2100
infl: 279 nm	E_1^1 55	

EtOH—NaOH N/10

max: 240 nm	E_1^1 289	ε 9900
infl: 269 nm	E_1^1 38	
max: 290.291 nm	E_1^1 98	ε 3350

Example 2

3-(2-[N-(2-[2-thienyl]ethyl)-N-propylamino]ethyl)phenol Hydrochloride

Stage A: N-[2-(3-methoxyphenyl)ethyl]-(2-thiophene)acetamide

A mixture of 15.1 g of 3-methoxy-benzene-ethanamine and 14.2 g of (2-thienyl)acetic acid was agitated for 30 minutes at 200°C under an inert atmosphere. After cooling to 20°C and taking up with 600 ml of a 1:1 mixture of diethyl ether and isopropyl ether heated to reflux temperature, filtering and distilling to dryness under reduced pressure, 28 g of a brown oil were obtained. This was crystallised from 28 ml of diethyl ether at about +5°C to give 25.5 g of product after vacuum-filtration. M.Pt.=50°C.

Stage B: N-[2-(3-methoxyphenyl)-ethyl]-N-[2-(2-thienyl]ethyl]amine Hydrochloride

21.90 g of N-[2-(3-methoxyphenyl)-ethyl]-(2-thiophene)acetamide were dissolved in 219 ml of anhydrous tetrahydrofuran, and at ambient temperature, 21.9 ml of a borane/dimethyl sulphide complex were added in one portion to the solution. The whole was heated gradually to reflux and agitated for one hour at reflux, and then after cooling to +5°C, 100 ml of 2 N hydrochloric acid were carefully added. The whole was agitated for one hour at reflux, after which the tetrahydrofuran was distilled away under reduced pressure. 300 ml of water were added to the residue and after washing with diethyl ether, rendering the aqueous phase alkaline with concentrated ammonia, extracting with methylene chloride, drying and distilling to dryness under reduced pressure, 21.5 g of product were obtained as a yellow oil. This was dissolved in 50 ml of diethyl ether, and a solution of HCl gas in ethyl acetate was added to the solution until a pH of 2 was reached. After vacuum-filtering and washing with diethyl ether, 21.70 g of the desired hydrochloride were obtained. M.Pt.=170°C.

Analysis: $C_{15}H_{19}N.O.S.HCl$: 297.84

Calculated:	C% 60.48	H% 6.77	N% 4.70	Cl% 11.95	S% 10.76
Found:	C% 60.6	H% 6.8	N% 4.5	Cl% 12.0	S% 10.6

UV Spectrum

EtOH

max 224 nm	E_1^1 435	ε 13000
infl 234 nm	E_1^1 283	
max 274 nm	E_1^1 65	ε 1950
max 280—281 nm	E_1^1 60	ε 1800

IR Spectrum

$CHCl_3$
General absorption region$^{\oplus}$
Aromatic 1605—1589—1490 cm^{-1}

Stage C: N-[2-(3-methoxyphenyl)-ethyl]-N-[2-(2-thienyl)ethyl]propylamine

21.70 g of N-[2-(3-methoxyphenyl)-ethyl]-N-[2-(2-thienyl)ethyl]amine, 50 g of 1-iodopropane and 50 g of potassium carbonate in 400 ml of absolute ethanol were agitated for 6 hours 30 minutes at reflux temperature. The ethanol was distilled off under reduced pressure, and 500 ml of water and 50 ml of sodium hydroxide solution were added to the residue. After extracting with methylene chloride, washing with salt water, drying and distilling to dryness under reduced pressure, 22 g of product were obtained. This product was used without purification in the following stage.

Stage D: 3-(2-[N-(2-[2-thienyl]ethyl)-N-propylamino]ethyl)phenol Hydrochloride

Under an inert atmosphere, 21 g of N-[2-(3-methoxyphenyl)-ethyl]-N-[2-(2-thienyl)-ethyl]propylamine in 42 ml of acetic acid and 42 ml of 48% hydrobromic acid were agitated for 5 hours at the reflux temperature of the medium. The whole was cooled, and 500 ml of ice were then added followed by 100 ml of concentrated ammonia. After extracting with methylene chloride, washing with salt water, drying and distilling to dryness under reduced pressure, 21 g of product were obtained as an oil. This was dissolved in 21 ml of isopropanol, and at +5°C, a solution of HCl gas in ethyl acetate was added until a pH of 1 was reached. After crystallisation, the crystals were separated by vacuum-filtration, washed with ispropanol and then with ether to give 16.5 g of the hydrochloride. M.Pt.=140°C.

This was dissolved in 20 ml of methanol and 1.5 litres of methylene chloride at reflux temperature, and treated with active charcoal. After filtering and concentrating to 50 ml, 300 ml of ethyl acetate were added. The whole was left for 2 hours at ambient temperature before vacuum-filtering, washing with ethyl acetate and drying at 90°C under reduced pressure to give 14 g of product. This was redissolved in 400 ml of isopropanol at reflux temperature, then after filtering and concentrating to 75 ml, 13 g of crystals were allowed to form. These were separated by vacuum-filtration and taken up in 150 ml of ethanol at reflux temperature. Then after filtering and concentrating to 50 ml, crystals were allowed to form once more. These were again separated by vacuum-filtration and then washed with ethanol followed by diethyl ether and dried at 85°C under reduced pressure to give 11.8 g of the expected product. M.Pt.=145°C.

Analysis: $C_{17}H_{23}$ N.O.S. HCl=325.89

Calculated:	C% 62.65	H% 7.42	N% 4.30	Cl% 10.88	S% 9.84
Found:	C% 62.5	H% 7.6	N% 4.1	Cl% 11.0	S% 9.7

UV Spectrum

EtOH		
max 225 nm	E_1^1=360	ε 11700
infl 235 nm	E_1^1=258	
max 274 nm	E_1^1= 66	ε 2150
infl 278 nm	E_1^1= 61	
EtOH—NaOH N/10		
max 237 nm	E_1^1=514	ε 16800
max 290—291 nm	E_1^1= 98	ε 3200

IR Spectrum "Nujol" (Registered Trade Mark)
associated OH: 3180 cm^{-1}
aromatic: 1615—1590—1486 cm^{-1}

Example 3

3-(2-[N-(2-cyclohexylethyl)-N-propylamino]ethyl)phenol Hydrochloride

Stage A: N-[2-(3-methoxyphenyl)-ethyl]-cyclohexaneacetamide

Under an inert atmosphere and with agitation, 20 g of 3-methoxy-benzene-ethanamine and 15.2 g of cyclohexylacetic acid were heated to 190—200°C for 3/4 of an hour. After cooling to 30°C, dissolving in ethyl acetate, washing with N sodium hydroxide, with N hydrochloric acid and then with water, drying and bringing to dryness, 29 g of oil was obtained. This was crystallised by adding petroleum ether (B.Pt.: 40—70°C), vacuum-filtering and drying. 21.3 g of the expect product were obtained in the form of a white solid melting at 74°C.

Stage B: N-(2-cyclohexylethyl)-N-[2-(3-methoxyphenyl)ethyl]amine Hydrochloride

To a suspension of 11.8 g of lithium aluminium hydride in 150 cm^3 of tetrahydrofuran was added at about 0°C and over 20 minutes, 21.3 g of N-[2-(3-methoxyphenyl)-ethyl]-cyclohexane-acetamide in solution in 100 ml of tetrahydrofuran. The whole was taken to reflux and after 4 hours, 6 g of lithium aluminium hydride were added, followed after a further 6 hours of refluxing by another 6 g dose of lithium aluminium hydride. After 22 hours and at 20—25°C, 500 cm^3 of tetrahydrofuran containing 20% of water were added, before filtering, distilling, extracting with methylene chloride, washing with water, drying and bringing to dryness to obtain 19.4 g of an oil. This was dissolved in 100 cm^3 of ethyl acetate, an excess of HCl gas dissolved in ethyl acetate was added, and the whole was left for 1 hour in a refrigerator. Vacuum-filtration, washing with ethyl acetate and then drying gave 20.6 g of the hydrochloride sought, which melted at 174°C.

Stage C: N-(2-cyclohexylethyl)-N-[2-(3-methoxyphenyl)ethyl]propylamine

The hydrochloride obtained in Stage B was converted to the free base (17.8 g) and then dissolved in 180 cm^3 of acetone. 48 g of potassium carbonate and 17.5 cm^3 of 1-iodopropane were added to the solution, and the whole was taken to reflux under inert atmosphere for 4 hours 30 minutes. After filtering, distilling to dryness, taking up the residue with diethyl ether, adding 100 cm^3 of 2 N sodium hydroxide, decanting, washing with water, drying and then bringing to dryness, 19.25 g of the product sought were obtained in the form of a yellow oil. This was used without further treatment in the following stage.

Stage D: 3-(2-[N-(2-cyclohexylethyl)-N-propylamino]ethyl)phenyl Hydrochloride

Under inert atmosphere, the 19.25 g of product obtained in Stage C were agitated in 95 cm^3 of 48% hydrobromic acid, and the whole was heated to reflux for 1 hour 30 minutes.

After cooling, rendering alkaline with concentrated ammonia, saturating with sodium chloride, extracting with ethyl acetate, washing with water, drying and bringing to dryness, 19 g of an oil were obtained. This was dissolved in 50 cm^3 of methylethylketone, and an excess of HCl dissolved in ethyl acetate was added to the solution. After initiating crystallisation, leaving for one night in the refrigerator, vacuum-filtering, and drying at 60°C under reduced pressure, 17.4 g of the expected hydrochloride were obtained.

After two successive recrystallisations from methylethylketone 16.35 g of a purified product were obtained, which melted at 100°C.

Analysis: $C_{19}H_{31}$ NO . HCl: 325.92

Calculated:	C% 70.02	H% 9.90	Cl% 10.88	N% 4.30
Found:	C% 70.0	H% 9.9	Cl% 10.8	N% 4.2

UV Spectrum

EtOH		
max 217 nm	E_1^1 184	ε 6000
max 275 nm	E_1^1 64	ε 2100
infl 279 nm	E_1^1 59	
EtOH—NaOH 0.1 N		
max 239 nm	E_1^1 285	ε 9300
max 291 nm	E_1^1 98	ε 3200

Example 4

3-(2-[N-(tricyclo[3,3,1,1$^{3-7}$]decan-1-yl)-N-propylamino]ethyl)-phenol Hydrochloride

Stage A: 3-methoxy-N-[tricyclo(3,3,1,1$^{3-7}$)-decan-1-yl]-benzeneacetamide

For one hour, under inert atmosphere and at ambient temperature, 33.4 g of 3-methoxybenzeneacetic acid, 15 g of 1-amino-adamantane and 40 g of dicyclohexylcarbodiimide were agitated in 500 cm^3 of ethyl acetate. At the end of that time, the solid was separated by filtration, washing with ethyl acetate, and the filtrate was washed twice with 200 cm^3 of N sodium hydroxide, twice with 200 cm^3 of N hydrochloric acid and once with 200 cm^3 of water. After drying with magnesium sulphate, filtering and distilling to dryness under reduced pressure, 40 g of a yellow oil were obtained. This was recrystallised from 30 cm^3 of isopropyl ether and recovered by vacuum-filtration to give 22.2 g of the product sought in crystalline form melting at 116°C.

Stage B: N-[tricyclo-(3,3,1,1,$^{3-7}$-decan-1-yl]-N-[2-(3-methoxyphenyl)ethyl]amine Hydrochloride

Over 5 minutes and at 5°C, the 22.2 g of crystalline product obtained in Stage A were added to 9 g of lithium aluminium hydride in 220 cm^3 of tetrahydrofuran. The whole was agitated at reflux for 1 hour 40 minutes, cooled to 10°C and then over 20 minutes, 40 cm^3 of tetrahydrofuran containing 50% of water were added, drop by drop. After filtering and distilling to dryness, 20 g of a colourless oil were obtained, which was dissolved in 20 cm^3 of ethyl acetate. A saturated solution of HCl in ethyl acetate was added, drop by drop, until a pH of 1 was reached, and then the solid was separated by vacuum-filtration to give 15 g of the product sought in the form of crystals melting at 226°C.

Stage C: N-[tricyclo-(3,3,1,1,$^{3-7}$-decan-1-yl)]-N-[2-(3-methoxyphenyl)ethyl]propylamine Hydrochloride

The product obtained in Stage B was converted into the free base, and 8.7 g of this base were heated to reflux under an inert atmosphere for 2 hours 30 minutes with 10 g of 1-iodopropane and 10 g of potassium carbonate. After cooling, extracting with three times 100 cm^3 of methylene chloride, washing with twice 100 cm^3 of water, drying with magnesium sulphate, filtering and distilling to dryness under reduced pressure, 11.2 g of the base of the product sought were obtained in the form of a yellow oil. This was purified by chromatography. The hydrochloride was then formed and crystallised to give 5.2 g of the product sought melting at 174°C.

Stage D: 3-[2-[N-(tricyclo-3,3,1,1,$^{3-7}$)decan-1-yl)N-propylamino]ethyl)phenol Hydrochloride

At reflux and under an inert atmosphere, 10.4 g of the hydrochloride obtained in Stage C were agitated with 104 cm^3 of 48% hydrobromic acid for one hour. The whole was then cooled and rendered alkaline with concentrated ammonia. The precipitate formed was extracted with three times 80 cm^3 of methylene chloride, and after washing with 100 cm^3 of water, drying with magnesium sulphate, filtering and distilling to dryness, 8.2 g of yellow oil were obtained. This was dissolved in 20 cm^3 of ethyl acetate and to the formed solution there was added, drop by drop, a solution of ethyl acetate saturated with HCl until a pH of 1 was reached. The solid was separated by vacuum filtration and then successively recrystallised from firstly a mixture of methanol and isopropanol and secondly a mixture of methanol and ethyl acetate. After vacuum-filtration, 5.9 g of the product sought were obtained, melting at 220°C.

Analysis: $C_{21}H_{31}$ NO, HCl=349.935

Calculated:	C% 72.07	H% 9.22	N% 4.00	Cl% 10.13
Found:	C% 72.2	H% 9.4	N% 3.9	Cl% 10.2

UV Spectrum

EtOH		
max 217 nm	E_1^1=185	ε=6500
max 275 nm	E_1^1= 62	ε=2150
infl 279 nm	E_1^1= 56	
EtOH—NaOH N/10		
max 240 nm	E_1^1=267	ε=9300
max 292 nm	E_1^1= 90	ε=3150

Example 5

3-[2-[N-cyclopentyl-N-propylamino]-ethyl)phenol Hydrochloride

Stage A: N-cyclopentyl-3-methoxy-N-propyl-benzene-ethanamine

At reflux, 3.4 g of the 3-methoxy-N-propyl-benzene-ethanamine obtained in Stage A, Example 1 was agitated with 4 g of potassium carbonate and 15 cm^3 of cyclopentyl bromide. After one hour, 5 g of potassium carbonate were added, followed after a further three hours by 5 g of potassium carbonate and 10 cm^3 of cyclopentyl bromide. After a total of seven hours, the whole was poured onto 50 cm^3 of water, and after extracting with three times 50 cm^3 of diethyl ether, drying, filtering and distilling to dryness, 4.5 g of the product sought were obtained in the form of a red oil. This was used without further treatment in the following stage.

Stage B: 3-[2-[N-cyclopentyl-N-propylamino]-ethyl)phenol Hydrochloride

A reflux and under an atmosphere of nitrogen, 4.35 g of the product obtained in Stage A were agitated for two hours with 43 cm^3 of 48% hydrobromic acid. After cooling, rendering alkaline with concentrated ammonia, extracting three times with methylene chloride, washing with twice 50 cm^3 of water drying with magnesium sulphate, filtering and distilling to dryness, 4 g of a brown oil were obtained. This was dissolved in 5 cm^3 of methanol, and a saturated solution of HCl in ethyl acetate was added dropwise until an acidic pH was obtained. After vacuum filtering and recrystallising from a mixture of methanol and ethyl acetate, 2.7 g of the product sought were obtained, melting at 140°C.

Analysis: $C_{16}H_{25}NO \cdot HCl=283.84$

Calculated:	C% 67.7	H% 9.23	N% 4.94	Cl% 12.49
Found:	C% 67.5	H% 9.5	N% 4.7	Cl% 12.7

UV Spectrum

Ethanol		
max 218 nm	$E^1_1=229$	ε 6500
max 274 nm	$E^1_1=76$	ε 2200
infl 279 nm	$E^1_1=69$	
Ethanol NaOH N/10		
max 241—242 nm	$E^1_1=329$	ε 9300
max 291 nm	$E^1_1=113$	ε 3200

Example 6

3-(2-[N-(2-[1H-imidazol-4-yl]ethyl)-N-propylamino]ethyl)-phenol Oxalate

Stage A: 3-methoxy-N-[2-(1H-imidazol-4-yl)-ethyl]-benzene-acetamide

27.6 g of histamine dihydrochloride were dissolved in 150 cm^3 of 2 N sodium hydroxide and the formed solution was distilled to dryness. 24.9 g of 3-methoxy-benzeneacetic acid were added and the whole was agitated for 30 minutes at 210°C, and then cooled to 50°C. After extracting with 1 litre of ethyl acetate at reflux temperature, filtering, distilling to dryness under reduced pressure and crystallising the formed residue from methylene chloride, 27.7 g of the product sought were obtained, melting at between 98 and 100°C.

Stage B: N-[2-(3-methoxyphenyl)-ethyl]-N-[2-(1H-imidazol-4-yl)ethyl]amine Dihydrochloride

For 1 hour 30 minutes and at reflux 5 g of the amide obtained in Stage A were agitated with 2.5 g of lithium aluminium hydride in 50 cm^3 of tetrahydrofuran. The whole was then cooled to 10°C, and 100 cm^3 of tetrahydrofuran containing 20% of water and 100 cm^3 of methylene chloride were added. After filtering and distilling to dryness, 4.7 g of a yellow oil were obtained. This was dissolved in 30 cm^3 of isopropanol and to the solution obtained was added a saturated solution of HCl in ethyl acetate until a pH of 1 was reached. After vacuum-filtering and washing with isopropanol, 3 g of the product sought were obtained in the form of colourless sparkling lamellae, melting at between 195 and 198°C.

Stage C: N-[2-(3-methoxyphenyl)-ethyl]-N-[2-(1H-imidazol-4-yl)ethyl]propylamine

At reflux and under an inert atmosphere, 3.2 g of the product obtained in Stage B were agitated for 19 hours with 5.1 g of potassium carbonate and 3.4 g of 1-iodopropane in 64 cm^3 of acetone. The acetone was then evaporated and 100 cm^3 of water and 2 cm^3 of sodium hydroxide were added. After extracting with three times 50 cm^3 of methylene chloride, washing with 100 cm^3 of water, drying with magnesium sulphate, filtering and distilling to dryness, 3.6 g of an oil were obtained. This was purified by chromatography on silica to give 900 mg of a yellow oil, which was used without further treatment in the following stage.

Thin-layer chromatography on silica ($CHCl_3$/Methanol, 70:30):Rf=0.20.

Stage D: 3-(2-[N-(2-(1H-imidazol-4-yl]ethyl)-N-propylaminoethyl)phenol Oxalate

At reflux and under an inert atmosphere, 800 mg of the product obtained in Stage C were agitated for one hour thirty minutes with 4 cm^3 of acetic acid and 4 cm^3 of 48% hydrobromic acid. The whole was then cooled and ice and an excess of concentrated ammonia were added. After extracting three times with 20 cm^3 of methylene chloride, drying with magnesium sulphate, filtering and distilling to dryness, 800 mg of a yellow oil were obtained. This was dissolved in 5 cm^3 of ethanol, and 365 mg of dihydrated oxalic acid were added and heated to dissolution. After cooling and vacuum-filtering, 600 mg of oxalate were obtained, melting at 165°C. After two recrystallisations from methanol the product melted at 170°C.

Analysis: $C_{18}H_{25}N_3O_5$=363.40

Calculated:	C% 59.49	H% 6.93	N% 11.56
Found:	C% 59.0	H% 6.8	N% 11.4

UV Spectrum

EtOH		
infl 214 nm	E_1^1=336	ε 12200
max 274 nm	E_1^1= 56	ε 2050
infl 280 nm	E_1^1= 51	
EtOH NaOH N/10		
max 240 nm	E_1^1=267	ε 9700
max 291 nm	E_1^1= 45	ε 3450

Example 7

3-(2-[N-(2-[1H-indol-3-yl]ethyl)-N-propylamino)ethyl)phenol Hydrochloride

Stage A: 3-methoxy-N-[2-(1H-indol-3-yl)ethyl]-benzene-acetamide

At 200°C and under an inert atmosphere, a mixture of 29 g of tryptamine with 30 g of 3-methoxy-benzene acetic acid was heated for one hour, after which it was cooled to 50°C. The crude product obtained was dissolved in 200 cm^3 of ethyl acetate, and after washing successively with N hydrochloride acid, with water, with 2 N sodium hydroxide and again with water, drying and bringing to dryness, 59 g of a reddish oil was obtained. This was crystallised from diethyl ether to give, after vacuum-filtering and drying, 47.2 g of the product sought in the form of a beige solid melting at 78°C. The product was used without further treatment in the following stage, but for purposes of identification it was recrystallised from diethyl ether. M.Pt. 82°C.

Stage B: N-[2-(3-methoxyphenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]amine Hydrochloride

30.6 g of the amide obtained in Stage A was dissolved in 150 cm^3 of tetrahydrofuran, and then under inert atmosphere 21 cm^3 of borane/dimethylsulphide complex (titrated at 1 cm^3$\simeq$1 m mole) were slowly added. The whole was taken to reflux for 2 hours 15 minutes, brought back to 20—25°C for the slow introduction of 150 cm^3 of 2 N hydrochloric acid, and reflux for a further 2 hours. The tetrahydrofuran was then evaporated away, and the residue rendered alkaline with 50 cm^3 of sodium hydroxide solution. After extraction with ethyl acetate, washing with water, drying with magnesium sulphate and bringing to dryness, 32 g of a crude product were obtained in the form of an orange oil. This was purified by chromatography on silica eluting with a mixture of methylene chloride, ethanol and acetic acid, 80:15:5, to give 22 g of the acetate (Rf 0.37), from which the free base was released with 6 N sodium hydroxide. The base was extracted with ethyl acetate, then after washing with water, drying and bringing to dryness, 14 g of the base were obtained in the form of an orange oil. This was dissolved in 70 cm^3 of ethyl acetate, and an excess of hydrochloric ethyl acetate was added to the formed solution. Finally, after vacuum-filtration, washing with ethyl acetate and drying, 13.95 g of a beige product were obtained, melting at 164°C then at 177°C, which was used without purification in the following stage.

Stage C: N-[2-(3-methoxyphenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]propylamine Hydrochloride

The hydrochloride obtained in Stage B was made into a paste with 100 cm^3 of water, and an excess of ammonia was added. After extracting with ethyl acetate, washing with water, drying and bringing to dryness, 13 g of an orange oil was obtained. This was dissolved in 200 cm^3 of acetone, to which was then added 29.3 g of potassium carbonate and 9.6 cm^3 of 1-iodopropane. The whole was taken to reflux for 6 hours, filtered and brought to dryness to obtain a residue which was taken up with 100 cm^3 of 2 N sodium hydroxide. Following extraction with ethyl acetate, the extracts were washed with water, dried and brought to dryness to obtain 15 g of a second orange oil, which was dissolved in 80 cm^3 of ethyl acetate. An excess of hydrochloric ethyl acetate was added and then crystallisation was initiated. Finally, after concentrating, leaving for one night in a refrigerator, vacuum-filtering, washing with ethyl acetate, and drying, 12.6 g of the hydrochloride sought were obtained, melting at 140°C.

Stage D: 3-(2-[N-(2-[1H-indol-3-yl]-ethyl)-N-propylamino]ethyl)phenol Hydrochloride

The hydrochloride obtained in Stage C was made into a paste with 50 cm^3 of water, to which was then added an excess of ammonia. Following extraction with ethyl acetate, washing with water, drying and bringing to dryness, 11.55 g of an orange oil were obtained. To this were added 45 g of pyridine hydrochloride, and the whole was taken to reflux at 220°C for two hours forty minutes under inert atmosphere before being cooled to 20°C and rendered alkaline with ammonia. Then after extraction with ethyl acetate, the extracts were washed with water, dried and brought to dryness to obtain 12.8 g of a reddish oil. This was dissolved in 60 cm^3 of isopropanol and an excess of hydrochloric ethyl acetate was added before distilling off the ethyl acetate and initiating crystallisation. After leaving for one night in a refrigerator, the solid was separated by vacuum-filtration, washed with isopropanol and dried to obtain 9.3 g of product in the form of a pale beige solid melting at 192°C, then 197°C. When recrystallised from ethanol, the product melted at 198°C.

Analysis: $C_{21}H_{26}N_2O . HCl=358.90$

Calculated:	C% 70.28	H% 7.58	N% 7.80	Cl% 9.88
Found:	C% 70.3	H% 7.7	N% 7.5	Cl% 10.1

UV Spectrum

EtOH		
max 220 nm	$E^1_1=1149$	ε 41200
max 274 nm	$E^1_1= 214$	
max 280 nm	$E^1_1= 220$	ε 7900
max 289 nm	$E^1_1= 155$	ε 5550
max 362 nm	$E^1_1= 3$	
max 380 nm	$E^1_1= 4$	
max 403 nm	$E^1_1= 3.5$	

EtOH—NaOH N/10		
infl 240 nm	$E^1_1= 305$	ε 10950
infl 275 nm	$E^1_1= 190$	
max 284 nm	$E^1_1= 232$	ε 8300
max 290 nm	$E^1_1= 233$	ε 8400
infl 295 nm	$E^1_1= 166$	ε 5950

Formulation 1

Compressed tablets were prepared according to the formula:

3-(2-[N-(2-cyclohexylethyl)N-propylamino]ethyl)phenol hydrochloride	10 mg
Excipient for one compressed tablet up to	200 mg

The excipient comprised lactose, starch, talc, and magnesium stearate.

Formulation 2

Compressed tablets were prepared according to the formula:

3-(2-[N-(2-[2-thienyl]-ethyl)-N-propylamino]ethyl)phenol hydrochloride	10 mg
Excipient for one compressed tablet up to	200 mg

The excipient comprised lactose, starch, talc and magnesium stearate.

Pharmacological Study

1) Rotation Behaviour After Unilateral Lesion of the Nigrostriatal Bundle with 6-hydroxydopamine

Technique

The tests were carried out on male rats of about 250 g. The lesion was effected by injection into the nigro-striatal passage of 8 μg of 6-hydroxydopamine (hydrochloride) in solution in 4 μl of physiological serum containing 1 mg/ml of ascorbic acid. (U. Ungerstedt, Acta physiol. Scand. 1971, *82,* suppl. 367, 69—93).

The compound under study was then administered by the intraperitoneal route.

To study the effect of the compounds, the treated animals were placed individually in a rotation meter, which enables the number of rotations made by each animal in both senses to be counted.

Results

Under the conditions of the test the compounds of Examples 2, 3, 5 and 7 brought about contralateral rotations after administration by intraperitoneal route at doses which are respectively equal to 0.5 mg/kg, 2 mg/kg, 5 mg/kg and 10 mg/kg.

These results show that the products studied and especially the products of Examples 2, 3 and 5 possess interesting dopaminergic stimulating properties.

2) Study of the Acute Toxicity

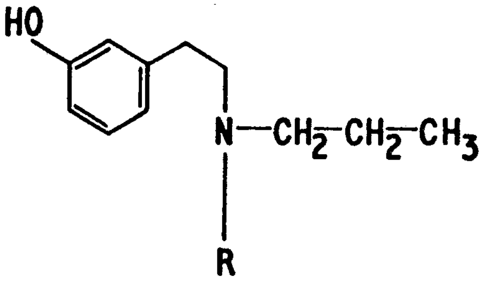
The lethal doses 50 (LD 50) of the compounds studied were evaluated after administration by intraperitoneal route in the mouse. The mortality rate was recorded forty-eight hours after the administration of the compounds.

Under the conditions of the test, the LD 50 of the compound of Example 1 is greater than 200 mg/kg and that of the compound of Example 2 equal to about 150 mg/kg.

In the following claims, all formulae and substituents referred to are, unless otherwise indicated, as first defined.

Claims

1. The derivatives of 3-(2-aminoethyl)phenol, being the compounds of general formula:



(I)

(wherein R may be a radical R′ or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms and substituted by a radical R′, the radical R′ being an aryl radical, a diaryl-methyl radical, a cycloalkyl radical or an aromatic heterocyclic radical, always providing that R may not represent a 2-phenylethyl radical) and the acid addition salts thereof formed with mineral or organic acids.

2. A derivative as claimed in Claim 1, wherein R′ represents a phenyl radical, a cyclopentyl radical, a cyclohexyl radical, an adamantyl radical, a thienyl radical, an indolyl radical or an imidazolyl radical.

3. A derivative as claimed in Claim 2, wherein the alkyl radical, where present, is an ethyl, *n*-propyl or *i*-propyl radical.

4. A derivative as claimed in Claim 1, wherein R represents a phenyl-propyl radical, a cyclohexyl-ethyl radical, a cyclopentyl radical, an adamantyl radical, a 2-(2-thienyl)-ethyl radical, a 2-[(1H)-indol-3-yl]-ethyl radical or a 2-[(1H)-imidazol-4-yl]-ethyl radical.

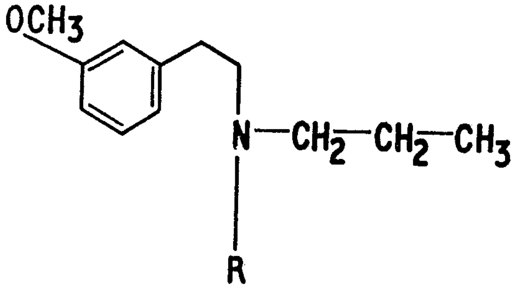
5. 3-(2-[N-(3-phenylpropyl)-N-propylamino]ethyl)phenol oxalate.

6. 3-(2-[N-(2-[2-thienyl]ethyl)-N-propylamino]ethyl)phenol hydrochloride.

7. 3-(2-[N-(2-cyclohexylethyl)-N-propylamino]ethyl)phenol hydrochloride.

8. 3-(2-[N-cyclopentyl-N-propylamino]ethyl)phenol hydrochloride.

9. A process for preparing the compounds of general formula I, in which process a compound of general formula:



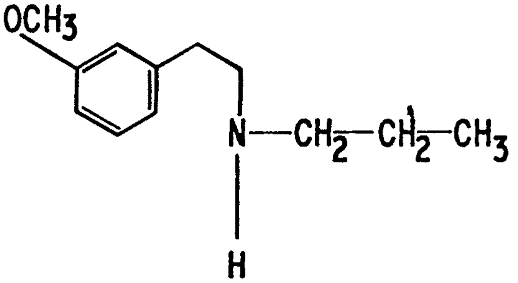
(II)

is hydrolysed to obtain the desired product of general formula I.

10. A process as claimed in Claim 9, in which the hydrolysis is carried out with a concentrated solution of hydrobromic acid or with pyridine hydrochloride, at the reflux temperature of the reaction mixture.

11. A process as claimed in Claim 10, in which the hydrolysis is followed by treatment of the hydrolysis product with ammonium hydroxide.

12. A process as claimed in any of Claims 9 to 11, in which a compound of general formula II, wherein R is the radical R′ or a straight or branched chain alkyl radical containing from 1 to 3 carbon atoms and substituted by the radical R′, is prepared by reacting a compound of the structural formula:



(III)

with a halide of general formula:

$$\mathrm{Hal—R_1} \quad \text{(IV)}$$

(in which Hal represents a chlorine, bromine or iodine atom and R_1 is the radical R′ or a straight or branched chain alkyl radical containing from 1 to 3 carbon atoms and substituted by the radical R′) to obtain the desired compound of general formula II.

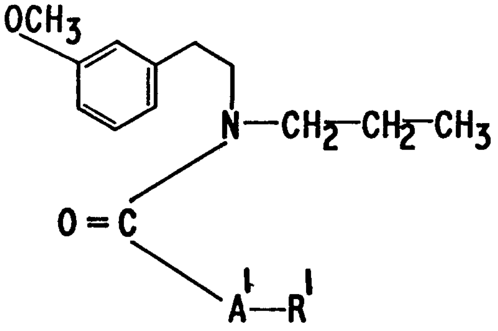
13. A process as claimed in Claim 12, in which the reaction of the compound of formula III with the halide of general formula IV is carried out in an alkanol and in the presence of an alkaline agent.

14. A process as claimed in Claim 13, in which the alkaline agent is sodium or potassium carbonate or triethylamine, and in which the reaction is performed at the reflux temperature of the reaction mixture.

15. A process as claimed in any of Claims 9 to 11, in which a compound of general formula II, wherein R represents a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and substituted at any position but the 1-position by the radical R′, is prepared by reacting the compound of formula III with an acid of general formula:

$$\mathrm{R'—A'—COOH} \quad \text{(V)}$$

(wherein A′ represents a straight or branched alkylene radical containing from 1 to 5 carbon atoms) to obtain a compound of general formula:



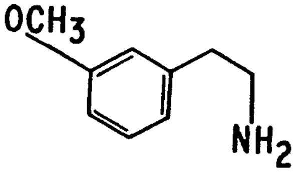
(VI)

which compound of general formula VI is reduced to obtain the desired compound of general formula II.

16. A process as claimed in Claim 15, in which the reaction of the compound of formula III with the acid of general formula V is carried out at the reflux temperature of the reaction mixture and in the presence of dicyclohexylcarbodiimide.

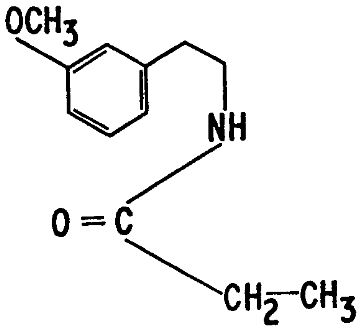
17. A process as claimed in Claim 15 or Claim 16, in which the reduction of the compound of general formula VI is carried out in an organic solvent using lithium aluminium hydride, diborane or the complex of diborane with dimethylsulphide as the reducing agent.

18. A process as claimed in any of Claims 12 to 17, in which the compound of formula III used as starting material is prepared by reacting a compound of structural formula:



(VII)

with propionic acid to obtain an amide of structural formula:



(VIII)

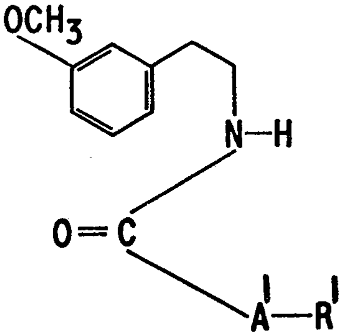
which amide is reduced to obtain the compound of formula III.

19. A process as claimed in any of Claims 12 to 17, in which the compound of formula III is prepared by reacting the compound of formula VII with a propyl halide of general formula:

$$\text{Hal—CH}_2\text{—CH}_2\text{—CH}_3 \qquad \text{(IX)}$$

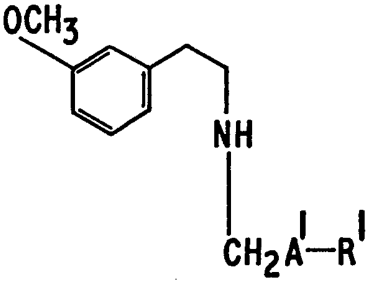
to obtain the compound of formula III.

20. A process as claimed in any of Claims 9 to 11, in which a compound of general formula II, wherein R represents a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and substituted at any position by the 1-position by the radical R', is prepared by reacting the compound of formula VII with an acid of general formula V to obtain a compound of general formula:



(X)

which compound of general formula X is reduced to obtain a compound of general formula:



(XI)

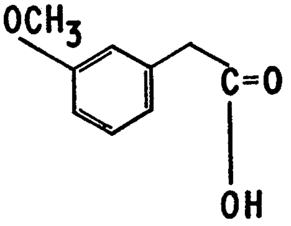
which compound of general formula XI is then reacted with a propyl halide of general formula IX to obtain the desired product of general formula II.

21. A process as claimed in Claim 20, in which the reaction of the compound of general formula VII with the acid of general formula V is carried out under the conditions described in Claim 16.

22. A process as claimed in Claim 20 or Claim 21, in which the reduction of the compound of general formula X is performed under the conditions described in Claim 17.

23. A process as claimed in any of Claims 20 to 22, in which the reaction of the compound of general formula XI with the propyl halide of formula IX is carried out in a polar organic solvent in the presence of an alkaline agent and at the reflux temperature of the reaction mixture.

24. A process as claimed in any of Claims 9 to 11, in which the compound of general formula II is prepared by a process in which an acid of structural formula:

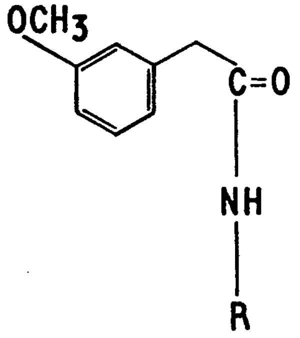


(XII)

is reacted with an amine of general formula:

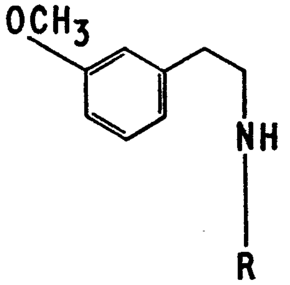
$$R-NH_2 \qquad (XIII)$$

to obtain a compound of general formula:



(XIV)

which compound of general formula XIV is reduced to obtain a compound of general formula:



(XI$_A$)

which compound of general formula XI$_A$ is reacted with a propyl halide of general formula IX finally to obtain the desired compound of general formula II.

25. A process as claimed in Claim 24, in which the reaction between the acid of formula XII and the amine of general formula XIII is carried out at substantially 200°C, or in the presence of a dehydrating agent.

26. A process as claimed in Claim 24 or Claim 25, in which the reduction of the compound of general formula XIV is carried out under the conditions described in Claim 17.

27. A process as claimed in any of Claims 24 to 26, in which the reaction between the compound of general formula XI$_A$ and the propyl halide of general formula IX is conducted under the conditions described in Claim 23.

28. A process for preparing the acid addition salts of the compounds of general formula I, in which process a mineral or organic acid is reacted, in substantially stoichiometric proportions, with a compound of general formula I (prepared according to a process as claimed in any of Claims 9 to 27) to form the desired acid addition salt.

29. A process for preparing a derivative as claimed in Claim 1, substantially as described herein with reference to any one of the Examples.

30. Pharmaceutical compositions containing as active ingredient one or more compounds of general formula I and/or acid addition salts thereof with pharmaceutically-acceptable mineral or organic acids, in association with a pharmaceutically acceptable vehicle.

31. A pharmaceutical composition as claimed in Claim 30, in which the active ingredient is a derivative as claimed in any of Claims 2 to 8.

32. A pharmaceutical composition as claimed in Claim 30, and substantially as described herein with reference to either of the Formulations.

33. The use of a derivative as claimed in any of Claims 1 to 8 in a method of treating the human or animal body by therapy practised on the human or animal body.

34. The compounds of general formula II.

New claims or amendments to claims filed on 18 Feb 1980.
Superseded claims 33.

New or Amended Claims

33. A derivative as claimed in any of Claims 1 to 8 for use in a method of treating the human or animal body by therapy.

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